Official Title: SAkuraBonsai: Clinical, Imaging and Biomarker Open-Label Study in Neuromyelitis Optica Spectrum Disorder (NMOSD) With Satralizumab as an Intervention

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PROTOCOL

TITLE:	**SAKURABONSAI: CLINICAL, IMAGING AND BIOMARKER OPEN-LABEL STUDY IN NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) WITH SATRALIZUMAB AS AN INTERVENTION**
PROTOCOL NUMBER:	MN42928
VERSION NUMBER:	1.0
EUDRACT NUMBER:	2021-001088-26
IND NUMBER:	118183
NCT NUMBER:	To be determined
TEST PRODUCT:	Enspryng (Satralizumab) (RO5333787)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd[a]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
09-Jul-2021 11:12:55	Company Signatory	[redacted]

CONFIDENTIAL

[a]Chugai will act as the Sponsor only in Japan. The specific details of the legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

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PROTOCOL ACCEPTANCE FORM

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your monitor.

PROTOCOL SYNOPSIS

TITLE:	**SAKURABONSAI: CLINICAL, IMAGING AND BIOMARKER OPEN-LABEL STUDY IN NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) WITH SATRALIZUMAB AS AN INTERVENTION**
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TEST PRODUCT:	Enspryng (Satralizumab) (RO5333787)
PHASE:	Phase IIIb
INDICATION:	Neuromyelitis Optica Spectrum Disorder
SPONSOR:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd (in Japan)

Objectives and Endpoints

This exploratory study will describe the efficacy and safety of satralizumab in patients with aquaporin-4 (AQP4) antibody seropositive neuromyelitis optica spectrum disorder (NMOSD), either treatment-naïve (no previous maintenance disease-modifying therapy [DMT] or immunosuppressive therapy [IST]) or inadequate responders to previous treatment with rituximab (RTX, or its biosimilar). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Objective:	
• To describe the efficacy of satralizumab in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	Clinical measures related to disease activity and progression over 96 weeks ***Related to relapse*** (see Section 4.5.5 for definition of relapse)***:*** • Proportion of relapse-free patients • Annualized relapse rate (ARR) • Time to first relapse (TFR) • Severity of relapses – hospitalization; use of corticosteroids; rescue therapy; need for plasma exchange; residual disability

Objectives	Corresponding Endpoints
	Related to disability progression‡: • Mean change from baseline in Expanded Disability Status Scale (EDSS) score over the course of the study • Time to onset of confirmed disability progression (CDP) sustained for at least 12 weeks and 24 weeks ***Related to cognitive evaluation:*** • Change from baseline in the Symbol Digital Modalities Test (SDMT) over the course of the study ***Related to ophthalmological evaluation:*** • Change in high-contrast (100%) and low-contrast (2.5%) visual acuity using appropriate high-and low-contrast letter acuity (LCLA) charts over the course of the study • Change in Visual Functioning Questionnaire -25 (VFQ-25) over the course of the study
Secondary Objectives:	
• To describe the evolution of advanced imaging outcomes over time in AQP4 antibody seropositive NMOSD patients treated with satralizumab, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	***Related to magnetic resonance imaging (MRI):*** **Brain and optic nerves** • Count, volume and regional distribution of T2-weighted fluid-attenuated inversion-recovery (FLAIR) hyperintense lesions, including new and enlarging lesions of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; Fazekas scoring • Contrast-enhancing T1-weighted lesions (CEL) of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; optionally meningeal enhancement • Diffusion abnormalities • Microbleeds • Cerebral perfusion alterations • Global and regional brain volume loss including basal ganglia, cerebellum and upper cervical spinal cord. Regional brain volume will be assessed only at screening, Week 48 and Week 96 **Spinal cord** • New and persisting short T1 inversion recovery (STIR)/Proton Density (PD) hyperintense lesions and T1-weighted contrast enhancement: Qualitative neuroradiological assessment

Objectives	Corresponding Endpoints
	Optional in selected participating sites • Quantitative T1 mapping (magnetization-prepared rapid gradient echo sequence [MP2RAGE]) • T2*/R* for iron concentration estimation • Quantitative diffusion/diffusion tensor imaging (DTI) ***Related to optical coherent tomography (OCT):*** Change in the following OCT outcomes over the course of the study: • Change in the retinal nerve fiber layer (RNFL) thickness • Change in the ganglion cell plus inner plexiform (GCIP) layer thickness
Exploratory Objectives:	
• To investigate the impact of satralizumab on patient-reported outcomes (PROs)	Change in the following PROs over the course of the study: • SymptoMScreen • Treatment Satisfaction Questionnaire for Medication (TSQM) • Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)
• To evaluate the adherence to satralizumab treatment in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	• Adherence to satralizumab treatment will be checked via the structured telephone interview conducted by site personnel on the following working day after every self-administration of satralizumab
• To investigate the impact of satralizumab therapy on biomarkers associated with neurodegenerative mechanisms and other aspects of disease pathophysiology	• Changes in the immune cell repertoire (including but not limited to CD19+ B cells and CD3+ T cells) in cerebrospinal fluid (CSF) and blood • Changes in molecular biomarkers associated with neuroinflammation in CSF, serum and/or plasma (e.g., neurofilament light [NfL] and glial fibrillary acidic protein [GFAP]) • Changes in ribonucleic acid (RNA) associated with neuroinflammation disease activity, or the immune cell repertoire in CSF and blood • Changes in autoantibody titers including but not limited to AQP4 in both CSF and serum • Assessment of humoral responses to vaccination including but not limited to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Objectives	Corresponding Endpoints
Correlations • To assess potential correlations between CSF, serum and/or plasma biomarkers and clinical and imaging measures	• Correlations between biomarker changes, imaging measures (MRI & OCT) and clinical measures (EDSS, relapse, cognition, visual acuity and functioning) over different timepoints
Pharmacokinetic Objective:	
• To assess pharmacokinetics of satralizumab in CSF and serum	• Satralizumab concentration in CSF & serum • Correlations between serum and CSF concentration of satralizumab and CSF, serum and/or plasma biomarkers • Correlations between covariates of interest and concentration of satralizumab in CSF and serum • Correlations between serum concentration of satralizumab and CSF biomarker or efficacy endpoints • Correlations between serum concentration of satralizumab and CSF biomarker or safety endpoints
Immunogenicity Objective:	
• To assess the immunogenicity of satralizumab	• Incidence of anti-satralizumab antibodies
Safety Objective:	
• To evaluate the safety of satralizumab in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	• Incidence and severity of adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) • Vital signs and clinical laboratory tests

‡Disability progression has been defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5. For patients with an EDSS of 0, progression is defined as a change ≥1.5 points. Disability progression is considered *confirmed* when the increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of neurological worsening.

Study Design

Description of Study

This is a prospective, multicenter, open-label, efficacy and safety study in AQP4 antibody seropositive NMOSD patients, either treatment-naïve (who have not received any prior maintenance DMT or IST) or inadequate responders to previous treatment with RTX (or its biosimilar). The study will include the following two cohorts.

- Cohort 1: treatment-naïve NMOSD patients (no history of DMTs or IST; n=60)
- Cohort 2: NMOSD patients who are inadequate responders to previous treatment with RTX (as last treatment and at least 2 infusions of RTX or its biosimilar; time since last RTX infusion is <6 months; n=40)

The study will consist of the following periods:

- Screening period: After providing informed consent, patients will enter a screening period of up to 4 weeks, to be evaluated for eligibility. For patients treated with oral corticosteroids, this duration could be adapted to maximum 4 weeks for adequate

tapering period and at least 1 week without oral corticosteroids before study start. Please see Appendix 2 for the detailed patient screening and inclusion process for patients in both cohorts depending on prior use of pulse steroids, plasma exchange and oral corticosteroids. Re-screening of patients is allowed in this protocol.

- Treatment period: Eligible patients will be treated with 120 mg satralizumab subcutaneously (SC) as monotherapy at Weeks 0, 2 (±3 days), 4 (±3 days), and then every 4 weeks (±3 days) till the last administration at Week 92 followed by a clinical evaluation at Week 96. The first dose at Week 0 (baseline visit) will be administered at the study site by the designated site staff during the scheduled study visit. All assessments (clinical, laboratory and imaging) should be performed before satralizumab administration. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique. Home dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose. A structured telephone interview will be conducted by site personnel on the following working day after every self-administration of satralizumab to confirm compliance with study drug treatment and to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events.
- Follow-up period: Patients who complete the 96-week treatment period and choose not to continue on satralizumab treatment outside this study, or who discontinue treatment early and choose not to continue on satralizumab treatment outside this study, will be followed up for 12 weeks after the last dose of satralizumab.

Number of Patients

The study will enroll approximately 100 patients (approximately 60 in Cohort 1 and approximately 40 in Cohort 2).

Target Population

Inclusion Criteria

All patients must meet the following criteria for study entry:

- Signed informed consent form.
- Age 18 to 74 years, inclusive, at the time of informed consent.
- Able to comply with the study protocol, in the investigator's judgment
- Have a diagnosis of AQP4 antibody seropositive NMOSD according to the International Panel for neuromyelitis optica (NMO) Diagnosis (IPND) criteria (Wingerchuk et al. 2015)
- For women of childbearing potential: agreement to either remain abstinent (refrain from heterosexual intercourse) or to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile as a result of surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception.

If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Additional specific inclusion criteria are as follows:

Cohort 1 (treatment-naïve NMOSD patients)

- Confirmation of NMOSD diagnosis with AQP4+ antibodies.
- Have clinical evidence of at least 1 documented attack or relapse (including first attack) in the last year prior to screening.
- Naive to maintenance therapy (DMT or IST).

Cohort 2 (NMOSD patients with inadequate response to RTX [or its biosimilar])

- Confirmation of NMOSD diagnosis and AQP4+ antibodies in the disease history of the patient.
- Have a length of disease duration from first symptom of ≤5 years.
- History of ongoing treatment with RTX (or its biosimilar) (at least 2 infusions) for NMOSD with a maximum duration of 6 months since last administration prior to enrolment in the study.
- Ongoing disease activity after last RTX (or its biosimilar) infusion i.e., relapse and/or any new inflammatory event, confirmed by MRI or ophthalmological assessment.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

Exclusion criteria for both the cohorts

- Inability to complete an MRI (contraindications for MRI include but are not restricted to gadolinium tolerance, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia, weight >140 kg, etc.).

Exclusions Related to General Health

- Participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of satralizumab.
    - Women of childbearing potential must have a negative serum pregnancy test result at screening and negative urine dipstick pregnancy test prior to initiation of study treatment.
- Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
- Evidence of other demyelinating disease, including MS or progressive multifocal leukoencephalopathy (PML).
- Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as: other nervous system disease, cardiovascular disease, hematologic/hematopoietic disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
- Active or presence of recurrent bacterial, viral, fungal, mycobacterial infection or other infection (excluding fungal infections of nail beds or caries dentium) at baseline.
- Infection requiring hospitalization or treatment with intravenous (IV) anti-infective agents within 4 weeks prior to baseline visit.
- Evidence of chronic active hepatitis B (see Section 4.5.12 for details).
- Evidence of active tuberculosis (TB).

- Screening for TB will be performed according to local guidance (or according to the instructions for TB screening if there is no local guidance).For further details on screening for TB, see Appendix 3.
- If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration.

- History or laboratory evidence of coagulation disorders.
- Receipt of a live or live-attenuated vaccine within 6 weeks prior to baseline.
- Presence or history of malignancy, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured).
- History of drug or alcohol abuse within 1 year prior to baseline.
- History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
- History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
- Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.

Exclusion criteria related to medications

- Treatment with any investigational agent within 6 months prior to baseline, or 5 drug elimination half-lives of the investigational agent (whichever is longer)

Note: Please see Appendix 2 for the detailed patient screening and inclusion process for patients in both cohorts depending on prior use of pulse steroids, plasma exchange and oral corticosteroids.

Cohort 1 (treatment-naïve NMOSD patients)

- Any previous treatment with IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation, stem-cell therapy, or bone marrow transplantation
- Any previous treatment with eculizumab, belimumab, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, siponimod, or ozanimod
- Any previous treatment with anti-CD4, cladribine or mitoxantrone
- Any previous treatment with B-cell depleting agents (e.g., RTX, ocrelizumab, ofatumumab, inebilizumab)
- Any previous treatment with immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus)

Note: Short-term treatment for management of acute relapses e.g., immediate pulse of steroids, plasma exchange or plasmapheresis will not be considered as NMOSD treatment.

Cohort 2 (NMOSD patients with inadequate response to RTX)

- Discontinued RTX (or biosimilar) treatment due to any other reason than inadequate response to treatment

Note: Prior treatment with an IST, DMT or other therapies are allowed in Cohort 2; however, the last treatment should be RTX (or its biosimilar) with a maximum duration of 6 months since last administration prior to enrolment in the study.

Laboratory exclusion criteria (at screening)*

The following laboratory abnormalities at screening:

- White blood cells (WBC) < $3.0 \times 10^3/\mu L$
- Absolute neutrophil count (ANC) < $2.0 \times 10^3/\mu L$
- Absolute lymphocyte count (ALC) < $0.5 \times 10^3/\mu L$
- Platelet count < $10 \times 10^4/\mu L$

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN)
- Positive serum beta human chorionic gonadotropin (hCG) measured at screening or positive urine dipstick pregnancy test prior to initiation of study treatment

*If retest is conducted, the last value of retest before baseline must meet study criteria.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

Length of Study

The total length of the study, from screening of the first patient to the end of the study depends on the recruitment rate and is expected to be approximately 188 weeks. This includes an enrolment period of 76 weeks.

Investigational Medicinal Products

Test Product (Investigational Drug)

Satralizumab 120 mg will be administered as monotherapy (SC) in the abdominal or femoral region at Weeks 0, 2 (±3 days), 4 (±3 days), and then every 4 weeks (±3 days) till the last administration at Week 92 followed by a clinical evaluation at Week 96. The first dose at Weeks 0 (baseline visit) will be administered at the study site by the designated site staff during the scheduled study visit. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique. Home dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose.

Non-Investigational Medicinal Products

Permitted concomitant medications/therapies during the study include the following:

1. Rescue therapy for clinical relapse: pulse IV corticosteroids, oral corticosteroids for tapering, intravenous immunoglobulin (IVIG) and/or apheresis (including plasma exchange and plasmapheresis)
2. Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).

   Starting of pain medications is permitted; however, the dose should be stable during the study period. In case pain control is insufficient, dose increase or change of pain medication is permitted.

Statistical Methods

The analysis of this study is exploratory and will primarily make use of descriptive statistical methods. No formal confirmatory hypothesis test will be conducted. No adjustment for multiple testing will be made.

The intent-to-treat (ITT) and Safety population will include all enrolled patients who received any dose of satralizumab. The per-protocol (PP) population will include all ITT patients without major protocol deviations deemed to potentially affect the efficacy endpoints. The PP population will be used for supportive efficacy analyses.

Unless otherwise specified, all endpoints will be analyzed separately for each cohort and by visit, if appropriate. Details will be specified in the statistical analysis plan (SAP).

Primary Analysis

The TFR up to week 96 will be assessed using the Kaplan-Meier method. The proportion of relapse-free patients after week 96 will also be calculated using the Kaplan-Meier estimator (at Week 96) and Greenwoods formula for the confidence interval. The ARR after Week 96 will be calculated descriptively by dividing the total number of relapses for all patients by the total years of drug exposure.

Severity of relapses assessed as hospitalization, use of corticosteroids, rescue therapy, need for plasma exchange, and residual disability will be summarized descriptively.

EDSS and EDSS change from baseline will be summarized descriptively up to week 96. Time to onset of CDP sustained for at least 12 weeks and 24 weeks will be analyzed using the Kaplan Meier method.

Change in visual acuity, VFQ-25 and SDMT will be analyzed descriptively using summary statistics.

Determination of Sample Size

Given the exploratory and descriptive nature of the trial, and because the rarity of the disease imposes severe restrictions on recruitment, the sample size (100 patients, including 60 patients in Cohort 1 and 40 in Cohort 2) was chosen based on feasibility.

Interim Analyses

No formal interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study, e.g., after all patients have completed the first 12 months of the treatment phase and the necessary data are available.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab(s)	Antibody(ies)
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AQP4	Aquaporin-4
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
CDP	Confirmed disability progression
CEL	Contrast-enhancing T1-weighted lesions
CRO	Contract research organization
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CYP	Cytochrome P
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
DTI	Diffusion tensor imaging
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion-recovery
FSS	Functional Systems Score
GCIP	Ganglion cell plus inner plexiform
GFAP	Glial fibrillary acidic protein
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IMP	Investigational medicinal product
IND	Investigational New Drug
INL	Inner nuclear layer
IRB	Institutional Review Board
IST	Immunosuppressive therapy
ITT	Intent-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IxRS	Interactive voice/web response system
LPLV	Last patient, last visit
MP2RAGE	Magnetization-prepared rapid gradient echo sequence
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NEI	National Eye institute
NfL	Neurofilament light chain
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis Optica Syndrome Disorder
NSD	Needle safety device
OCT	Optical coherent tomography
ON	Optic neuritis
PBMC	Peripheral blood mononuclear cell
PD	Proton density
PFS	Prefilled syringe
PLEX	Plasma exchange
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PP	Per-protocol
PRO	Patient-reported outcomes
RA	Rheumatoid arthritis
RBR	Research Biosample Repository
RNA	Ribonucleic acid
RNFL	Retinal nerve fiber layer
RTX	Rituximab
SAEs	Serious adverse events

Abbreviation	Definition
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SC	Subcutaneous
SDMT	Symbol Digital Modalities Test
STIR	Short T1 inversion recovery
TB	Tuberculosis
TFR	Time to first relapse
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
USPI	US prescribing information
VFQ-25	Visual Functioning Questionnaire-25
WBC	White blood cells
WES	Whole exome sequencing
WGS	Whole genome sequencing
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1. BACKGROUND

1.1 BACKGROUND ON NEUROMYELITIS OPTICA (NMO) AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) are severe demyelinating inflammatory autoimmune neurological disorders. The estimated global pooled prevalence of NMOSD is 1.82 per 100 000 people (Etemadifar et al. 2015). The disorder is characterized by inflammatory lesions in the optic nerve, spinal cord, brainstem, and cerebrum; and clinically by optic neuritis (ON) and/or transverse myelitis causing potentially severe motor and sensory impairment, bladder dysfunction, vision loss, pain, and other debilitating symptoms (Wingerchuk et al. 2015). Recovery is variable, and inflammatory attacks often result in permanent disability. Untreated, the risks of severe disability or death are substantial (Jarius et al. 2014).

One of the key features of NMOSD is the presence of antibodies against the water channel protein aquaporin-4 (AQP4; Lennon et al. 2005). More than two-thirds of patients meeting clinical criteria for NMOSD are AQP4-immunoglobulin G (IgG) seropositive (Wingerchuk et al. 2007; Sepúlveda et al. 2016). Interleukin-6 (IL-6) is thought to have a key role in the disease activity of NMOSD. Serum and cerebrospinal fluid (CSF) IL-6 levels are elevated during and after relapse, are associated with increased disability following relapse (Uzawa et al. 2010) and correlate with CSF AQP4-IgG titers (Jarius et al. 2014).

NMOSD is radiologically and prognostically distinct from multiple sclerosis (MS), and has a pathophysiology unresponsive to typical MS treatment (Weinshenker 2007; Oh, and Levy et al. 2012). There are four aspects of treatment of NMOSD in the current treatment algorithm: 1) acute treatment of relapses 2) prevention of relapses 3) symptom management and 4) rehabilitation. Pulse steroids and plasma exchange are typically used for acute relapse treatment. Given that relapses often cause irreversible neurological deficits, maintenance immunosuppression for relapse prevention has become standard practice, and is mainly based on off-label use of immunosuppressive drugs such as azathioprine, mycophenolate mofetil, or rituximab (RTX; Jacob et al. 2013).

In view of the potential of a single relapse to cause significant and permanent disability, there was clearly a high unmet need for a safe and effective treatment for NMOSD that could be used after the initial presentation (i.e., first attack). The development of a disease-specific drug therapy without general immunosuppression and suitable for long-term therapy is a central goal in NMOSD therapeutics. In line with this, three new medications have been developed and licensed for the treatment of NMOSD in adult patients, who are anti-AQP4 antibody positive. Eculizumab (Soliris), a complement 5 (C5) inhibitor was approved by the European Commission on 27 August 2019, by the Food and Drug Administration (FDA) on 27 June 2019, and in Japan on 22 November 2019. Inebilizumab (Uplizna), a CD19-directed cytolytic antibody was approved by the

FDA on 12 June 2020. Satralizumab (Enspryng), an IL-6 receptor antagonist was approved in Canada on 1 June 2020, in Japan on 29 June 2020, by the FDA on 14 August 2020, and by the European Medicines Agency (EMA) on 24 June 2021. It is currently approved in 22 countries, including Switzerland and China.

1.2 BACKGROUND ON SATRALIZUMAB

Satralizumab is a humanized anti-human interleukin-6 receptor (IL-6R)-blocking monoclonal antibody that was designed by application of recycling antibody technology. Antibody engineering techniques were utilized to give satralizumab pH-dependent binding affinity to IL-6R so that it binds to IL-6R under neutral conditions in plasma but dissociates under the slightly acidic conditions in endosomes, and is recycled to the plasma instead of being degraded in lysosomes, resulting in a longer plasma half-life. In addition, satralizumab is a modified IgG2 isotype with reduced Fc-mediated effector functions.

The Clinical Development Program of satralizumab in NMOSD currently consists of two ongoing pivotal placebo-controlled, randomized, double-blind Phase III studies: Study BN40898 in adult and adolescent patients treated with 120 mg subcutaneous (SC) satralizumab in addition to background immunosuppressive therapy (IST) and Study BN40900 in adult patients treated with 120 mg SC satralizumab as a monotherapy. Both studies are ongoing in open-label extension.

Data from the completed double-blind periods of the pivotal Phase III Studies BN40898 (Yamamura et al. 2019) and BN40900 (Traboulsee et al. 2020) in adult and adolescents with NMOSD demonstrated a substantial magnitude of clinical benefit. Treatment with satralizumab led to significant reductions in the risk of protocol-defined relapse of 62% in Study BN40898 (hazard ratio [HR]=0.38; 95% CI: 0.16 to 0.88) and 55% in Study BN40900 (HR=0.45; 95% CI: 0.23 to 0.89) compared with placebo. Benefit was evident across multiple subgroups and was particularly high in the subgroup of patients who were AQP4-IgG seropositive, with risk reductions of 79% (HR=0.21; 95% CI: 0.058 to 0.750; p=0.0086) and 74% (HR=0.26; 95% CI: 0.108 to 0.627; p=0.0014) in Studies BN40898 and BN40900, respectively. Evidence of benefit in the subgroup of patients who were AQP4-IgG seronegative was inconclusive.

Based on the results of the studies summarized above, satralizumab has been approved by multiple health authorities as monotherapy or in combination with IST for the treatment of NMOSD in adult and adolescent patients who are anti-AQP4 seropositive (indication statement may vary slightly depending on the country), and is currently under review by other health authorities worldwide.

See the current Investigator's Brochure (IB) for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The efficacy and safety of satralizumab in NMOSD patients has been demonstrated in two Phase 3 studies, as monotherapy (BN40900; Traboulsee et al. 2020) and as add-on treatment to baseline IST [BN40898; Yamamura et al. 2019]. The studied populations represent a substantial proportion of those encountered in routine clinical practice, however there are significant populations where further detailed study is warranted, namely newly-diagnosed, treatment-naïve and those with prior B-cell depletion.

Although prior B-cell depleting therapy with RTX was permitted, there was a restriction on the time since the last infusion of ≥6 months prior to entry, and overall, the number of patients entering with prior RTX treatment amounted to fewer than 20 patients in total from the study program. This population of NMOSD patients treated with RTX represents a significant proportion of the overall patient population (Mouchet et al. 2020) and includes those with an inadequate clinical response (Mealy et al. 2014; Yang et al. 2018; Gao et al. 2019). This population warrants further study in particular with respect to the timing of prior RTX (or its biosimilar) treatment (i.e., within 6 months), and it is also important to elucidate the potential basis for RTX treatment failure, and the effect of treating this population with satralizumab with respect to understanding mechanistic elements correlated with imaging and clinical effects.

NMOSD is a relapsing disease with repeated attacks leading to accumulating neurological damage and disability (Wingerchuk et al. 2007), and therefore a key principle of management is early intervention of maintenance therapy to reduce the risk of subsequent relapses and the attendant disability. The SAkuraSky study (BN40898; Yamamura et al. 2019) recruited patients with established relapsing disease, as patients were required to have had at least two relapses in the 2 years before screening, with at least one relapse occurring in the previous 12 months. In the monotherapy SAkuraStar study (BN40900; Traboulsee et al. 2020), patients were required to have clinical evidence of at least one documented attack in the 12 months before screening, which in principle allowed newly-diagnosed or treatment-naïve patients. The recruited population included six AQP4 seropositive treatment-naïve patients (Palace et al. 2020). Therefore, the effects of early intervention with satralizumab in newly-diagnosed, treatment-naïve patients warrant further study, to not only gauge clinical effects, but in addition patient-reported outcomes (PROs), prospective imaging, optical coherent tomography (OCT) and mechanistic elements included in this protocol.

With established diagnostic criteria (Wingerchuk et al. 2015), there remains a need to characterize patient's prognosis and ideally identify markers of disease activity including predictors of relapse or stability. In contrast to MS, the role of magnetic resonance imaging (MRI) in NMOSD disease management is not so well established, and key questions remain with respect to the optimal use of imaging techniques including the potential for subclinical 'silent' activity or progression unrelated to relapses. To date, no systematic prospective study of the correlation of clinical, imaging or biomarker activity

has been conducted in NMOSD patients (Rocca et al. 2020).

Examination of disease biomarkers represents an important opportunity to further understand disease pathogenesis and the mechanism of action of a therapeutic treatment. Besides the role of anti-AQP4-IgG, NMOSD pathophysiology is considered to be based on inflammation, antibody production, blood-brain barrier disruption and cellular mediated damage. Pathology suggests the existence of three types of damage in NMOSD lesions: astrocyte damage, demyelination, and neuronal damage (Lucchinetti et al. 2014). Both serum levels of glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), which are intermediate markers of astrocyte and neuron filaments, respectively, may serve as clinically useful biomarkers of disease activity and disability in NMOSD (Watanabe et al. 2019). Higher levels of GFAP and NfL have been observed in NMOSD patients as compared to MS patients and healthy controls, both during relapses as well as during remission; and correlated with differences in Expanded Disability Status Scale [EDSS] (Watanabe et al. 2019; Takano et al. 2010).

Further, both B cell- and T cell-related immunity are likely to exert a central role in the pathogenesis of NMOSD. T Helper 17 and T Follicular Helper cells produce IL17a and IL6 cytokines, which promote granulocyte and B cell activation, have been reported to be higher in NMOSD than in MS patients, and increase during clinical relapses (Rocca et al. 2020). Other possible indices of disease activity or response to therapy are the levels of the terminal complex of the complement cascade and the proportion of Th17 and plasmablasts. However, all these parameters are not standardized, and not currently evaluated in clinical practice. Moreover, the measurement of markers of damage is mainly performed on CSF rather than serum, thus preventing their routine examination (Rocca et al. 2020).

Besides neuroimmunologic markers related to pathogenesis, paraclinical markers such as OCT and MRI can provide useful information not only for diagnosis but also for prognosis after an acute attack and monitoring disease progression (Rocca et al. 2020). Therefore, a combined approach, including clinical, immunological, OCT and MRI biomarkers might provide an efficient approach to monitor disease progression and predict treatment response in NMOSD.

As there is limited data on the efficacy of satralizumab in early, treatment-naive NMOSD patients and patients who are inadequate responders to previous treatment with RTX (or its biosimilar), a dedicated prospective study to specifically evaluate the clinical profile of satralizumab in these populations is required and justified given the favorable benefit-risk profile of satralizumab. The study will also seek to explore various biomarkers (immunological and imaging) associated with response to satralizumab, to better understand the mechanism of action and immunological changes following treatment in NMOSD.

1.3.1 Coronavirus Disease 2019 and Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination Benefit-Risk Assessment

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID 19) pandemic on the benefit/risk assessment of this study protocol, including, but not limited to, the patient population under study, study treatment being evaluated. Based on that assessment, the safety monitoring, management guidelines, and the risk mitigation measures provided in the study protocol are considered adequate.

An assessment was conducted to determine whether there is any impact of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines on the benefit-risk assessment of this study protocol. General information for vaccines provided in Section 4.4 Concomitant Therapy and Section 5.1 Safety Plan are also applicable to SARS-CoV-2 vaccines. Based on this assessment, no additional risk-mitigation measures related to SARS-CoV-2 vaccination are proposed at this time. The recommendations and management plan provided in the study protocol are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This exploratory study will describe the efficacy and safety of satralizumab in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve (no previous maintenance disease-modifying therapy [DMT] or IST) or inadequate responders to previous treatment with RTX (or its biosimilar).

Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Objective:	
• To describe the efficacy of satralizumab in patients with AQP4 antibody seropositive NMOSD, either treatment naive or inadequate responders to previous treatment with RTX (or its biosimilar)	Clinical measures related to disease activity and progression over 96 weeks ***Related to relapse*** (see Section 4.5.5 for definition of relapse)***:*** • Proportion of relapse-free patients • Annualized relapse rate (ARR) • Time to first relapse (TFR) • Severity of relapses - hospitalization; use of corticosteroids; rescue therapy; need for plasma exchange; residual disability ***Related to disability progression***[‡]*:* • Mean change from baseline in EDSS score over the course of the study • Time to onset of confirmed disability

Objectives	Corresponding Endpoints
	progression (CDP) sustained for at least 12 weeks and 24 weeks ***Related to cognitive evaluation:*** • Change from baseline in the Symbol Digital Modalities Test (SDMT) over the course of the study ***Related to ophthalmological evaluation:*** • Change in high-contrast (100%) and low-contrast (2.5%) visual acuity using appropriate high-and low-contrast letter acuity (LCLA) charts over the course of the study • Change in Visual Functioning Questionnaire-25 (VFQ-25) over the course of the study
Secondary Objectives:	
• To describe the evolution of advanced imaging outcomes over time in AQP4 antibody seropositive NMOSD patients treated with satralizumab, either treatment-naive or inadequate responders to previous treatment with RTX (or its biosimilar)	***Related to MRI:*** **Brain and optic nerves** • Count, volume and regional distribution of T2-weighted fluid-attenuated inversion-recovery (FLAIR) hyperintense lesions, including new and enlarging lesions of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; Fazekas scoring • Contrast-enhancing T1-weighted lesions (CEL) of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; optionally meningeal enhancement • Diffusion abnormalities • Microbleeds • Cerebral perfusion alterations • Global and regional brain volume loss including basal ganglia, cerebellum and upper cervical spinal cord. Regional brain volume will be assessed only at screening, Week 48 and Week 96. **Spinal cord** • New and persisting short T1 inversion recovery (STIR)/proton density (PD) hyperintense lesions and T1-weighted contrast enhancement: Qualitative neuroradiological assessment **Optional in selected participating sites** • Quantitative T1 mapping (magnetization-prepared rapid gradient echo sequence [MP2RAGE]) • T2*/R* for iron concentration estimation

Objectives	Corresponding Endpoints
	• Quantitative diffusion/diffusion tensor imaging (DTI) ***Related to OCT:*** Change in the following OCT outcomes over the course of the study: • Change in the retinal nerve fiber layer (RNFL) thickness • Change in the ganglion cell plus inner plexiform (GCIP) layer thickness
Exploratory Objectives:	
• To investigate the impact of satralizumab on PROs	Change in the following PROs over the course of the study: • SymptoMScreen • Treatment Satisfaction Questionnaire for Medication (TSQM) • Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)
• To evaluate the adherence to satralizumab treatment in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	• Adherence to satralizumab treatment will be checked via the structured telephone interview conducted by site personnel on the following working day after every self-administration of satralizumab
• To investigate the impact of satralizumab therapy on biomarkers associated with neurodegenerative mechanisms and other aspects of disease pathophysiology	• Changes in the immune cell repertoire (including but not limited to CD19+ B cells and CD3+ T cells) in CSF and blood • Changes in molecular biomarkers associated with neuroinflammation in CSF, serum and/or plasma (e.g., NfL and GFAP) • Changes in ribonucleic acid (RNA) associated with neuroinflammation disease activity, or the immune cell repertoire in CSF and blood • Changes in autoantibody titers including but not limited to AQP4 in both CSF and serum • Assessment of humoral responses to vaccination including but not limited to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Correlations • To assess potential correlations between CSF, serum and/or plasma biomarkers and clinical and imaging measures	• Correlations between biomarker changes, imaging measures (MRI & OCT) and clinical measures (EDSS, relapse, cognition, visual acuity and functioning) over different timepoints
Pharmacokinetic Objective:	
• To assess pharmacokinetics of	• Satralizumab concentration in CSF &

Objectives	Corresponding Endpoints
satralizumab in CSF and serum	serum • Correlations between serum and CSF concentration of satralizumab and CSF, serum and/or plasma biomarkers • Correlations between covariates of interest and concentration of satralizumab in CSF and serum • Correlations between serum concentration of satralizumab and CSF biomarker or efficacy endpoints • Correlations between serum concentration of satralizumab and CSF biomarker or safety endpoints
Immunogenicity Objective:	
• To assess the immunogenicity of satralizumab	• Incidence of anti-satralizumab antibodies
Safety Objective:	
• To evaluate the safety of satralizumab in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve or inadequate responders to previous treatment with RTX (or its biosimilar)	• Incidence and severity of adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESIs) • Vital signs and clinical laboratory tests

‡Disability progression has been defined as an increase of ≥1.0 point from the baseline EDSS score that is not attributable to another etiology (e.g., fever, concurrent illness, or concomitant medication) when the baseline score is 5.5 or less, and ≥0.5 when the baseline score is above 5.5. For patients with an EDSS of 0, progression is defined as a change ≥1.5 points. Disability progression is considered *confirmed* when the increase in the EDSS is confirmed at a regularly scheduled visit at least 12 weeks after the initial documentation of neurological worsening.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a prospective, multicenter, open-label, efficacy and safety study in patients with AQP4 antibody seropositive NMOSD, either treatment-naïve (who have not received any prior maintenance DMT or IST) or inadequate responders to previous treatment with RTX (or its biosimilar). The study will include the following two cohorts.

- Cohort 1: treatment-naïve NMOSD patients (no history of DMTs or IST; n=60)
- Cohort 2: NMOSD patients who are inadequate responders to previous treatment with RTX (as last treatment and at least 2 infusions of RTX or its biosimilar; time since last RTX infusion is <6 months; n=40)

Patients will be assessed for efficacy and safety as described in the Schedule of Assessments in Appendix 1.

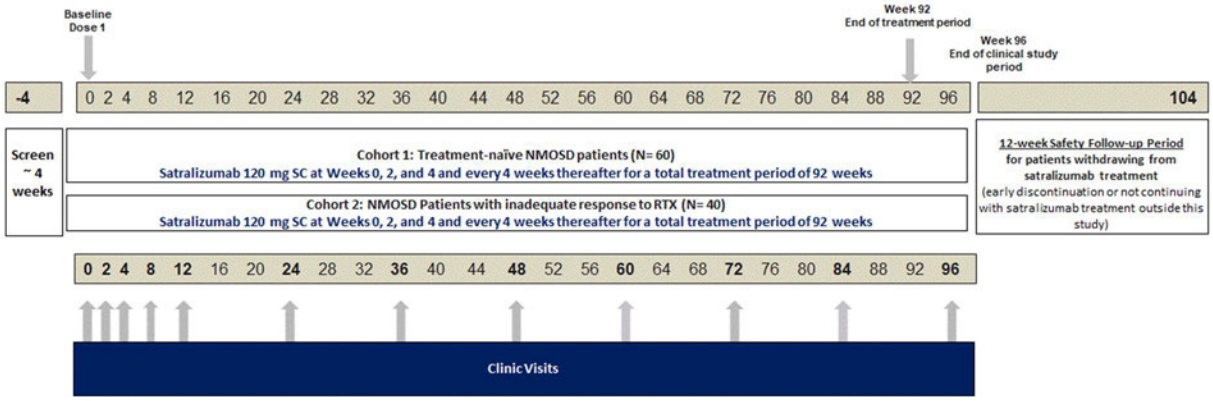
The study will consist of the following periods:

- Screening period: Up to 4 weeks. For patients treated with oral corticosteroids, this duration could be adapted to maximum 4 weeks for adequate tapering period and at least 1 week without oral corticosteroids before study start.
- Treatment period: Open-label treatment period of 96 weeks (treatment duration of 92 weeks followed by a clinical evaluation at Week 96).
- Follow-up period of 12 weeks after the last dose of satralizumab.

3.1.1 Overview of Study Design

Figure 1 presents an overview of the study procedures. A schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



NMOSD = Neuromyelitis Optica Syndrome Disorder; RTX = Rituximab, SC = Subcutaneous.

Unscheduled visits should be performed in case of a relapse.

For patients treated with oral corticosteroids, this duration could be adapted to maximum 4 weeks for adequate tapering period and at least 1 week without oral corticosteroids before study start.
The first dose at Week 0 (baseline visit) will be administered at the study site by the designated site staff during the scheduled study visit. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique.

3.1.2 Screening

After providing informed consent, patients will enter a screening period of up to 4 weeks to be evaluated for eligibility. For patients treated with oral corticosteroids, this duration could be adapted to maximum 4 weeks for adequate tapering period and at least 1 week without oral corticosteroids before study start. Please see Appendix 2 for the detailed patient screening and inclusion process for patients in both cohorts depending on prior use of pulse steroids, plasma exchange and oral corticosteroids.

Re-screening of patients is allowed in this protocol.

3.1.3 Treatment Period

Eligible patients will be treated with 120 mg satralizumab SC as monotherapy at Weeks 0, 2 (±3 days), 4 (±3 days), and then every 4 weeks (±3 days) till the last administration at Week 92 followed by a clinical evaluation at Week 96. The first dose at Weeks 0 (baseline visit) will be administered at the study site by the designated site staff during the scheduled study visit. All assessments (clinical, laboratory and imaging) should be performed before satralizumab administration. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique. Home-dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose.

A structured telephone interview will be conducted by site personnel on the following working day after every self-administration of satralizumab to confirm compliance with study drug treatment and to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events.

Clinical, imaging and biomarker outcomes will be collected as per the Schedule of Assessments in Appendix 1.

3.1.4 Follow up Period

Patients who complete the 96-week treatment period and choose not to continue on satralizumab treatment outside this study, or who discontinue treatment early and choose not to continue on satralizumab treatment outside this study, will be followed up for 12 weeks after the last dose of satralizumab.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

The total length of the study, from screening of the first patient to the end of the study depends on the recruitment rate and is expected to be approximately 188 weeks. This includes an enrolment period of 76 weeks.

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase 3b prospective, multicenter, open-label study to assess the efficacy and safety of satralizumab in treatment-naïve NMOSD patients and patients who are inadequate responders to previous treatment with RTX (or its biosimilar). As the efficacy and safety of satralizumab has already been demonstrated in pivotal double-blind,

randomized controlled trials as described in Section 1.2, a non-comparative approach, where the goal is to characterize the clinical profile of the drug in treatment-naïve patients and inadequate responders to prior RTX treatment (or its biosimilar), is considered to be appropriate for this study.

The efficacy of satralizumab will be evaluated based on various clinical outcomes related to disease progression over a period of 96 weeks.

One of the key outcome measures is relapse, which is a clinically relevant measure in NMOSD patients. Time to onset of first relapse, ARR and proportion of patients who are relapse free are acceptable parameters to assess relapse-status in NMOSD clinical trials (EMA/CHMP/SAWP/712652/2014, 2015).

EDSS is the most widely used and well-known scale to assess changes in disability in NMOSD. Evaluation of change from baseline in EDSS score over the course of the study will provide an overall estimate of the dysfunction that was experienced by the patient during the study period. Another outcome measure is time to onset of CDP sustained for at least 12 weeks and 24 weeks, with CDP defined as 1-point or greater worsening in EDSS from baseline when the baseline score is 5.5 or less, and ≥ 0.5 when the baseline score is above 5.5. To ensure that worsening in EDSS score represents permanent physical disability rather than an exacerbation-related temporary fluctuation in neurological status, a worsening EDSS score has to be sustained for at least 12 weeks for disease progression to be considered confirmed.

Paraclinical markers such as OCT and MRI can provide useful information not only for diagnosis but also for prognosis after an acute attack and for monitoring disease progression in NMOSD (Rocca et al. 2020) and therefore, these will be evaluated as secondary endpoints. Subclinical damage reported in NMOSD patients could predispose to full attacks causing severe sequelae (Contentti and Correale 2020). Longitudinal brain MRI scans could be a useful measure to evaluate ongoing subclinical disease activity as well as to monitor response of the treatment in NMOSD patients (Contentti and Correale 2020). Asymptomatic lesions in brain and spinal cord MRI have been described in NMOSD patients (Kim et al. 2016; Flanagan et al. 2015). Both first myelitis relapse and ON without prior myelitis can be associated with asymptomatic spinal cord lesions in AQP4 positive NMOSD patients (Flanagan et al. 2015). In addition, brain atrophy, spinal cord atrophy, and reductions of mean upper cervical cord area have been reported in AQP4 positive NMOSD even without a clinical history of relapses or previous spinal cord lesions on MRI (Ventura et al. 2016).

OCT provides non-invasive, highly reliable, reproducible measures of neuro-axonal damage in NMOSD patients. RNFL thickness correlates with visual functional system score of EDSS, and a thickness below 71.41 micron is associated with incomplete visual recovery (Nakamura et al. 2010). Cross-sectional measurement of peripapillary RNFL (pRNFL), inner nuclear layer (INL), GCIP layer, foveal thickness (FT) and macular

volume (MV) in AQP4-seropositive NMOSD compared to healthy controls has revealed a significant reduction of all measures except INL in eyes with previous ON, whereas both RNFL and INL were shown to be preserved in non-ON eyes (Oertel et al. 2018). Independent studies have reported that, in the absence of ON recurrence, RNFL thickness remains stable in NMOSD patients compared to healthy controls, whereas GCIP layer undergoes a progressive thinning (Oertel et al. 2018; Pisa et al. 2019). Therefore, change in RNFL thickness and GCIP layer thickness will be assessed using OCT in all patients. Visual Functional Questionnaire -25, filled out by the investigator, should complete the ophthalmological evaluation of the patients.

The PROs evaluated in this study are relevant measures for monitoring disease progression in NMOSD patient. SymptoMScreen is a one-page instrument that enables rapid assessment of symptom severity. It consists of a battery of 7-point Likert scales for 12 distinct neurological domains: mobility, dexterity, spasticity, body pain, sensation, bladder function, fatigue, vision, dizziness, cognition, depression, and anxiety. It has been validated for use in the MS population and has excellent psychometric properties (Green et al. 2017). In a study comparing self-reported symptom severity in patients with NMOSD and gender-, race-, age-and disease duration-matched MS controls using SymptoMScreen, relevant clinical differences were observed between NMOSD and MS patients. For example, worse vision, bladder function, spasticity, pain scores and better cognition and anxiety scores were noted in NMOSD patients compared to MS; however, the overall symptom burden (total scores) were similar in both the populations (Green et al. 2016). Treatment satisfaction with satralizumab will be evaluated using the validated TSQM (version 1.4). The TSQM 1.4 is a 14-item patient-rated questionnaire that uses a 7-point Likert-type scale and has shown good psychometric properties in chronic diseases (Atkinson et al. 2004). The Work Productivity and Activity Impairment Index will be used to assesses the effect of NMOSD on ability to work and perform regular activities.

Finally, the impact of satralizumab therapy on biomarkers associated with neurodegenerative mechanisms and other aspects of disease pathophysiology will be explored (see Section 3.3.3) along with the correlations between biomarkers and clinical and imaging markers. The main analyses will be in the form of descriptive statistics examining change from baseline to endpoint across the outcome parameters.

3.3.1 Rationale for Satralizumab Dose and Schedule

The dose level of satralizumab administered in the study is 120 mg SC at Weeks 0, 2, 4 and every 4 weeks thereafter, as per the label.

3.3.2 Rationale for Patient Population

The study will include treatment-naïve NMOSD patients with recent relapse and without previous DMT or IST (Cohort 1) and NMOSD patients who are inadequate responders to previous treatment with RTX (or its biosimilar; Cohort 2).

Being naïve to maintenance therapy is the key entry criterion to ensure inclusion of newly-diagnosed NMOSD patients in Cohort 1.

In order to ensure inclusion of NMOSD patients who are inadequate responders to previous treatment with at least 2 infusions of RTX (or its biosimilar) in Cohort 2, RTX should be the last NMOSD treatment and ongoing disease activity i.e., relapse and/or new inflammatory event while on RTX (or its biosimilar) treatment will need to be confirmed by MRI or ophthalmological assessment. Patients who discontinued RTX treatment due to any other reason than inadequate response to treatment will be excluded.

The upper age limit of 74 years in both the cohorts is consistent with the age eligibility criteria in the Phase 3 studies (BN40900 and BN40898).

3.3.3 Rationale for Biomarker Assessments

Pathological examinations suggest the existence of three types of damage in NMOSD lesions: astrocyte damage, demyelination, and neuronal damage (Lucchinetti et al. 2014). Both serum levels of GFAP and NfL, which are intermediate markers of astrocyte and neuron filaments, respectively, may serve as clinically useful biomarkers of disease activity and disability in NMOSD (Watanabe et al. 2019). Higher levels of GFAP and NfL have been observed in NMOSD patients as compared to MS patients and healthy controls, both during relapses as well as during remission; and correlate with differences in EDSS (Watanabe et al. 2019; Takano et al. 2010). Further, both B cell- and T cell-related immunity are likely to exert a central role in the pathogenesis of NMOSD. T Helper 17 and T Follicular Helper cells, which produce IL17a and IL6 cytokines (which in turn promote granulocyte and B cell activation), have been reported to be higher in NMOSD than MS patients, and increase during clinical relapses (Rocca et al. 2020). Other possible indices of disease activity or response to therapy are the levels of the terminal complex of the complement cascade, and the proportions of Th17 cells and plasmablasts. However, these parameters are not standardized and not currently evaluated in clinical practice. Moreover, the measurement of markers of damage is mainly performed on CSF rather than serum, thus preventing their routine examination (Rocca et al. 2020). Therefore, this study will explore various biomarkers associated with response to satralizumab to better understand the mechanism of action and immunological changes following treatment in NMOSD.

Recently, vaccines against the SARS-CoV-2 virus have received authorizations for use from regulatory agencies. Vaccine efficacy data, and vaccine effectiveness from real world settings have shown that the available vaccines lead to a significant reduction in the number of coronavirus disease (COVID-19) infections and the number of severe cases that require hospitalization or result in fatal outcomes. Available data from the vaccine trials demonstrate that these vaccines can induce an antibody response as well as T cell responses. While not fully understood, accruing evidence suggests that both antibodies and T cell-mediated immunity have a protective role against future SARS-

CoV-2 infection and severe clinical presentations. Currently, evidence on the SARS-CoV-2 vaccine response in persons taking immunomodulatory treatments is lacking, including in patients with NMOSD treated with satralizumab. Therefore, humoral responses to vaccination including but not limited to SARS-CoV-2, will be evaluated.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll approximately 100 patients (approximately 60 in Cohort 1 and approximately 40 in Cohort 2).

4.1.1 Inclusion Criteria

All patients must meet the following criteria for study entry:

- Signed informed consent form.
- Age 18 to 74 years, inclusive, at the time of informed consent.
- Able to comply with the study protocol, in the investigator's judgment.
- Have a diagnosis of AQP4 antibody seropositive NMOSD according to the International Panel for NMO Diagnosis (IPND) criteria (Wingerchuk et al. 2015).
- For women of childbearing potential: agreement to either remain abstinent (refrain from heterosexual intercourse) or to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile as a result of surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception.

  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Additional specific inclusion criteria are as follows:

Cohort 1 (treatment-naïve NMOSD patients)

- Confirmation of NMOSD diagnosis with AQP4+ antibodies
- Have clinical evidence of at least 1 documented attack or relapse (including first attack) in the last year prior to screening.
- Naive to maintenance therapy (DMT or IST).

Cohort 2 (NMOSD patients with inadequate response to RTX [or its biosimilar])

- Confirmation of NMOSD diagnosis and AQP4+ antibodies in the disease history of the patient
- Have a length of disease duration from first symptom of ≤5 years
- History of ongoing treatment with RTX (or its biosimilar) (at least 2 infusions) for NMOSD with a maximum duration of 6 months since last administration prior to enrolment in the study.
- Ongoing disease activity after last RTX (or its biosimilar) infusion i.e., relapse and/or any new inflammatory event, confirmed by MRI or ophthalmological assessment.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

Exclusion criteria for both the cohorts

- Inability to complete an MRI (contraindications for MRI include but are not restricted to gadolinium tolerance, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia, weight >140 kg etc.).

Exclusions Related to General Health

- Participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of satralizumab.
    - Women of childbearing potential must have a negative serum pregnancy test result at screening and negative urine dipstick pregnancy test prior to initiation of study treatment.
- Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
- Evidence of other demyelinating disease, including MS or progressive multifocal leukoencephalopathy (PML).
- Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as: other nervous system disease, cardiovascular

disease, hematologic/hematopoietic disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.

- Active or presence of recurrent bacterial, viral, fungal, mycobacterial infection or other infection (excluding fungal infections of nail beds or caries dentium) at baseline.
- Infection requiring hospitalization or treatment with intravenous (IV) anti-infective agents within 4 weeks prior to baseline visit.
- Evidence of chronic active hepatitis B (see Section 4.5.12 for details).
- Evidence of active tuberculosis (TB).
    - Screening for TB will be performed according to local guidance (or according to the instructions for TB screening if there is no local guidance). For further details on screening for TB, see Appendix 3.
    - If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration.
- History or laboratory evidence of coagulation disorders.
- Receipt of a live or live-attenuated vaccine within 6 weeks prior to baseline.
- Presence or history of malignancy, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured).
- History of drug or alcohol abuse within 1 year prior to baseline.
- History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
- History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
- Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.

Exclusion criteria related to medications

- Treatment with any investigational agent within 6 months prior to baseline or 5 drug elimination half-lives of the investigational agent (whichever is longer).

Note: Please see Appendix 2 for the detailed patient screening and inclusion process for patients in both cohorts depending on prior use of pulse steroids, plasma exchange and oral corticosteroids.

Cohort 1 (treatment-naïve NMOSD patients)

- Any previous treatment with IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation, stem-cell therapy, or bone marrow transplantation

- Any previous treatment with eculizumab, belimumab, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, siponimod, or ozanimod
- Any previous treatment with anti-CD4, cladribine or mitoxantrone
- Any previous treatment with B-cell depleting agents (e.g., RTX, ocrelizumab, ofatumumab, inebilizumab)
- Any previous treatment with immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus)

  Note: Short-term treatment for management of acute relapses e.g., immediate pulse of steroids, plasma exchange or plasmapheresis will not be considered as NMOSD treatment.

Cohort 2 (NMOSD patients with inadequate response to RTX)

- Discontinued RTX (or biosimilar) treatment due to any other reason than inadequate response to treatment

  Note: Prior treatment with an IST, DMT or other therapies are allowed in Cohort 2; however, the last treatment should be RTX (or its biosimilar) with a maximum duration of 6 months since last administration prior to enrolment in the study

Laboratory exclusion criteria (at screening)*

The following laboratory abnormalities at screening:

- White blood cells (WBC) < 3.0×10^3/µL
- Absolute neutrophil count (ANC) < 2.0×10^3/µL
- Absolute lymphocyte count (ALC) < 0.5×10^3/µL
- Platelet count < 10×10^4/µL
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN)
- Positive serum beta human chorionic gonadotropin (hCG) measured at screening or positive urine dipstick pregnancy test prior to initiation of study treatment

*If retest is conducted, the last value of retest before baseline must meet study criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. No randomization, treatment assignment or blinding is planned.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is satralizumab. Rescue medications and pain medications are considered non-investigational medicinal products (NIMPs; see details in Section 4.4).

4.3.1 Study Treatment Formulation and Packaging

Satralizumab injection will be supplied by the Sponsor as a sterile, preservative-free, clear, colorless to slightly yellow solution in single-dose prefilled syringe (PFS) with needle safety device (NSD). Each carton contains one single-dose 120 mg/mL PFS. For more information, see the satralizumab US prescribing information (USPI) or the IB.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Satralizumab monotherapy will be given as an SC injection (120 mg) in the abdominal or femoral region at Weeks 0, 2 (±3 days), 4 (±3 days), and then every 4 weeks (±3 days) till the last administration at Week 92 followed by a clinical evaluation at Week 96. The first dose at Weeks 0 (baseline visit) will be administered at the study site by the designated site staff during the scheduled study visit. All assessments (clinical, laboratory and imaging) should be performed before satralizumab administration. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. Patients should remain at the study center for at least 1 hour after satralizumab administration in order to receive medication immediately if anaphylaxis occurs at the baseline and Week 2 visit.

After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique. Home dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose.

If an injection of satralizumab is missed, for any reason other than increases in liver enzymes, it should be administered as described in Table 2.

Table 2 Recommended Dosage for Delayed or Missed Doses

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

SC = Subcutaneous.

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

Details on treatment administration for the first dose (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated AEs, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience AEs are provided in Section 5.1.1.

See the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.3.3 Rescue Medication

Rescue therapy for clinical relapse includes pulse IV corticosteroids, oral corticosteroids for tapering, intravenous immunoglobulin (IVIG) and/or apheresis (including plasma exchange and plasmapheresis).

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the interactive voice/web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs. If patients are administered satralizumab outside of the study site, IMP may be given to the patient to take home during a study site visit, or may be shipped to the patient's home from the study site (in special circumstances). Patients will be asked to return all IMP boxes at their next on-site visit.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate

documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the satralizumab IB or USPI for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Satralizumab

The Sponsor will offer continued access to Roche IMP satralizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP satralizumab after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP satralizumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for NMOSD
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment within 4 weeks prior to the screening visit to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Immunizations and Vaccinations

It is recommended for all patients to keep up to date with all immunizations according to local immunization guidelines prior to randomization in the study.

- The use of any **live and live attenuated vaccines** is not allowed within 6 weeks prior to randomization and during the entire duration of the study.
- Vaccines (including **SARS-CoV-2 vaccines**) **other than live or live attenuated** are permitted during the study. Vaccines may be less effective in immunocompromised patients, however, the effect of satralizumab upon the efficacy of vaccinations is currently unknown. It is recommended that vaccines should be given in accordance with the approved/authorized vaccine label and official local immunization guidance.

Refer to the Satralizumab Investigator's Brochure for further details regarding vaccinations. Please contact the Medical Monitor for questions on vaccinations in patients participating in this study

4.4.2 Permitted Therapy

Permitted concomitant medications/therapies during the study include the following:

- Rescue therapy for clinical relapse (described in Section 4.3.3)
- Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).

Starting of pain medications is permitted; however, the dose should be stable during the study period. In case pain control is insufficient, dose increase or change of pain medication is permitted.

4.4.3 Prohibited Therapy

The following are prohibited prior to baseline and till the end of the study in Cohort 1:

- IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab
- Total body irradiation, stem-cell therapy, bone marrow transplantation
- Eculizumab, belimumab, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, siponimod, or ozanimod
- Anti-CD4, cladribine or mitoxantrone

- Immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus)
- Other B-cell depleting agents (e.g., ocrelizumab, ofatumumab, inebilizumab, RTX)

  Note: Short-term treatment for management of acute relapses e.g., immediate pulse of steroids, plasma exchange or plasmapheresis will not be considered as NMOSD treatment. Please see Appendix 2 for the detailed patient screening and inclusion process for patients depending on prior use of pulse steroids, plasma exchange and oral corticosteroids.

The following are prohibited from 6 months prior to baseline or 5 drug elimination half-lives of an investigational agent (whichever is longer) to the end of the study for both cohorts:

- Treatment with any investigational agent (other than satralizumab).

The following are prohibited from 6 weeks prior to baseline to the end of the study, for both cohorts:

- Immunization with live or live-attenuated vaccine.

The following is prohibited till the end of the study for both cohorts:

- IVIG (excepting as rescue therapy for clinical relapse)

The following are prohibited from baseline to the end of the study for Cohort 2:

- IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab
- Total body irradiation, stem-cell therapy, bone marrow transplantation
- Eculizumab, belimumab, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, siponimod, or ozanimod
- Anti-CD4, cladribine or mitoxantrone
- Immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, tacrolimus)
- Other B-cell depleting agents (e.g., ocrelizumab, ofatumumab, inebilizumab)

  Note: Short-term treatment for management of acute relapses e.g., immediate pulse of steroids, plasmapheresis will not be considered as NMOSD treatment. Please see Appendix 2 for the detailed patient screening and inclusion process for patients depending on prior use of pulse steroids, plasma exchange and oral corticosteroids.

In addition, the Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Assessments scheduled on the day of study drug administration should be performed prior to administration of study drug, unless otherwise noted in the schedule of activities (Appendix 1). The sequence of assessments should be PROs first followed by clinical assessments, laboratory assessments, MRI, lumbar puncture (for CSF assessment) and satralizumab administration .

If a patient misses a scheduled visit without notice, the Investigator and/or site staff should try to contact the patient via telephone or another way in order to confirm if there has been an adverse event (AE) or a relapse. The Investigator and/or site staff should encourage the patient to visit the study site for an assessment as soon as possible.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed consent forms (ICFs) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Patients' demographics (age, gender and self-reported race/ethnicity) and neurological examination will be collected. Medical History will include clinically significant diseases, surgeries, reproductive status, smoking history, SARS-CoV-2 vaccine status, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. In addition, use of any previous NMOSD medication (as applicable) should be recorded.

NMOSD disease history:

First NMOSD symptom: date, symptoms, severity.

Diagnosis of NMOSD:

Date, disease status, and, when available, criteria on which the diagnosis is based.

Baseline disease status:

EDSS, Number of relapses (including description of relapse and symptoms) in the previous year, MRI lesions, ophthalmological status, working/employment status.

Treatment history (only for Cohort 2):

Start and stop dates and reason for change.

RTX antibody status and level before start of satralizumab treatment should be evaluated to understand the reason of RTX treatment failure (only for Cohort 2).

Height will be recorded at screening and weight will be recorded at screening, baseline and every 24 weeks thereafter.

4.5.3 Physical Examinations

A complete physical examination will be conducted at the screening and early termination visits. At all other visits, a limited symptom-directed physical examination will be conducted. The complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, respiratory rate, temperature and systolic and diastolic blood pressure while the patient is in a seated position for at least 5 minutes. At the baseline and Week 2 visit when satralizumab is administered at the study site, vital signs will be measured before and after study drug administration. Pulse rate, respiratory rate, temperature, systolic and diastolic blood pressure should be measured immediately before and then at 15 (±5) and 60 (±5) minutes after study drug administration. At all other visits, only one measurement of vital signs will be taken.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Neurological Examinations including Relapse Assessment

Neurological examinations will be used to distinguish relapse in NMOSD from another neurological disorder. Potential relapses should be recorded throughout the treatment period. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

Patients should report all new or worsening neurological events compatible with NMOSD immediately to the sites and a visit for relapse assessment should be scheduled as soon as possible. Patients who attend the study center for a protocol-specified visit that includes an EDSS/Functional Systems Score (FSS) assessment (see Appendix 1) should be assessed to determine whether a clinical relapse has occurred or not. Any clinical relapse should be reported and assessed if it meets the criteria for protocol-defined relapse. An EDSS/FSS assessment by an appropriately qualified assessor should be performed in every case of potential relapse.

Relapse is the occurrence of new or worsening neurological symptoms attributable to NMOSD. Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, change in mood, adverse reactions to medications). New or worsening neurological symptoms that occur less than 31 days following the onset of a relapse will be considered part of the same relapse (i.e., if 2 relapses have onset days that are within 30 days of one another, they will be counted only as 1 relapse), and the onset date used in the analysis will be the onset date of the first relapse.

Protocol-defined relapse: the new or worsening neurologic symptoms must meet any of the following criteria:

- An increase of at least 1.0 point on the EDSS score excepting increase to 1.0 or 1.5 from zero (i.e., a 2.0-point increase on the EDSS is required if the baseline was zero)
- An increase of at least 2.0 points on one of the appropriate FSSs
- An increase of at least 1.0 point on two or more of the appropriate FSSs 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 is one or more.

The basis of comparison for the increase is the score at the most recent scheduled EDSS/FSS assessment visit prior to the relapse.

The appropriate FSS change must affect at least one of the following functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder or visual (single eye). Sexual dysfunction and cerebral function will not suffice to establish a relapse.

All patients with new or worsened neurological symptoms suggestive of a relapse should have an EDSS/FSS assessment performed and entered into the eCRF. If a patient becomes aware of signs or symptoms that might indicate a relapse, the patient will contact the site immediately and return to the site for a relapse assessment visit as soon as possible. The EDSS/FSS assessment should be performed within 7 days after the patient reports the symptoms to the site. The Investigator should treat the patient as

necessary based on his/her evaluation of the symptoms after the completion of relapse assessments. MRI findings might be supportive for evaluation of a relapse.

If a patient has difficulty visiting the study site as a result of severity of the relapse, the patient can visit a local clinic/hospital for immediate management of a relapse, and then visit the study site as soon as possible (which may be during or immediately after acute relapse/rescue therapy).

If the patient is seen at a clinical facility other than the study site, the patient should show the patient ID card, which includes the investigator's contact information, to the treating physicians/nurses at the local clinic/hospital and the study site should make every effort to obtain medical records from the facility, including information on treatment administered and the nature of the symptoms and signs observed.

4.5.6 Expanded Disability Status Scale

The EDSS is frequently used as a quantitative measure of disability and for assessment of severity of relapse for patients with MS as well as NMOSD. The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus "other") rated and scored as FSSs. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see Appendix 4).

The EDSS/FSS assessment should be performed by a qualified assessor and preferably by the same qualified assessor for all the assessments, whenever it is feasible.

4.5.7 Symbol Digit Modalities Test

The aim of SDMT testing is to detect impairment of key neurocognitive functions that underlie many substitution tasks, including sustained attention, visual scanning, and recent memory. The test consists of a sequence of 110 symbols to be displayed in a maximum 90 seconds and a reference key legend (3 versions are available) with 9 symbols in a given order and their respective matching digits from 1 to 9. The test measures the speed (number of correct paired responses) to pair abstract symbols with specific digits in 90 seconds time (SDMT manual). See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

4.5.8 Visual Acuity

Best corrected high-contrast (100%) and low-contrast (2.5%) visual acuities will be measured at distances of both 4 and 1 meters with the appropriate eye charts. Each eye will be tested individually. No visual acuities will be obtained with both eyes open. The patient will read the charts from left to right starting with the top line (largest letters). The patient will proceed to each lower line until he/she cannot see the letters. The total

number of letters read correctly will be recorded for each eye. Visual acuity should be measured before any drops are instilled into the eye and before OCT assessments.

4.5.9 Visual Functioning Questionnaire-25 (VFQ-25)

The National Eye institute (NEI) VFQ-25 captures a patient's perception of vision-related functioning and vision-related quality of life. The core measures include 25 items that comprise 11 vision-related subscales and one item on general health (Mangione et al. 2001). The NEI VFQ-25 also includes an appendix of additional items that can be used to expand the scales up to 39 total items. The composite score and the subscale scores range from 0 to 100, with higher scores indicating better vision-related functioning. Subscale scores include General Vision, Ocular Pain, Near Activities, Distance Activities, Social Functioning, Mental Health, Role Difficulties, Dependency, Driving, Color Vision, and Peripheral Vision. A change of 4 points or more on the NEI VFQ-25 Composite, Near Activities and Distance Activities subscales is considered clinically meaningful in neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME). This questionnaire takes approximately 10 minutes on average to administer in the interviewer format. Please refer to Appendix 5 for a sample copy of the VFQ-25 (interviewer format).

4.5.10 Magnetic Resonance Imaging

During the screening period, patients who are classified as PML based on the local imaging assessment will be excluded. If patients who show lesions suspicious for PML by brain MRI, John Cunningham Virus (JCV) will be measured in the CSF; if the result is "detectable" or "undetectable with high clinical suspicion", the patient must be excluded.

MRI will be used to monitor central nervous system (CNS) lesions and potentially other pathophysiology, such as inflammation and neurodegeneration. MRI scans will be obtained at the day of study visit or before the study visit depending on the availability of the MRI as shown in the Schedule of Assessments (see Appendix 1).

MRI scans will be read by a centralized reading center for efficacy endpoints. Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI scanners are described in a separate MRI technical manual. MRI assessments will include the following:

Brain and optic nerves:

- Count, volume and regional distribution of T2-weighted FLAIR hyperintense lesions, including new and enlarging lesions of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; Fazekas scoring
- CEL of the cerebrum, optic nerves, optic chiasm, area postrema, brainstem and cerebellum; optionally meningeal enhancement
- Diffusion abnormalities

- Microbleeds
- Cerebral perfusion alterations
- Global and regional brain volume loss including basal ganglia, cerebellum and upper cervical spinal cord. Regional brain volume will be assessed only at screening, Week 48 and Week 96.

Spinal cord:

- New and persisting STIR/PD hyperintense lesions and T1-weighted contrast enhancement: Qualitative neuroradiological assessment

Optional in selected participating sites:

- Quantitative T1 mapping (MP2RAGE)
- T2*/R* for iron concentration estimation
- Quantitative diffusion/DTI

4.5.11 Optical Coherence Tomography

OCT assessments will include the following:

- Change in the RNFL thickness
- Change in the GCIP layer thickness

Multicolor OCT will be performed only at selected sites.

4.5.12 Laboratory, Biomarker, and Other Biological Samples

Laboratory assessments (performed in the central laboratory, except specified otherwise) are described below. Blood and CSF samples will be taken at the site on the day of clinic visit. Laboratory results for hematology and liver enzymes should be available to the investigator before the next visit. See Appendix 1 for the timing of assessments. There should be at least 4 weeks gap between the treatment of the acute relapse and the baseline CSF sampling.

- Hematology: hemoglobin, hematocrit, quantitative platelet count, red blood cell [RBC] count, WBC count, percent and absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils]).
- Serum chemistry: total bilirubin, alkaline phosphatase (ALP), AST, ALT, gamma-glutamyl transpeptidase (GGT), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides, CH50, Complement C3, Complement C4, and fibrinogen.
- Anti-AQP4 antibody test.
- Urine dipstick at site for standard urinalysis (including urinary glucose, urinary protein, urinary occult blood, urobilinogen).

- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. A urine pregnancy test should be performed at home by the patients before each subsequent dose.
  If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
  Pregnancy tests (serum or urine) must have a sensitivity of at least 25 mIU/mL.
- Viral serology and detection:
  - Hepatitis B screening: Patients who are hepatitis B surface antigen (HBsAg) positive will be excluded from the study. Patients for whom a positive result for antibody to HbsAg (HBsAb) is clearly associated with hepatitis B virus (HBV) vaccination can be enrolled. If not, hepatitis B viral deoxyribonucleic acid (DNA) will be measured. If total hepatitis B core antibody (HBcAb) status is positive, hepatitis B viral DNA will be measured. If hepatitis B viral DNA is detectable, the patient must be excluded. If undetectable, the patient may be enrolled. In these cases, hepatitis B viral DNA measurements must be performed regularly at approximately 12-week intervals during the study.
  - PK analysis: serum and CSF samples will be collected for determination of satralizumab concentration.
  - Immunogenicity analysis: Serum samples will be collected for determination of anti-satralizumab antibodies in both Cohort 1 and Cohort 2 as per the schedule of assessments (Appendix 1). In addition, serum samples will be collected for determination of anti-RTX antibodies in Cohort 2 at baseline.

Biomarkers

Biomarker samples for the following tests should be drawn according to the appropriate schedule of activities timepoint (Appendix 1). Except for CSF flow cytometry, which will be done locally (only at selected sites), all other samples will be sent to the central laboratory and/or to the Sponsor or designated processing site, and may be processed by the Sponsor's laboratory or the Sponsor's qualified designated laboratory (contract research organization [CRO] and/or academic research laboratory affiliated with the study):

- Blood: analysis of B cells, T cells, and other leukocytes which may include but will not be limited to number, activation status or markers, functional attributes, activity, and/or molecular status of cells
- CSF: analysis of the immune cell repertoire including but not limited to B cells and T cells, which may include but will not be limited to number, activation status or markers, functional attributes, activity, and/or molecular status of cells (supernatant, i.e., non-cellular portion of sample to be aliquoted, frozen, and sent to central laboratory and/or Sponsor or designee); single-cell ribonucleic acid (RNA) sequencing
- CSF supernatant: analysis may include but will not be limited to NfL and GFAP, levels of soluble neurodegeneration markers, and/or inflammatory markers
- Quantitative immunoglobulin: Ig levels (including total Ig, IgG, IgM, and IgA isotype)

- Serum and plasma: analysis may include but will not be limited to levels of soluble neurodegeneration markers (i.e., NfL and GFAP) and/or inflammatory markers
- Blood samples for RNA for exploratory research on non-inherited biomarkers, which may include but not be limited to immune gene expression markers
- Serum samples for assessment of autoantibody titers including but not limited to anti-AQP4 antibodies (Abs)
- Serum samples for assessment of vaccine-induced antibody titers including but not limited to anti-SARS-CoV-2
- Peripheral blood mononuclear cells (PBMCs): B- and T-cell numbers, other cell types, activation markers, functional attributes, activity, and/or molecular status of cells, levels of soluble inflammatory markers, and single cell RNA sequencing may be tested

Exploratory biomarker research may include, but will not be limited to, the assessments listed above.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exception{s}:

- Serum samples collected for PK and immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood and CSF samples collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.13 Patient-reported Outcome Assessments

PRO instruments will be completed to assess the treatment benefit of satralizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with satralizumab.

PRO data will be collected through the use of the following instruments:

SymptoMScreen
The SymptoMScreen is a composite score based upon a battery of seven-point Likert scales and assesses symptom severity in 12 distinct neurologic domains: mobility, dexterity, spasticity, body pain, sensation, bladder function, fatigue, vision, dizziness, cognition, depression, and anxiety. Total score and subscale scores are assessed over the study duration (Green et al. 2017). Higher scores indicate greater severity of symptoms.

Treatment Satisfaction Questionnaire For Medication
TSQM II is a 14-item subject assessed evaluation of treatment medication using a 7-point Likert-type scale rated as follows: 1=Extremely Dissatisfied to 7= Extremely Satisfied. Domain scores range from 0–100, with higher scores representing higher satisfaction. TSQM has been validated using a national panel study of chronic disease (Atkinson et al. 2004).

Note: the TSQM II scores at baseline will be considered as the general status of the patients (with or without prior treatments); the scores from next visit will be considered for treatment satisfaction with satralizumab.

WPAI:GH
The WPAI:GH is a questionnaire to assess the effect of NMOSD on ability to work and perform regular activities.

Please refer to Appendix 6 for a sample copy of the PROs.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigator site prior to the completion of other study assessments and the administration of study drug. Patients must complete these measures prior to the patient having any tests and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site. The recommended order of administration is first the SymptoMScreen, followed by TSQM II, and finally WPAI:GH. PRO assessments will be performed as outlined in the schedule of assessments (see Appendix 1).

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.15) will not be applicable at that site.

4.5.14.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to satralizumab or NMOSD:

- Blood sample collected at baseline for DNA (if the sample is not collected at baseline, it can be collected at any of the subsequent visits)
- Leftover blood, serum, plasma, CSF, PBMC, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for

developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AEs.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.14.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.14.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.14.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Severe/serious hypersensitivity or anaphylactic reaction to satralizumab
- Pregnancy
- Meets the discontinuation criteria in the risk mitigation and dose modification strategy (see Section 5.1)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients who discontinue study treatment early and choose not to continue on satralizumab treatment outside this study will be followed up for 12 weeks after the last dose of satralizumab.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- AE
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with satralizumab in completed and ongoing studies, as well as experience with molecules in the same class. The anticipated safety risks for satralizumab are outlined below. See the most recent satralizumab IB for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. The safety risks for satralizumab or anti-IL-6R antibodies and recommendations for vigilance with signs and symptoms of particular safety events are summarized in the following sections.

5.1.1 Risks or Laboratory Abnormalities Associated with Satralizumab

5.1.1.1 Infections

Treatment with IL-6R inhibitors suppresses acute phase reactions (fever, increase in C-reactive protein [CRP], etc.) induced by IL-6 and accordingly suppresses signs and symptoms associated with infection, which may delay the detection of infections and they may become more severe as a result of initial masking.

The following patients will be excluded from this study:

- Patients with active infection or presence of recurrent bacterial, viral, fungal, mycobacterial infection or other infection (excluding fungal infections of nail beds or caries dentium) at baseline.
- Patients with infection requiring hospitalization or treatment with intravenous (IV) anti-infective agents within 4 weeks prior to baseline visit.
- Patients with evidence of active TB.
- Patients with chronic active hepatitis B.
- Patients who received any live or live-attenuated vaccine within 6 weeks prior to baseline.

Management of Infections and serious infections:

- Patients should be closely monitored for the development of signs and symptoms of infection, because signs and symptoms of acute inflammation may be lessened as a result of suppression of the acute phase reactants.
- Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.
- If a patient develops an infection, administration of satralizumab is to be interrupted until the infection is controlled. However, if a patient develops a serious infection or ≥ grade 3 infection, administration of satralizumab is to be interrupted until the infection is resolved. Upon resolution of the infection, the treating physician should conduct a benefit-risk assessment before resuming treatment with satralizumab.
- Live or live attenuated vaccines should not be given during the course of the study as clinical safety has not been established.

5.1.1.2 Serious Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions are considered a potential risk for all biologic medications, including satralizumab.

The symptoms/signs of hypersensitivity include, but are not limited to, blood pressure decrease, dyspnea, loss of consciousness, dizziness, queasiness, vomiting, itchiness, flushing, etc. A decision to continue/discontinue treatment with satralizumab should be made taking into account the risks and benefits if any of these events are observed.

Management of (serious) hypersensitivity reactions:

- If an anaphylactic reaction or other serious hypersensitivity reaction occurs, satralizumab should be discontinued.
- For other hypersensitivity reactions, a decision to continue or discontinue treatment with satralizumab will be made by the investigator in consultation with the medical monitors, taking into account the benefits and risks.
- At baseline and Week 2 visit when satralizumab is administered at the study site, the SC injections should be administered under close supervision in a setting where medications (e.g., corticosteroid, antihistamine, and epinephrine) and resuscitation facilities are available. Patients should stay in the clinic/hospital for at least 1 hour after study treatment administration in order to receive medication immediately if anaphylaxis occurs.
- Administration of satralizumab PFS outside of the study site may be allowed (see Section 4.3.2) if the investigator determines that it is appropriate. Home-dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose.
- Patients/caregivers should be instructed to recognize the signs and symptoms of hypersensitivity reactions and instructed to seek immediate medical attention if the patient develops symptoms of acute hypersensitivity reactions. Patients/caregivers should confirm with the investigator whether treatment with satralizumab may be continued.

5.1.1.3 Liver Enzyme Elevations and Potential Risk of Hepatotoxicity

Liver function markers should be closely monitored especially when satralizumab is administered, concomitantly with hepatotoxic drugs, or administered in patients with elevated transaminases.

Recommended dose interruption based on transaminases is shown in Table 3.

Table 3 Hepatic Enzyme Risk Mitigation

AST or ALT values	Action
>1 to 3x ULN*	• Reduction (if necessary, interruption) of concomitant hepatotoxic drugs could be considered. • For persistent increases in this range, satralizumab could be interrupted until AST and ALT is below ULN*.
>3 to 5x ULN	Laboratory tests (ALT, AST, ALP and TBL) should be repeated within 72 hours to confirm value. The presence of clinical symptoms should be queried. Patients who are far away from the trial site may be retested locally if prompt return to the trial site is difficult. Satralizumab should be interrupted until AST and ALT is below 3x ULN and follow recommendations above for >1 to 3x ULN.

	If at least one of following associated, satralizumab should be discontinued. • Total bilirubin >2x ULN and/or • INR >1.5x ULN and/or • Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
>5x ULN	Laboratory tests (ALT, AST, ALP, and TBL) should be repeated within 72 hours. If value is confirmed, satralizumab should be discontinued immediately and gastroenterology expert should be contacted. The presence of clinical symptoms should be queried. If prompt return to the trial site is difficult the patients may be retested locally.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal
* ULN or patient's baseline whichever is higher.

5.1.1.4 Neutropenia

Patients with a low neutrophil count (<2 x 103/mL) will be excluded from this study.

Recommended dose interruption based on ANC results is shown in Table 4.

Table 4 Neutropenia Risk Mitigation

ANC (/uL)	Action
>1,000	Maintain dose
500 – 1,000	• If neutropenia persists, satralizumab should be interrupted until ANC is above 1,000/uL. • If ANC is under 1,000/uL at the previous laboratory test, ANC must be checked before treatment with the satralizumab (e.g., ANC test at site).
<500	Satralizumab should be discontinued

ANC = absolute neutrophil count

5.1.1.5 Thrombocytopenia

Patients with platelet count <10 x 104/ µL will be excluded from the study.

Recommended dose interruption based on platelet counts is shown in Table 5.

Table 5 Thrombocytopenia Risk Mitigation

Platelet count (/uL)	Action
>75,000	Maintain dose
50,000 – 75,000	If thrombocytopenia persists, satralizumab should be interrupted until platelet count is above 75,000/uL.
<50,000	Satralizumab should be discontinued.

5.1.1.6 Elevation in Lipid Parameters

Patients should be managed according to local guidelines for the management of hyperlipidemia.

5.1.1.7 Laboratory Findings Associated with Pharmacodynamic Effects

In addition to the above abnormal laboratory values, decreases in CRP, fibrinogen, and complement (C3, C4, and CH50) were observed in Studies BN40898 and BN40900. These are anticipated PD effects of satralizumab.

5.1.1.8 Cytochrome P450 (CYP450) Enzyme Normalization

No interaction studies have been performed. Population PK analyses did not detect any effect of azathioprine, oral corticosteroids, or mycophenolate mofetil on the clearance of satralizumab.

Both in vitro and in vivo studies have shown that the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6. Although modestly raised IL-6 levels have been reported in patients with NMOSD, mainly during times of increased disease activity, this was not evident in patients enrolled in Studies BN40898 and BN40900.

However, caution should be exercised when starting or discontinuing satralizumab treatment in patients also receiving substrates of CYP450 3A4, 1A2, 2C9 or 2C19, particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin, and theophylline), and doses adjusted if needed.

Given the prolonged terminal half-life of satralizumab, the effect of satralizumab may persist for several weeks after stopping therapy.

5.1.2 Other Risks Associated with IL-6R Inhibitors

5.1.2.1 Gastrointestinal Perforations (Complications of Diverticulitis)

Gastrointestinal perforations have been reported rarely in patients with RA administered with other anti-IL6R antibodies. IL-6 inhibition may suppress the acute symptoms (abdominal pain, pyrexia, etc.) associated with diverticulitis, etc., causing delayed diagnosis and progression to perforation.

- Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, hemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of gastrointestinal perforation and appropriate measures taken.
- Patients should be made aware of the symptomatology potentially indicative of complicated diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise.

- In patients who receive corticosteroids and/or non-steroidal anti-inflammatory drugs, prophylactic treatment with proton pump inhibitors or H2 blocker should be considered.

5.1.2.2 Malignancies

Patients with a history of malignancy within the last 5 years will be excluded from the study.

Satralizumab should be discontinued in patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin that is completely excised with free margins).

5.1.2.3 Other Demyelinating Disorders

Demyelination-related diseases have been reported in patients with RA administered another anti-IL-6R antibody, but it is not known whether there is a causal relationship.

Patients with evidence of demyelinating disease other than AQP4 antibody positive NMOSD will be excluded from this study.

In case of symptoms or other clinical evidence suggestive of a demyelination-related disease, other than NMOSD differential diagnosis of the patient should be performed.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Treatment Interruption

Satralizumab treatment may be temporarily suspended in patients who experience an adverse event or abnormal laboratory values (see Section 5.1). If satralizumab has been withheld for >12 weeks, resumption of treatment should be discussed with the Medical Monitor. Satralizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
    - This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events. The data should be recorded in the eCRF on the adverse event page and on the special form for that particular adverse event.

- Infections (including serious infections and opportunistic infections)
- Injection reaction (adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 12 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table 6 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living b, c
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event d

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For all adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 ULN) in combination with either an elevated total bilirubin (>2 ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3 ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of NMOSD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of NMOSD, “neuromyelitis optica spectrum disorder progression” should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NMOSD

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on relapse related clinical data. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization because of a NMOSD relapse
- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For satralizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.}
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.}
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.}
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.}
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.}

In addition, all special situations associated with satralizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.}
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.}
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.}
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.}
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.}
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for all sites

Medical Monitor: [redacted] (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted] (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track

all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 12 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the end of the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of

the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, PFS with NSD is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 24 weeks after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the following document:

- Satralizumab IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this study is exploratory and will primarily make use of descriptive statistical methods. No formal confirmatory hypothesis test will be conducted. No adjustment for multiple testing will be made.

The statistical summaries will be descriptive if not otherwise specified. For continuous variables, the mean, median, SD, 25th and 75th percentiles, minimum and maximum will be used as a default. For categorical variables, number and percentage in each category will be displayed. For time to event endpoints, such as the TFR, a descriptive analysis based on the Kaplan-Meier method will be performed. Pearson/Spearman correlation coefficients (as appropriate, along with corresponding scatter plots) will be produced to evaluate correlations among endpoints.

Unless otherwise specified, all endpoints will be analyzed separately for each cohort and by visit, if appropriate. Details will be specified in the statistical analysis plan (SAP). The intent-to-treat (ITT) and Safety population will include all enrolled patients who received any dose of satralizumab. The per-protocol (PP) population will include all ITT patients without major protocol deviations deemed to potentially affect the efficacy endpoints. The PP population will be used for supportive efficacy analyses.

6.1 DETERMINATION OF SAMPLE SIZE

Given the exploratory and descriptive nature of the trial, and because the rarity of the disease imposes severe restrictions on recruitment, the sample size (100 patients, including 60 patients in Cohort 1 and 40 in Cohort 2) was chosen based on feasibility.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrolment, satralizumab administration, and discontinuations from the study will be summarized using descriptive statistics. Patient disposition and the incidence of treatment discontinuation for different reasons will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics (age, gender, and self-reported race), working/employment status, medical history and neurological examination will be summarized. The following will also be summarized: NMOSD disease history (duration since first NMOSD symptoms, duration of NMOSD since diagnosis, relapses in the past year), baseline measures of MRI, EDSS and other important variables.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The TFR up to week 96 will be assessed using the Kaplan-Meier method. The proportion of relapse-free patients after week 96 will also be calculated using the Kaplan-Meier estimator (at week 96) and Greenwoods formula for the confidence interval. The ARR after Week 96 will be calculated descriptively by dividing the total number of relapses for all patients by the total years of drug exposure.

Severity of relapses assessed as hospitalization, use of corticosteroids, rescue therapy, need for plasma exchange, and residual disability will be summarized descriptively.

EDSS and EDSS change from baseline will be summarized descriptively up to week 96. Time to onset of CDP sustained for at least 12 weeks and 24 weeks will be analyzed using the Kaplan Meier method.

Change in visual acuity, VFQ-25 and SDMT will be analyzed descriptively using summary statistics.

6.4.2 Secondary Efficacy Endpoints

The secondary endpoints related to MRI and OCT are described in Section 2. The MRI variables will be analyzed descriptively by cohort and visit. The change in OCT variables will be described descriptively up to Week 96.

6.4.3 Exploratory Endpoints

SymptoMScreen (Total Score and domains), TSQM, and WPAI:GH (all domains) will be summarized descriptively up to Week 96 (absolute scores and change from baseline respectively).

Adherence to satralizumab treatment will be checked via the structured telephone interview conducted by the site personnel on the following working day after every self-administration of satralizumab and will be described descriptively.

Immune cell repertoire in CSF and blood, molecular biomarkers associated with neuroinflammation in CSF and serum, autoantibody titers in both CSF and serum will be summarized descriptively up to Week 96 (absolutes values and change from baseline respectively).

Correlations between biomarker changes (CSF, serum and/or plasma), imaging measures (MRI & OCT) and clinical measures (EDSS, relapse, cognition, visual acuity and functioning) over different timepoints will be calculated using spearman's correlation coefficient.

6.5 SAFETY ANALYSES

All safety analyses will be performed on the Safety population. Safety variables to be assessed are AEs, AESIs, SAEs, injection site reactions, patient withdrawals due to AEs, measurements of laboratory parameters, and vital signs (including body weight).

Summary tables for number and percentage of patients with AEs, SAEs, AEs leading to withdrawal, AEs leading to death will be tabulated.

Adverse events will be summarized by system organ class (SOC) and preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) coding, and grade of severity.

Laboratory values (including hematology, blood chemistry, and urinalysis), frequencies of laboratory abnormalities, and vital signs will be summarized. Measurement and change from Baseline in continuous laboratory parameters (hematology, clinical chemistry, and urinalysis), vital signs (blood pressures and pulse rate), and body weight will be summarized using descriptive statistics. When analyzing categorical data, the number and percentage of patients in each category will be presented. In addition, shift tables may be used to evaluate the number and percentage of patients having a different post-baseline status when compared to their baseline status. Numbers of patients who meet the marked abnormality criteria will also be presented.

6.6 PHARMACOKINETIC ANALYSES

Correlation coefficients of satralizumab concentrations in CSF and serum and various covariates of interest such as biomarkers and selected efficacy and safety endpoints will be calculated for different timepoints.

6.7 IMMUNOGENICITY ANALYSES

Incidence of anti-drug antibody (ADA) will be described by visit and by cohort using descriptive statistics. Time to first ADA will be described using descriptive analysis based on the Kaplan-Meir method.

6.8 HANDLING OF MISSING DATA

Handling of missing data will be specified in the SAP.

6.9 INTERIM ANALYSES

No formal interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study, e.g., after all patients have completed the first 12 months of the treatment phase and the necessary data are available.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A CRO will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of

transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., AE rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Roche, and will be managed by Roche and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

An IxRS will be used to assign patient numbers, monitor enrolment and patient status, and to manage study treatment requests and study drug shipments.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

	Screening[a]	Treatment Period[b]												Un-sched-uled Visit (due to relapse)	Early Termination Visit	Safety Follow-Up[c]
Week	**-4 to -1**	**0 (Base-line)**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**			
Day	**–28 to –1**	**1**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**169 (±7)**	**253 (±7)**	**337 (±7)**	**421 (±7)**	**505 (±7)**	**589 (±7)**	**673 (±7)**			
Informed consent[d]	X															
Medical history/demographic data[e]	X															
Review of inclusion and exclusion criteria	X	X														
Physical examination[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Weight	X	X					X		X		X		X	X	X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments																
Hematology, chemistry, and urine analysis[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B screening[j]	X															
Hepatitis B viral DNA[j]	X					(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)			
CSF specimen (LP)[k]	(X)[l]	X[l]					(X)		X				X	(X)		
Quantitative Ig (total Ig, IgA, IgG, IgM, Ig A isotype)		X					X		X		X		X	X	X	

Appendix 1: Schedule of Activities (cont.)

	Screening[a]	Treatment Period[b]												Un-sched-uled Visit (due to relapse)	Early Termination Visit	Safety Follow-Up[c]
Week	**-4 to -1**	**0 (Base-line)**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**			
Day	**–28 to –1**	**1**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**169 (±7)**	**253 (±7)**	**337 (±7)**	**421 (±7)**	**505 (±7)**	**589 (±7)**	**673 (±7)**			
Blood TBNK/Immune cell subset panels		X		X	X	X	X		X		X		X	X	X	
Plasma sample [m]		X		X	X	X	X		X		X		X	X	X	
Serum sample [m]		X		X	X	X	X		X		X		X	X	X	
Autoantibody titers, including AQP4[n]	X	X		X	X	X	X		X		X		X	X		
Antibody titers, anti-SARS-CoV-2	X	X		X	X	X	X		X		X		X	X	X	
PBMC		X		X	X	X	X		X		X		X	X	X	
RNA [o]		X		X	X	X	X		X		X		X	X	X	
Optional Sample for Blood RBR (RBR DNA sample)[p]		X														
Satralizumab concentration in CSF		X					(X)		X				X	(X)		
Satralizumab concentration in serum		X		X	X	X	X		X		X		X	X	X	
Satralizumab ADA		X		X	X	X	X		X		X		X	X	X	X
RTX ADA[q]		X														
Clinical assessments																
Neurological assessments		X		X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS[r]		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Relapse assessment[s]		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 1: Schedule of Activities (cont.)

	Screening[a]	Treatment Period[b]												Un-sched-uled Visit (due to relapse)	Early Termination Visit	Safety Follow-Up[c]
Week	**-4 to -1**	**0 (Base-line)**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**			
Day	**–28 to –1**	**1**	**15 (±3)**	**29 (±7)**	**57 (±7)**	**85 (±7)**	**169 (±7)**	**253 (±7)**	**337 (±7)**	**421 (±7)**	**505 (±7)**	**589 (±7)**	**673 (±7)**			
SDMT		X					X		X		X		X	X		
Visual acuity		X					X		X		X		X	X		
VFQ-25 (investigator administered)		X					X		X		X		X	X		
OCT[t]		X					X		X		X		X	X		
MRI (brain, spinal cord)[u,v]	(X)[w]	X[w]		X	X	X	X		X		X		X	X		
PRO assessments																
SymptoMScreen		X					X		X		X		X	(X)		
TSQM		X					X		X		X		X	(X)		
WPAI:GH		X					X		X		X		X	(X)		
Safety assessments																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Satralizumab administration[x]		X	X	X	X	X	X	X	X	X	X	X				
Telephone contact on the following working day after every self-administration of satralizumab to confirm adherence to treatment and adverse events[y]			X	X	X	X	X	X	X	X	X	X				

ADAs = anti-drug antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beata human chorionic gonadotrophin; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSS = functional system score; GGT =

gamma-glutamyl transpeptidase; Ig = immunoglobulin; IVMP = intravenous methylprednisolone; GFAP = glial fibrillary acidic protein HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HDL = high density lipoprotein; JC = John Cunningham; LDL = low density lipoprotein; LP = lumbar puncture; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OCT = optical coherence tomography; ON = optic neuritis; NfL = Neurofilament light chain; PBMC = Peripheral blood mononuclear cells; PLEX = plasma exchange; PML = progressive multifocal leukoencephalopathy; PROs = patient reported outcomes; RNA = ribonucleic acid; RTX = rituximab; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SDMT = Symbol Digital Modalities Test; TBNK = T and B lymphocyte and natural killer cell; TSQM = Treatment Satisfaction Questionnaire for Medication; VFQ-25 = Visual Functioning Questionnaire-25; WPAI:GH = Work Productivity and Activity Impairment Questionnaire: General Health

Note: (X) indicates that an assessment is optional, or will be done only if needed.

[a] For patients treated with oral corticosteroids, the screening duration could be adapted to maximum 4 weeks for adequate tapering and at least 1 week without oral corticosteroids before study start. Please see Appendix 2 for the detailed patient screening and inclusion process for patients in both cohorts depending on prior use of pulse steroids, plasma exchange and oral corticosteroids. Re-screening of patients is allowed in this protocol.
[b] Assessments scheduled on the day of study drug administration should be performed prior to administration of study drug, unless otherwise noted. The sequence of assessments should be PROs first followed by clinical assessments, laboratory assessments, MRI, lumbar puncture (for CSF assessment) and satralizumab administration. If a patient misses a scheduled visit without notice, the Investigator and/or site staff should try to contact the patient via telephone or another way in order to confirm if there has been an adverse event or a relapse. The Investigator and/or site staff should encourage the patient to visit the study site for an assessment as soon as possible.
[c] The Safety Follow-up Period will begin only if the patient discontinues from treatment early and does not continue on satralizumab treatment outside this study or completes the study and does not continue on satralizumab treatment outside the study. Patients will be assessed in safety follow-up, once at the end of 12 weeks following the last dose of satralizumab.
[d] Written informed consent will be obtained from all patients during screening in order to be eligible. Informed consent must be obtained prior to first screening assessment.
[e] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, SARS-CoV-2 vaccine status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 4 weeks prior to the screening visit. In addition, use of any previous NMOSD medication (as applicable) should be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. NMOSD disease history (details of first NMOSD symptoms and NMOSD diagnosis), baseline disease status (EDSS, number of relapses in the previous year [including description of relapse and symptoms], MRI lesions, ophthalmological status, working/employment status), treatment history (only for Cohort 2), start and stop dates and reason for change, and RTX antibody status and level before start of satralizumab treatment (only for Cohort 2), will be recorded.
[f] A full physical examination will be conducted at the screening and early termination visits. At all other visits, a limited symptom-directed physical examination will be conducted. Any abnormality identified at baseline should be recorded on the eCRF. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened clinically significant abnormalities should be recorded as adverse events, if appropriate.
[g] Vital signs will include the measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. At the baseline and Week 2 visit when satralizumab is administered at the study site, vital signs will be measured before and after study drug administration. Pulse rate, respiratory rate, temperature, systolic and diastolic blood pressure should be measured immediately before and then at 15 (±5) and 60 (±5) minutes after study drug administration. At all other visits, only one measurement of vital signs will be taken.
[h] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, quantitative platelet count. Chemistry will include total bilirubin, ALP, AST, ALT, and GGT, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, CH50, Complement C3, Complement C4, and fibrinogen. Standard urinalysis (including urinary glucose, urinary protein, urinary occult blood, urobilinogen) will be used to assess kidney function, using urine dipstick at site. If the screening assessment has been conducted within 14 days prior

to baseline dosing, it does not need to be conducted again prior to baseline dosing. Results should be available prior to dosing (may be taken up to 14 days prior to dosing) to ensure patient eligibility per the investigator's discretion.

[i] Serum β-hCG must be performed at screening in women of childbearing potential within 14 days prior to initiation of study drug. A urine pregnancy test should be performed at home by the patients before each subsequent dose. If urine pregnancy test is positive, satralizumab should be withheld and pregnancy status should be confirmed with serum β-hCG test. Pregnancy tests (serum or urine) must have a sensitivity of at least 25 mIU/mL.

[j] Hepatitis B screening: Patients who are HBsAg positive will be excluded from the study. Patients for whom a positive result for antibody to HbsAg (HBsAb) is clearly associated with HBV vaccination can be enrolled. If not, hepatitis B viral DNA will be measured. If total HBcAb status is positive, hepatitis B viral DNA will be measured. If hepatitis B viral DNA is detectable, the patient must be excluded. If undetectable, the patient may be enrolled. In these cases, hepatitis B viral DNA measurements must be performed regularly at approximately 12-week intervals during the study.

[k] CSF samples will be drawn at screening/baseline, Week 48 and Week 96 for both cohorts. Additional optional CSF samples may be drawn at Week 24 and all unscheduled visits due to relapse in consenting patients. There should be at least 4 weeks gap between the treatment of the acute relapse and the baseline CSF sampling. The baseline CSF sample should be collected on the day of informed consent form (before the start of any treatment for the acute attack/event). CSF flow cytometry will be done locally only at selected sites.

[l] The first LP will be conducted at baseline for patients previously treated with IVMP/PLEX ± oral corticosteroids. For patients without prior acute IVMP or PLEX treatment, the first LP will be conducted at screening visit and will be considered as the baseline CSF assessment.

[m] Serum and plasma analysis may include but will not be limited to levels of soluble neurodegeneration markers (i.e., NfL and GFAP) and/or inflammatory markers. Samples should be collected before satralizumab administration.

[n] Serum samples for biomarker assessments including but not limited to autoantibody titers (anti-AQP4 Ab).

[o] Blood samples for RNA extraction for exploratory research on non-inherited biomarkers, which may include but not be limited to immune gene expression markers

[p].If the RBR DNA sample is not collected at baseline, it may be collected at any of the subsequent visits.

[q].Only for patients in Cohort 2.

[r]The EDSS/FSS assessment should be performed by a qualified assessor and preferably by the same qualified assessor for all the assessments, whenever it is feasible.

[s] Severity of relapses will be assessed based on hospitalization, use of corticosteroids, rescue therapy, need for plasma exchange, and residual disability.

[t].Multicolor OCT will be performed only at selected sites.

[u] On MRI, patients who are classified as PML or MS must be excluded. If PML cannot be ruled out, JC virus in the CSF will be measured.

[v] MRI should be performed before lumbar puncture if both are performed at the same visit. MRI should be performed before satralizumab administration if done at the same visit. Regional brain volume will be assessed at screening, Week 48 and Week 96.

[w] The first MRI will be conducted at baseline for patients previously treated with IVMP/PLEX ± oral corticosteroids. For patients without prior acute IVMP or PLEX treatment, the first MRI will be conducted at screening visit and will be considered as the baseline MRI assessment.

[x] Satralizumab will be administered at a dose of 120 mg SC at Weeks 0, 2 (±3 days), 4 (±3 days), and then every 4 weeks (±3 days) till the last administration at Week 92 followed by a clinical evaluation at Week 96. The first dose at Weeks 0 (baseline visit) will be administered at the study site by the designated site staff. The next dose at Week 2 will be self-administered by the patient/patient caregiver under the supervision of a designated study staff at the study site. After adequate training on how to prepare and perform the injection, an adult patient/caregiver may administer all other doses at home if the treating physician determines that it is appropriate and the adult patient/caregiver can perform the injection technique. Home dosing will not be allowed if the patient experienced a serious systemic injection reaction following any prior satralizumab dose. **All assessments (clinical, laboratory and imaging) should be performed before satralizumab administration, if satralizumab is administer on the day of scheduled clinic visit**.

[y].A structured telephone interview will be conducted by site personnel on the following working day after every self-administration of satralizumab to confirm compliance with study drug treatment and to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events.

Appendix 2
Patient screening and selection process

Cohort 1: Treatment-Naïve Patients (Patients with NO previous maintenance DMT or IST)

1a: Patient presenting with a very first attack of (suspected) NMOSD (SUSPECTED NMOSD: to be confirmed during screening)	**1b: Patient presenting with an acute attack or relapse which took place (<1 year since last event) and has been treated already with IVMP/PLEX and NO oral corticosteroids**	**1c: Patient presenting with an acute attack or relapse which took place (<1 year since last event) and has been treated alr eady with IVMP/PLEX and oral corticosteroids**
Screening		
• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4+ evaluation) • Serum pregnancy test for women at childbearing age • MRI • LP and peripheral biomarker assessment • Treatment of acute event or relapse with IVMP/PLEX	• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4+ evaluation) • Serum pregnancy test for women at childbearing age **Duration of the screening period of 2 to 4 weeks between IVMP/PLEX and baseline visit**	• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4 status evaluation) • Serum pregnancy test for women at childbearing age • Tapering of chronic corticosteroid treatment (not longer than 4 weeks) to 0 to 4 weeks after IVPM/PLEX and 1 week OFF corticosteroid treatment
Baseline visit		
2 to 4 week after IVMP or PLEX • PROs • Clinical assessments • OCT • Start of satralizumab	• PROs • Clinical assessments • MRI • OCT • LP and peripheral biomarker assessment • Start of Satralizumab	• PROs • Clinical assessments • MRI • OCT • LP and peripheral biomarker assessment • Start of Satralizumab
Further study implementation: see Appendix 1 (schedule of activities) for assessments during the study period		

AQP4 = Aquaporin-4; DMT = disease-modifying therapy; ICF = Informed consent form; IVMP = intravenous methylprednisolone; IST = Immunosuppressive therapy; LP = lumbar puncture; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder; OCT = optical coherence tomography; PLEX = Plasma exchange; PROs = Patient-reported outcomes

Cohort 2: Patients treated with RTX (or its biosimilar) monotherapy (without concomitant DMT or IST) previous as last treatment (last infusion < 6 months, and at least 2 RTX full doses/courses) and disease history of ≤ 5 years

2a: Acute relapse and prior to acute IVMP or PLEX treatment	**2b: Patient presenting with a relapse which took place (after the last RTX infusion) and has been treated already with IVMP/PLEX and NO oral corticosteroids**	**2c: Patient presenting with a relapse which took place (after the last RTX infusion) and has been treated already with IVMP/PLEX and oral corticosteroids**
Screening		
• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4+ evaluation) • Serum pregnancy test for women at childbearing age • MRI • LP and peripheral biomarker assessment • Treatment of acute event or relapse with IVMP or PLEX	• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4+ evaluation) • Serum pregnancy test for women at childbearing age **Duration of the screening period of 2 to 4 weeks between IVMP/PLEX and baseline visit**	• ICF for screening and possible study participation (inclusion/exclusion criteria, including AQP4 status evaluation) • Serum pregnancy test for women at childbearing age • Tapering of chronic corticosteroid treatment (not longer than 4 weeks) to 0 to 4 weeks after IVPM/PLEX and 1 week OFF corticosteroid treatment
Baseline visit		
2 to 4 week after IVMP or PLEX • PROs • Clinical assessments • OCT • Start of satralizumab	• PROs • Clinical assessments • MRI • OCT • LP and peripheral biomarker assessment • Start of Satralizumab	• PROs • Clinical assessments • MRI • OCT • LP and peripheral biomarker assessment • Start of Satralizumab
Further study implementation: see Appendix 1 (schedule of activities) for assessments during the study period		

AQP4 = Aquaporin-4; DMT = disease-modifying therapy; ICF = Informed consent form; IVMP = intravenous methylprednisolone; IST = Immunosuppressive therapy; LP = lumbar puncture; MRI = magnetic resonance imaging; OCT = optical coherence tomography; PLEX = Plasma exchange; PROs = Patient-reported outcomes; RTX = Rituximab

Appendix 3
Instruction for Tuberculosis (TB) Screening and Treatment

Interpretation of TB screening results

Immunosuppressant biologic treatments have been shown to increase the risk of tuberculosis (TB) infection or to cause conversion from latent to active TB in some circumstances. Because of this, patients must be screened for active or latent TB prior to entry to this study.

Definitions

Active TB is a disease caused by *Mycobacterium tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source which tests positive for TB or if there is radiographic evidence of TB. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine or elsewhere) and can spread the infection to others.

Latent TB is said to exist when an individual is infected with *Mycobacterium tuberculosis,* as evidenced by a positive Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA - such as Quantiferon-TB Gold) but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others. Such individuals must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration in this study.

TB screening

TB screening must be performed prior to initiation of study drug treatment. TB screening should be conducted per local guidance (or the table described below if none exist). For reference, the US CDC notes on TB testing may be found at http://www.cdc.gov/TB/TOPIC/testing/default.htm.

- As part of recording the patient's medical history, the patient will be asked if they have had either active or latent TB in the past and whether they have received a BCG vaccination. They will also be asked if they have been in contact with any individuals known to have active TB.
- TB test (e.g. TST [Purified Protein Derivative, PPD] and/or IGRA [e.g. Quantiferon-TB Gold]) is required at screening.
- A chest X-ray is required at screening and is recommended to be performed and reported by a qualified radiologist.

Note:

1) The TST may be positive if the patient has had a BCG vaccination or has been infected with TB in the past; IGRA results may also be positive in some cases of past infection.

2) Positive results of the TST and IGRA test may be reduced by immune suppression.

3) Local guidance may vary depending upon the sensitivity of strains of Mycobacterium tuberculosis present locally.

In case of any doubt as to the diagnosis of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor is consulted.

A combination of the medical history, the results of the TST test, the IGRA test, chest X-ray and any other investigations deemed appropriate by the Investigator based on clinical signs and symptoms indicative of TB infection elsewhere in the body will be used by the Investigator to determine study eligibility at screening for this study as follows:

	TST or IGRA result	**Chest X-ray**		**Interpretation / Action**
		Evidence of current, active TB	**Evidence of old TB**	
a)	Positive TST or IGRA	Positive	Positive or negative	Active TB present. Ineligible for entry to study.
b)	Positive TST	Negative	Positive or negative	Could be either i) prior BCG vaccine, ii) past history of TB, iii) latent TB or iv) extra-pulmonary active TB. Perform IGRA test to exclude i) then follow instructions in section c) below.
c)	Positive IGRA	Negative	Positive or negative	Possible latent TB or extra-pulmonary TB present. Exclude extra-pulmonary TB using further investigations appropriate to any sign/symptoms. Once extra-pulmonary TB has been excluded patient is only eligible for study entry after at least 3 weeks of prophylactic anti-mycobacterial therapy prior to initiating study treatment administration and if committed to completing this course of treatment.
d)	Negative TST or IGRA	Positive	Positive or negative	Likely anomalous TST/IGRA result. Repeat TST/IGRA test if in doubt. Ineligible for entry to study.

	TST or IGRA result	Chest X-ray		Interpretation / Action
		Evidence of current, active TB	Evidence of old TB	
e)	Negative TST or IGRA	Negative	Positive	Prophylactic anti-mycobacterial therapy should be considered, according to local guidelines (if such exist) because there may be a false negative TST or IGRA if the patient has been on prior immunosuppressants. Such prophylactic therapy is not compulsory but is at the Investigator's discretion. The patient may be eligible for study treatment with or without prophylactic anti-mycobacterial treatment. (If in doubt about TST/IGRA result, repeat tests.)
f)	Negative TST or IGRA	Negative	Negative	Eligible for study entry.
g)	Indeterminate TST or IGRA	Positive	Positive or negative	Likely anomalous TST/IGRA result. Repeat TST/IGRA test if in doubt. Ineligible for entry to study.
h)	Indeterminate TST or IGRA	Negative	Positive or negative	Possible anomalous TST/IGRA result or latent TB. Repeat IGRA test. If result still indeterminate, and there are no signs/symptoms of extra-pulmonary, follow instructions in section e) or f) above. If result of repeat IGRA negative, follow instructions in section e) or f) above.

TB Treatment

If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 3 weeks prior to initiating study treatment administration. Treatment regimens should be followed by the local guidance. If no local guidance exists for treatment of immunocompromised individuals, then the US CDC must be followed (http://www.cdc.gov/TB/publications/LTBI/default.htm).

In case of any doubt as to the appropriate course of anti-mycobacterial therapy of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor is consulted.

Management of signs/symptoms of TB during the study

If new signs/symptoms of TB infection develop during the study, perform diagnostic tests as above. If TB infection is diagnosed, interrupt study treatment and consult the Medical Monitor. Report TB infection as a "Selected Adverse Event".

Appendix 4
Expanded Disability Status Scale (EDSS)

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

EDSS steps

0	Normal neurological exam (all FS grade 0)
1.0	No disability, minimal signs in one FS (one FS grade 1)
1.5	No disability, minimal signs in more than one FS (more than one FS grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Fully ambulatory but with moderate disability in one FS (one FS grade 3, others 0 or 1) **OR** Fully ambulatory but with mild disability in three or four FS (three / four FS grade 2, others 0 or 1)
3.5	Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; **OR** Fully ambulatory with two FS grade 3 (others 0 or 1); **OR** Fully ambulatory with five FS grade 2 (others 0 or 1)
4.0	**Fully ambulatory for ≥500 meters without aid or rest**; up and about some 12 hours a day characterized by relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5	**Ambulatory for 300 - 500 meters without aid or rest**; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0	**Ambulatory for 200 - 300 meters without aid or rest** (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5	**Ambulatory for 100 - 200 meters without aid or rest**
6.0	**Ambulatory for at least 100 meters with intermittent or constant unilateral assistance** (cane or crutch) with or without rest **OR** Ambulatory < 100 meters without help or assistance **OR** Ambulatory ≥ 50 meters with unilateral assistance **OR** Ambulatory ≥ 120 meters with bilateral assistance
6.5	**Ambulatory for at least 20 meters with constant bilateral assistance (canes or crutches)** without rest **OR** Ambulatory for < 50 meters with unilateral assistance (cane or crutch) **OR** Ambulatory 5 to 120 meters with constant bilateral assistance (canes or crutches)
7.0	**Unable to walk 5 meters even with aid, essentially restricted to wheelchair**; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5	**Unable to take more than a few steps; restricted to wheelchair**; may need some help in transferring and in wheeling self
8.0	**Essentially restricted to bed or chair or perambulated in wheelchair**, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	**Essentially restricted to bed much of the day**; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10	Death due to MS

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and EDSS
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

Functional System Scores

1. Visual FSS

0	normal
1	disc pallor and / or small scotoma and / or visual acuity (corrected) of worse eye less than 20 / 20 (1.0) but better than 20 / 30 (0.67)
2	worse eye with maximal visual acuity (corrected) of 20 / 30 to 20 / 59 (0.67 – 0.34)
3	worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20 / 60 to 20 / 99 (0.33 – 0.21)
4	worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20 / 100 to 20 / 200 (0.2 – 0.1); grade 3 plus maximal acuity of better eye of 20 / 60 (0.33) or less
5	worse eye with maximal visual acuity (corrected) less than 20 / 200 (0.1); grade 4 plus maximal acuity of better eye of 20 / 60 (0.33) or less
6	grade 5 plus maximal visual acuity of better eye of 20 / 60 (0.33) or less

2. Brainstem FSS

0	normal
1	signs only
2	moderate nystagmus and / or moderate EOM impairment and / or other mild disability
3	severe nystagmus and / or marked EOM impairment and / or moderate disability of other cranial nerves
4	marked dysarthria and / or other marked disability
5	inability to swallow or speak

3. Pyramidal FSS

0	normal
1	abnormal signs without disability
2	**minimal disability**: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups
3	**mild to moderate paraparesis or hemiparesis**: BMRC grade 4 in >two muscle groups; and/or **BMRC grade 3 in one or two muscle groups** (movements against gravity are possible); and/or **Severe monoparesis**: BMRC grade 2 or less in one muscle group
4	**marked paraparesis or hemiparesis:** usually BMRC grade 2 in two limbs and/or **monoplegia:** BMRC grade 0 or 1 in one limb; and/or **moderate tetraparesis:** BMRC grade 3 in ≥ three limbs
5	**paraplegia**: BMRC grade 0 or 1 in all muscle groups of the lower limbs; and/or **marked tetraparesis:** BMRC grade 2 or less in ≥ three limbs; and/or **hemiplegia**
6	**tetraplegia**: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

4. Cerebellar FSS

0	normal
1	abnormal signs without disability
2	mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible
3	moderate limb ataxia and/or moderate or severe gait/truncal ataxia
4	severe gait/truncal ataxia and severe ataxia in three or four limbs
5	unable to perform coordinated movements due to ataxia
X	pyramidal weakness (BMRC grade ≤3) or sensory deficits interfere with cerebellar testing

5. Sensory FSS

0	normal
1	mild vibration or figure-writing or temperature decrease only in 1 or 2 limbs
2	mild decrease in touch / pain / position sense or moderate decrease in vibration in 1 or 2 limbs and/or mild vibration or figure-writing or temperature decrease alone in more than 2 limbs
3	moderate decrease in touch / pain / position sense or marked reduction in vibration in 1 or 2 limbs and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in > 2 limbs
4	marked decrease in touch or pain in 1 or 2 limbs and/or moderate decrease in touch or pain and/or marked reduction of proprioception > 2 limbs
5	loss (essentially) of sensation in one or two limbs and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6	sensation essentially lost below the head

6. Bowel/Bladder FSS

0	normal
1	mild urinary hesitancy, urgency **and/or** constipation
2	moderate urinary hesitancy/retention **and/or** moderate urinary urgency/incontinence **and/or** moderate bowel dysfunction
3	frequent urinary incontinence or intermittent self-catheterization; needs enema or manual measures to evacuate bowels
4	in need of almost constant catheterization
5	loss of bladder or bowel function; external or indwelling catheter
6	loss of bowel and bladder function

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

7. Cerebral FSS

0	normal
1	signs only in decrease in mentation; mild fatigue
2	mild decrease in mentation; moderate or severe fatigue
3	moderate decrease in mentation
4	marked decrease in mentation
6	dementia

8. Ambulation score

0	unrestricted
1	Fully ambulatory ≥ 500 meters without help or assistance but not unrestricted (pyramidal or cerebellar FS ≥ 2)
2	Ambulatory ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0, defined by FSS)
3	Ambulatory ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4	Ambulatory ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5	Ambulatory < 100 meters without help or assistance (EDSS 6.0)
6	Ambulatory ≥ 50 meters with unilateral assistance (EDSS 6.0)
7	Ambulatory ≥ 120 meters with bilateral assistance (EDSS 6.0)
8	Ambulatory < 50 meters with unilateral assistance (EDSS 6.5)
9	Ambulatory ≥ 5 meters, but < 120 meters with bilateral assistance, (EDSS 6.5)
10	Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11	Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12	essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

Standardized Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

Source: 55TUhttp://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-DisabU55T

Appendix 5
Visual Functioning Questionnaire – 25 (VFQ-25)

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. **Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. **How much difficulty do you have <u>reading street signs or the names of stores</u>?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. **Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. **Because of your eyesight, how much difficulty do you have seeing how people react to things you say?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

i

16. How much difficulty do you have <u>driving at night</u>? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your <u>overall health</u>, on a scale where zero is <u>as bad as death</u> and 10 is <u>best</u> possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have <u>reading the small print in a telephone book, on a medicine bottle, or on legal forms</u>? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A7. Because of your eyesight, how much difficulty do you have <u>taking part in active sports or other outdoor activities that you enjoy</u> (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A8. Because of your eyesight, how much difficulty do you have <u>seeing and enjoying programs on TV</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have <u>entertaining friends and family in your home</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DRIVING

A10. [This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.....	1	2	3	4	5

Appendix 6
Patient-Reported Outcomes

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

SYMPTOM SCREEN

Please circle one number that best describes how each MS symptom has affected your everyday life activities. For example, if it takes you longer to type or text, your hand function may have a 'mild limitation' (circle '2'), but if you gave up typing or texting completely, your hand function may have a 'severe limitation' (circle '4').

	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5 – very severe limitation/ I'm unable to do many daily activities	6 – total limitation/ I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily pain Achiness, tenderness	0	1	2	3	4	5	6
Sensory Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, urinary frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress, panic attacks	0	1	2	3	4	5	6

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____

NO ____ YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

_____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____HOURS

4. During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

This is a sample form provided for reference only. The form for use in the study will be provided to the site separately.

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied