Official Title: A Multicenter, Single Arm, Open-Label Study to Evaluate the Long-Term Safety and Efficacy of Satralizumab in Patients With Neuromyelitis Optica Spectrum Disorder (NMOSD)

NCT Number: NCT04660539

Document Date: Protocol Version 1: 28-July-2020

PROTOCOL

TITLE:	**A MULTICENTER, SINGLE ARM, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF SATRALIZUMAB IN PATIENTS WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)**
PROTOCOL NUMBER:	WN42349
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-003413-35
IND NUMBER:	To be determined
NCT NUMBER:	To be determined
TEST PRODUCT:	Satralizumab (SA237) (RO5333787)
MEDICAL MONITOR:	[redacted] M.D.
SPONSORS:	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
27-Jul-2020 20:15:04	Company Signatory	[redacted]
28-Jul-2020 17:11:11	Deputy EU QPPV	Tanrikulu, Yusuf (tanrikuy)

[a] Chugai will act as the Sponsor only in Taiwan and 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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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 local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, SINGLE ARM, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF SATRALIZUMAB (SA237) IN PATIENTS WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)**
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EUDRACT NUMBER:	2020-003413-35
IND NUMBER:	To be determined
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TEST PRODUCT:	Satralizumab (SA237) (RO5333787)
PHASE:	Phase IIIb
INDICATION:	Neuromyelitis Optic Spectrum Disorder (NMOSD)
SPONSOR:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd. [a]

[a] Chugai will act as the Sponsor only in Taiwan and 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.

Objectives and Endpoints

This study will evaluate the long-term safety, efficacy, and pharmacokinetics/ pharmacodynamics of satralizumab and will provide continued treatment with satralizumab to patients with Neuromyelitis Optic Spectrum Disorder (NMOSD) who completed the open-label extension (OLE) periods of the Phase III Studies BN40898 and BN40900. Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective

The primary safety objective for this study is:

- To evaluate the long-term safety of satralizumab in patients with NMOSD

The secondary safety objective for this study is:

- To further evaluate the risks of serious infections and hepatotoxicity in patients with NMOSD who are treated with satralizumab

Safety outcome measures:

- Incidence and severity of adverse events (AE), adverse events of special interest (AESI), serious AEs (SAE), and selected AEs
- Vital signs (temperature, blood pressure, and pulse rate), clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECG), and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS])

Efficacy Objectives

The efficacy objective for this study is to evaluate long-term efficacy of satralizumab on the basis of the following endpoints:

- Time to first relapse (TFR) and proportion of relapse-free patients
- Annualized relapse rate (ARR)
- Change in Expanded Disability Status Scale (EDSS) score
- Time to EDSS worsening and proportion of patients without EDSS worsening
- Change in visual acuity

Pharmacodynamic Objective

The pharmacodynamics (PD) objective for this study is to further characterize the target engagement in response to satralizumab treatment on the basis of the assessment of IL-6, soluble IL-6R (sIL-6R) and C-reactive protein (CRP).

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to further characterize the satralizumab PK profile on the basis of the following endpoint:

- Serum concentration of satralizumab at specified timepoints

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of satralizumab on the basis of the following endpoints:
  - Relationship between serum concentration or PK parameters for satralizumab and efficacy endpoints
  - Relationship between serum concentration or PK parameters for satralizumab and safety endpoints
- To evaluate potential relationships between selected covariates and exposure to satralizumab on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for satralizumab

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to satralizumab on the basis of the following endpoint:

- Incidence of anti-drug antibodies (ADAs) from the first dose of satralizumab in Studies BN40898 or BN40900 (parent studies)

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, and PK endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that can provide evidence of satralizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and/or related pathways, on the basis of the following endpoint:

- Relationship between biomarkers in blood and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with satralizumab on the basis of the following endpoint:

- Change in EuroQol 5-Dimension Questionnaire (3-level version; EQ-5D-3L) index-based and Visual Analogue Scale (VAS) scores

Study Design

Description of Study

This Phase IIIb study is a multicenter, single-arm, open-label study for approximately 127 patients who completed the OLE period of Study BN40898 and Study BN40900, (i.e., were receiving ongoing treatment with satralizumab prior to study entry in this Study WN42349). The study aims to evaluate the long-term safety and efficacy of satralizumab in patients with NMOSD.

Informed consent should be obtained from participants while they are in the parent Studies BN40898 or BN40900. Patients will be transitioned from their ongoing Study BN40898 or BN40900 at a planned dosing visit to allow for continuous dosing with subcutaneous (SC) satralizumab at a dose of 120 mg (fixed dose) every 4 weeks (Q4W). Safety and efficacy will be assessed at the baseline visit in this study. Efforts will be made to transition patients, at a 12-week or 24-week visit in their visit schedule in the parent study to reduce burden of assessments on patients.

Patients will receive satralizumab as monotherapy or in combination with one of the following background immunosuppressive treatments: azathioprine (AZA), mycophenolate mofetil (MMF), or oral corticosteroids. Patients aged less than 18 years at the time of informed consent for Study BN40898 can continue treatment with a combination of oral corticosteroids and either AZA or MMF. It is at the discretion of the investigator to modify the background treatment after the baseline visit in this study. For patients who experience a relapse during the study, appropriate acute relapse/rescue therapy will be initiated.

Patients who experience either a relapse or active infection or do not meet one of the retreatment criteria based on laboratory assessments in the parental study, should continue in the ongoing parental study and be transitioned to this study once the patient is stabilized after the relapse, the infection controlled, or the laboratory assessment allows retreatment. If the patient cannot be enrolled within 12 weeks from the initial event preventing the transition to this study, the site should discuss with the Medical Monitor.

Number of Patients

This study includes patients with NMOSD who participated in Study BN40898 or Study BN40900 and are ongoing on satralizumab treatment in the OLE period of these studies prior to study entry in Study WN42349. Approximately 127 patients with NMOSD will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Participated in Study BN40898 or Study BN40900 with satralizumab in NMOSD, are on ongoing satralizumab treatment and were aquaporin-4 (AQP4) IgG seropositive at screening in these studies. Patients with NMOSD who were AQP4 IgG seronegative at screening in Study BN40898 or Study BN40900 can be enrolled if the investigator considers the continued treatment with satralizumab to be beneficial for the patient.
- Signed Informed Consent Form (ICF)
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 3 months after the final dose of satralizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to 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 following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

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, symptothermal, or postovulation 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 ICF.

Exclusion Criteria

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

- Use of prohibited medication.
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of study drug. Women of childbearing potential must have a negative urine pregnancy test result on the baseline visit prior to initiation of study drug.
- Evidence of any serious uncontrolled concomitant diseases that may preclude patient participation, such as:

  other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
- Known active infection that requires delaying the next satralizumab dose at the time of enrollment[a]

  [a] In case of an active infection, the patient should remain in the parent study, as governed by that protocol, and may enroll in this study once the active infection is controlled.
- NMOSD relapse at the time of enrollment[b]

  [b] In case of a relapse, the patient should remain in the parent study, as governed by that protocol, and may enroll in this study once the patient is stable.
- Laboratory abnormalities at the last assessment in Study BN40898 or Study BN40900 that preclude re-treatment with satralizumab [c]

  [c] If a patient does not meet the criteria to restart treatment with satralizumab based on laboratory assessments, the patient should remain in the parent study and the baseline visit should be delayed. The last assessment before enrollment must meet the re-treatment criteria.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs. The treatment period ends 3 years after the date the first patient enrolls in the study. The end of the study is expected to occur in second quarter of 2024.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 3 years and 3 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is satralizumab.

Non-Investigational Medicinal Products

Acute relapse rescue therapy administered in case of a NMOSD relapse, and allowed background immunosuppressive therapy (IST) are considered non-investigational medicinal products (NIMP).

Statistical Methods

Primary Analysis

All safety analyses will be performed on the Safety Population (SAF). Safety variables to be assessed are AEs, AESIs, SAEs, selected AEs, injection site reactions, patient withdrawals due to AEs, change in 12-lead ECGs, measurements of laboratory parameters, and vital signs (including body weight).

Summary tables for number and percentage of patients and rate of AEs per 100PY with adverse drug reactions (i.e., AEs related to study drug as assessed by the investigator) will be generated.

Adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT), based on Medical Dictionary for Regulatory Activities (MedDRA) coding, and grade of severity. The incidence of treatment emergent AEs will also be displayed by severity and relationship to the study drug, respectively. In addition, the incidence of AEs leading to withdrawal from treatment and SAEs will be tabulated.

Incidence of Selected AEs will be tabulated. AEs will be further analyzed according to whether they meet Sampson's criteria for diagnosis of anaphylaxis.

Laboratory values (including hematology, blood chemistry, and urinalysis), frequencies of laboratory abnormalities, vital signs (temperature, blood pressure, and pulse rate), 12-lead ECG, and suicidality (C-SSRS) will be summarized. Measurement and change from baseline in continuous laboratory parameters (hematology, clinical chemistry, and urinalysis), continuous ECG, vital signs (blood pressures and pulse rate), and body weight will be summarized with use of descriptive statistics. Body weight by change from randomization/first dose of satralizumab of more than/less than 7% and 15% will also be analyzed descriptively. 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 with their baseline status. Numbers of patients who meet the marked abnormality criterion will also be presented.

Determination of Sample Size

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 127 patients but will be determined by the number of patients who complete Studies BN40898 and BN40900 and enroll in this study.

All safety variables will be analyzed on the basis of the SAF. The SAF population will include all randomized or enrolled patients who have received at least one dose of study drug either during the parental studies or this study. It will encompass all patients from the parent studies, even if they do not participate in this study. Patients will be analyzed as treated for analysis purposes in the SAF.

Interim Analyses

No formal confirmatory effectiveness or safety interim analyses are planned. Exploratory analyses of selected endpoints and in particular periodic analyses of safety data are planned to be performed during the course of the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug (satralizumab) antibodies
AE	adverse event
AESI	adverse event of special interest
ALLSA	all-patients-treated (all satralizumab)
AQP4	aquaporin-4
AQP4-IgG	anti–aquaporin-4 IgG antibody
ARR	annualized relapse rate
AZA	azathioprine
CCOD	clinical cutoff date
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EOS	end of study
EOT	end of treatment
EQ-5D-3L	EuroQol 5-Dimension Questionnaire (3rd level version)
EU	European Union
FDA	Food and Drug Administration
Fc	fragment crystallizable
FSS	Functional System Score
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IgG	immunoglobulin G
IL-6	interleukin-6

Abbreviation	Definition
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	injection-related reaction
IST	immunosuppressive therapy/immunosuppressive treatment
ITT	intent-to-treat
IxRS	interactive voice or Web response system
LPLV	last patient, last visit
MMF	mycophenolate mofetil
MS	multiple sclerosis
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
NSD	needle safety device
OLE	open-label extension
PD	pharmacodynamic(s)
PDR	protocol defined relapse
PFS	prefilled syringe
PK	pharmacokinetic(s)
PK-PPS	pharmacokinetic per-protocol set
Q4W	every 4 weeks
QTcF	QT interval corrected for heart rate with use of Fridericia's Formula
RA	rheumatoid arthritis
RBR	Research Biosample Repository
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	subcutaneous(ly)
SFU	safety follow-up
sIL-6R	soluble interleukin-6 receptor
TBL	total bilirubin
TFR	time to first relapse
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale

1. BACKGROUND

1.1 BACKGROUND ON NEUROMYELITIS OPTICA SPECTRUM DISORDER

1.1.1 Introduction to Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica (NMO), originally named Devic's disease, is a severe demyelinating inflammatory autoimmune disorder of the central nervous system (CNS). In 2015, the International Panel for Neuromyelitis Optica Diagnosis defined the unifying term "neuromyelitis optica spectrum disorder" (NMOSD), which includes serologic testing of anti–aquaporin-4 IgG antibody (AQP4-IgG) and distinguishes aquaporin 4 (AQP4) antibody seropositive or seronegative NMOSD. NMOSD is clinically characterized by optic neuritis and/or transverse myelitis (Wingerchuk et al. 2015), leading to disabling neurologic symptoms such as visual impairment (including blindness), disturbance of ambulation sensory disturbances, and/or bowel and bladder dysfunction. Fatigue and pain are common symptoms of NMOSD and significantly impact the patient's quality of life. Disability in NMOSD is usually a consequence of relapses, which can be severe, even fatal, and result in residual disability.

Despite being clinically similar, NMOSD is distinct from MS radiologically, has a worse prognosis, and has a pathophysiology that is unresponsive to typical MS treatment (Weinshenker 2007; Oh and Levy 2012). Unlike in MS, secondary progression is uncommon in NMOSD. Other distinguishing features of NMOSD include an even stronger female preponderance, longitudinally extensive spinal cord lesions, and absence of oligoclonal IgG bands in the cerebrospinal fluid (CSF).

There are four aspects of NMOSD treatment 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 neurologic deficits, the goal for maintenance NMOSD therapy is relapse prevention. Since 2019, three medications for NMOSD have been approved in at least one country for the prevention of NMOSD relapses: satralizumab, eculizumab, and inebilizumab (for more information on satralizumab see Section 1.2). Prior to 2019 the standard maintenance therapy included oral corticosteroids and/or immunosuppressants (IST) such as azathioprine (AZA) or mycophenolate mofetil (MMF). In some countries rituximab, although approved only for treatment of rheumatoid arthritis (RA) and non-Hodgkin lymphoma, is used as off-label NMOSD maintenance therapy. In addition, chemotherapies, such as methotrexate and mitoxantrone, are used. Residual symptoms during in the remission phase of NMOSD, such as pain, fatigue, stiffness, and bladder and bowel symptoms, are common and are managed by symptomatic therapy.

1.1.2 Interleukin-6 as a Target Molecule for the Treatment of NMOSD

One of the key features of NMOSD is the presence of pathological autoantibodies against AQP4 (AQP4-IgG), a major water channel protein in the CNS (Lennon et al. 2005). Transfer of AQP4-IgG was shown to exacerbate experimental autoimmune encephalomyelitis in animal models. Yamamura and co-workers identified the CD19intCD27highCD38highCD180− (and CD20−) plasmablast B-cell subset, which is associated with production of AQP4-IgG in patients with NMOSD (Chihara et al. 2011).

Survival of plasmablasts is promoted by interleukin-6 (IL-6), and IL-6 was suggested to enhance antibody production by these plasmablasts; in vitro IL-6 receptor (IL-6R) blockade reduced survival of AQP4-IgG-producing plasmablasts. IL-6 is a proinflammatory cytokine with pleiotropic functions, including inflammatory response, induction of the differentiation and proliferation of various types of cells, regulation of immune response, and thrombocytosis (Kishimoto 2010; Tanaka and Kishimoto 2012).

In addition to effects on B cells (e.g., AQP4-IgG production), IL-6 has also been suggested to contribute to NMOSD pathogenesis by promoting the differentiation of pro-inflammatory Th17 cells which, in turn, can also support B-cell differentiation to antibody-secreting plasmablasts (Lin et al. 2016); and by increasing blood-brain barrier permeability, thus facilitating entry of pathological AQP4-IgG and inflammatory cells such as granulocytes (Takeshita et al. 2017) into the CNS.

1.2 BACKGROUND ON SATRALIZUMAB

Satralizumab (RO5333787; ENSPRYNG®) is a humanized anti-human 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, which reduces 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 their open-label extension (OLE) periods.

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 (ENSPRYNG) 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, and is currently under review by other Health Authorities worldwide.

A multicenter, open-label, uncontrolled study to evaluate the pharmacokinetics, efficacy, safety, tolerability, and pharmacodynamic effects of satralizumab in children from 2 to less than 12 years of age is planned to start in the first quarter of 2021.

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Satralizumab has been developed for the treatment of NMOSD, a serious condition that has substantial impact on day-to-day functioning of patients. Satralizumab has demonstrated a positive benefit/risk profile in the treatment of NMOSD in adult and adolescents patients who are AQP4 IgG seropositive.

The double-blind periods of both Study BN40898 and Study BN40900 have been completed (see summary of results in Section 1.2), and the studies remain ongoing in their OLE periods. Thus, patients ongoing in the OLE period can still benefit from the continuation of therapy with satralizumab in order to reduce the frequency and severity of NMOSD relapses.

Study WN42349 is an open-label, single-arm, rollover study of satralizumab that allows for patients ongoing in Study BN40898 and Study BN40900 to continue with long-term treatment with satralizumab for up to 3 years. The study aims to collect longitudinal safety and efficacy data. Analyzing the long-term safety and efficacy of satralizumab is of importance to help clinicians make informed decisions on the most appropriate therapy for their patients with NMOSD, a chronic disease requiring long-term maintenance relapse prevention therapy.

Although analysis of efficacy in the subgroup of patients who have AQP4-IgG seronegative NMOSD in Studies BN40898 and BN40900 was inconclusive, individual patients might benefit from continued treatment with satralizumab. Therefore, patients who were AQP4-IgG seronegative at screening in the pivotal studies may be enrolled in

this study, if the investigator considers continued treatment with satralizumab beneficial for the individual patient.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the long-term safety, efficacy, and pharmacokinetics/ pharmacodynamics of satralizumab and will provide continued treatment with satralizumab to patients with NMOSD who completed the OLE periods of the Phase III Studies BN40898 and BN40900. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

The primary safety objective for this study is:

- To evaluate the long-term safety of satralizumab in patients with NMOSD

The secondary safety objective for this study is:

- To further evaluate the risks of serious infections and hepatotoxicity in patients with NMOSD who are treated with satralizumab

Safety outcome measures:

- Incidence and severity of adverse events (AE), adverse events of special interest (AESI), serious AEs (SAE), and selected AEs
- Vital signs (temperature, blood pressure, and pulse rate), clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECG), and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS])

2.2 EFFICACY OBJECTIVES

The efficacy objective for this study is to evaluate long-term efficacy of satralizumab on the basis of the following endpoints:

- Time to first relapse (TFR) and proportion of patients who are relapse-free
- Annualized relapse rate (ARR)
- Change in Expanded Disability Status Scale (EDSS) score
- Time to EDSS worsening and proportion of patients without EDSS worsening
- Change in visual acuity

Further information on the efficacy endpoints is provided in Section 6.5.

2.3 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamics (PD) objective for this study is to further characterize the target engagement in response to satralizumab treatment on the basis of the assessment of IL-6, soluble IL-6R (sIL-6R) and C-reactive protein (CRP).

2.4 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to further characterize the satralizumab PK profile on the basis of the following endpoint:

- Serum concentration of satralizumab at specified timepoints

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of satralizumab on the basis of the following endpoints:
  - Relationship between serum concentration or PK parameters for satralizumab and efficacy endpoints
  - Relationship between serum concentration or PK parameters for satralizumab and safety endpoints
- To evaluate potential relationships between selected covariates and exposure to satralizumab on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for satralizumab

2.5 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to satralizumab on the basis of the following endpoint:

- Incidence of anti-drug antibodies (ADAs) from the first dose of satralizumab in Studies BN40898 or BN40900 (parent studies)

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, and PK endpoints

2.6 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that can provide evidence of satralizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and/or related pathways, on the basis of the following endpoint:

- Relationship between biomarkers in blood (listed in Section 4.5) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.7 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with satralizumab on the basis of the following endpoint:

- Change in EuroQol 5-Dimension Questionnaire (3-level version; EQ-5D-3L) index-based and Visual Analogue Scale (VAS) scores

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This Phase IIIb study is a multicenter, single-arm, open-label study for approximately 127 patients who completed the OLE period of Study BN40898 and Study BN40900, (i.e., were receiving ongoing treatment with satralizumab prior to study entry in this Study WN42349). The study aims to evaluate the long-term safety and efficacy of satralizumab in patients with NMOSD.

Informed consent should be obtained from participants while they are in the parent Studies BN40898 or BN40900. Patients will be transitioned from their ongoing Study BN40898 or BN40900 at a planned dosing visit to allow for continuous dosing with SC satralizumab at a dose of 120 mg (fixed dose) every 4 weeks (Q4W). Safety and efficacy will be assessed at the baseline visit in this study. Efforts will be made to transition patients, at a 12-week or 24-week visit in their visit schedule in the parent study to reduce burden of assessments on patients.

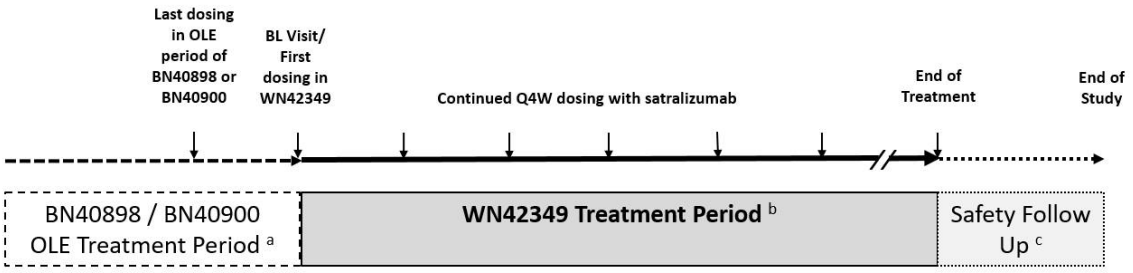
Patients will receive satralizumab as monotherapy or in combination with one of the following background immunosuppressive treatments: AZA, MMF, or oral corticosteroids. Patients aged less than 18 years at the time of informed consent for Study BN40898 can continue treatment with a combination of oral corticosteroids and either AZA or MMF. It is at the discretion of the investigator to modify the background treatment after the baseline visit in this study (see Section 4.4.1). For patients who experience a relapse during the study, appropriate acute relapse/rescue therapy will be initiated.

The treatment period with satralizumab will be 3 years from the date the first patient enrolls in this study. Patients who withdraw from treatment will be asked to complete an End of Treatment visit followed by a Safety Follow Up (SFU) period of 12 weeks from the last dose of study drug prior to the End of Study visit (see Section 4.6).

Patients who experience either a relapse or active infection or do not meet one of the retreatment criteria based on laboratory assessments as specified in Section 5.1 in the parental study, should continue in the ongoing parental study and be transitioned to this study once the patient is stabilized after the relapse, the infection controlled, or the laboratory assessment allows retreatment (see Section 4.1 and Section 4.1.2). If the patient cannot be enrolled within 12 weeks from the initial event preventing the transition to this study, the site should discuss with the Medical Monitor.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Design



BL=baseline; OLE=open-label extension; Q4W=every 4 weeks

[a] Patients are to be discontinued from Studies BN40898 or BN40900 on the day of the BL visit and first subcutaneous injection with satralizumab in Study WN42349.

[b] The Treatment period lasts up to 3 years from the date of enrollment of the first patient.

[c] Safety follow up (SFU),12 weeks after the last injection for all patients who received at least one dose of satralizumab (except for patients who continue with satralizumab treatment outside of this study).

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. The treatment period ends 3 years after the date the first patient enrolls in the study. The end of the study is expected to occur in second quarter of 2024.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 3 years and 3 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Satralizumab Dose and Schedule

Based on PK and PD assessments in the Studies BN40898 and BN40900, satralizumab 120 mg SC, administered Q4W will be used as the maintenance dose in this study.

3.3.2 Rationale for Patient Population

This study will enroll patients with NMOSD who participated in Studies BN40898 or BN40900 with satralizumab and who are currently undergoing ongoing satralizumab treatment in the OLE period of these studies, in order to evaluate the long-term safety, and efficacy of satralizumab treatment.

3.3.3 Rationale for Biomarker Assessments

The following biomarker assessments will be used to investigate the effects of continued satralizumab treatment on the underlying NMOSD pathology:

- Exploratory Biomarker samples will be used for research purposes to identify pathway and/or disease biomarkers, including those that may be reflective of immune cell activity and CNS inflammation or damage.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study includes patients with NMOSD who participated in Study BN40898 or Study BN40900 and are ongoing on satralizumab treatment in the OLE period of these studies prior to study entry in Study WN42349. Approximately 127 patients with NMOSD will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Participated in Study BN40898 or Study BN40900 with satralizumab in NMOSD, are on ongoing satralizumab treatment and were AQP4-IgG seropositive at screening in these studies. Patients with NMOSD who were AQP4-IgG seronegative at screening in Study BN40898 or Study BN40900 can be enrolled if the investigator considers the continued treatment with satralizumab to be beneficial for the patient.
- Signed Informed Consent Form (ICF)
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 3 months after the final dose of satralizumab.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to 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 following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  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, symptothermal, or postovulation 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 ICF.

4.1.2 Exclusion Criteria

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

- Use of prohibited medication (see Section 4.4.2).
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of study drug. Women of childbearing potential must have a negative urine pregnancy test result on the baseline visit prior to initiation of study drug.
- Evidence of any serious uncontrolled concomitant diseases that may preclude patient participation, such as:

  other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
- Known active infection that requires delaying the next satralizumab dose at the time of enrollment [a]

  [a] In case of an active infection, the patient should remain in the parent study, as governed by that protocol, and may enroll in this study once the active infection is controlled.
- NMOSD relapse at the time of enrollment[b]

  [b] In case of a relapse, the patient should remain in the parent study, as governed by that protocol, and may enroll in this study once the patient is stable.
- Laboratory abnormalities at the last assessment in Study BN40898 or Study BN40900 that preclude re-treatment with satralizumab (see Section 5.1.1)[c]

  [c] If a patient does not meet the criteria to restart treatment with satralizumab based on laboratory assessments, the patient should remain in the parent study and the baseline visit should be delayed. The last assessment before enrollment must meet the re-treatment criteria.

4.2 TREATMENT ASSIGNMENT

This is a non-randomized open-label, single-arm study where patients who participated in either Study BN40898 or Study BN40900 continue treatment with open-label satralizumab. After initial written informed consent has been obtained and eligibility has been established for a patient, the study site will obtain treatment kit assignment from an interactive voice or Web-based response system (IxRS). The IxRS interaction (Studies BN40898 or BN40900 completion) should happen no more than 3 days prior the baseline visit.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is satralizumab. Acute relapse rescue therapy administered in case of a NMOSD relapse, and allowed background IST are considered non-investigational medicinal products (see Section 4.4.1).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Satralizumab

Satralizumab will be supplied by the Sponsor as prefilled syringe (PFS) with a needle safety device (NSD). For information on the satralizumab formulation, see the pharmacy manual and/or local prescribing information for Enspryng (satralizumab).

4.3.2 Dosage, Administration, and Compliance

Satralizumab 120 mg will be administered by SC injection in the abdominal or femoral region by the Investigator or designated person after all other study-related procedures have been performed at a site visit.

Patients will receive an SC injection of satralizumab at the baseline visit and every Q4W thereafter, with the last study drug administration on or before the date 3 years after the first patient was enrolled.

Patients who experience a relapse during the study will continue administration of satralizumab at the discretion of the investigator.

In accordance with local regulations, administration of satralizumab prefilled syringes outside of the study site (e.g., self-administration or administration by a caregiver after completing training) may be allowed on scheduled study drug administration days that do not require additional assessments that must be performed on site (Appendix 1).

If study drug cannot be administered within the scheduled visit window and is subsequently administered outside the visit window, the next dose of study drug should be administered on schedule (minimum dosing interval should be 14 days).

The treatment regimen is summarized in Section 3.1.

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

Details on treatment administration (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 adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.

4.3.3 Investigational Medicinal Product 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, with use of the 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 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.

Either the study site will dispose of IMPs according to the study site's institutional standard operating procedure or the IMPs will 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.

See the pharmacy manual and/or or local prescribing information for information on IMP handling, including preparation and storage, and accountability.

4.3.4 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 wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NMOSD
- 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

Data on medications reported as ongoing in Study BN40898 or Study BN40900 up to the day of enrollment in Study WN42349 (e.g., prescription drugs and over-the-counter drugs) will be transcribed into the Concomitant Medications section of the eCRF.

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 from the day of the baseline visit and first administration of satralizumab in this study to the end of treatment visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Background IST with any of the drugs listed below is permitted. The dose must not exceed the dose defined below. Initiation, change or termination of background IST is permitted.
  - AZA[a]: 3 mg/kg/day
  - MMF[a]: 3000 mg/day
  - Oral corticosteroids: 15 mg/day (prednisolone equivalent)

  [a] Combination with oral corticosteroids (15 mg/day [prednisolone equivalent]) can be continued in patients who were aged 12 to 17 years at the time of informed consent in Study BN40898.
- Acute relapse (rescue) therapy for NMOSD relapse; pulse intravenous or oral corticosteroids, intravenous IG, and/or apheresis (including plasma exchange and plasmapheresis).

  Acute relapse therapy should be provided at the discretion of the Investigator after the EDSS/Functional System Score (FSS) assessment has been completed at a relapse assessment visit (except when urgent treatment is required before the patient can undergo this assessment). Satralizumab treatment can be continued as scheduled, concurrently with acute relapse therapy.
- Treatment with corticosteroids (e.g., oral, nasal) for AEs (i.e., indications other than background IST or acute relapse therapy) is permitted; the treatment duration should be kept as short as possible.

4.4.2 Prohibited Therapy

Between the first administration of satralizumab in Study BN40900 or Study BN40898 and the last administration of satralizumab in Study WN42349:

- Other IL-6R inhibitory therapy (e.g., tocilizumab), alemtuzumab, eculizumab, anti–B-lymphocyte stimulator monoclonal antibody (e.g., belimumab), any other treatment for prevention of MS relapse (e.g., interferon, glatiramer acetate, fingolimod, natalizumab, teriflunomide, or dimethyl fumarate), anti-CD4, cladribine, mitoxantrone, anti-CD20 or anti-CD19 treatment (e.g., rituximab, ocrelizumab, ofatumumab, or inebilizumab)
- Total body irradiation, bone marrow transplantation
- Immunization with live or live attenuated vaccines
- Treatment with any investigational agent (other than satralizumab)

4.5 STUDY ASSESSMENTS

4.5.1 Description of 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 (see Appendix 1).

If study drug cannot be administered on the scheduled visit, every effort should be made to perform the assessments at the visit.

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 AE or relapse. The Investigator and/or site staff should encourage the patient to visit the study site for an assessment as soon as possible.

Administration of satralizumab prefilled syringes outside of the study site (home dosing) may be allowed, in accordance with local regulations, only if no on-site assessments are scheduled for that dosing day. Patients should be followed up by phone to monitor if there has been an AE or neurological worsening.

During extraordinary circumstances like the SARS-CoV-2 (COVID-19) pandemic, when patients cannot attend a study site for a scheduled visit, administration of satralizumab outside of the study site will be allowed for all scheduled dosing days. Patients should be followed up by phone around the time of the scheduled visit to confirm patient compliance with study drug treatment, and to collect information on safety and/or neurological worsening the patient might experience. Safety laboratory assessments may be performed at a local laboratory when possible and any clinically significant abnormal laboratory values reported as AEs in the eCRF as described in Section 5.3.

4.5.2 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. All screening evaluations must be reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

No new medical history will be collected. Medical history/baseline conditions, AEs, NMOSD relapses, and concomitant medication reported in Studies BN40898 or BN40900 that are ongoing at the baseline visit in Study WN42349, will be transcribed into the eCRF.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

Limited, symptom-directed physical examinations should be performed at baseline and specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. In addition, height will be obtained at baseline and weight will be obtained at the specified visits.

4.5.5 Vital Signs

Vital signs will include measurements of pulse rate, temperature and blood pressure while the patient is in a seated position for at least 5 minutes. At dosing visits at the study site, vital signs will be measured. Measurement of pulse rate, temperature, and blood pressure should take place immediately before study drug administration.

Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.6 Relapse Assessment

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 study visit that includes an EDSS/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 (see Section 4.5.6.2). An EDSS/FSS assessment by an appropriately Neurostatus qualified examining assessor should be performed in every case of potential relapse.

4.5.6.1 Procedure for Detection of Potential Relapse

All patients with new or worsened neurological symptoms suggestive of a relapse should have the EDSS/FSS 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 list of assessments to be obtained at the relapse assessment visit is listed in Appendix 1. The Investigator should treat the patient as necessary based on his/her evaluation of the symptoms after the completion of relapse assessments. Magnetic resonance imaging 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.

4.5.6.2 Protocol-Defined Relapse

Protocol-defined 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, or adverse reactions to medications). New or worsening neurological symptoms that occur less than 31 days following the onset of a protocol-defined relapse will be considered part of the same relapse (i.e., if two relapses have onset days that are within 30 days of each another, they will be counted only as one relapse), and the onset date used in the analysis will be the onset date of the first relapse. The new or worsening neurologic symptoms must meet either of following:

1. An increase of at least 1.0 point on the EDSS score, or a 2.0 point increase on the EDSS if the EDSS score at baseline in the parent study was zero
2. An increase of at least 2.0 points on one of the appropriate FSS
3. An increase of at least 1.0 point on two or more of the appropriate FSS if the score at baseline in the parent study was one or more
4. An increase of at least 1.0 point in single eye FSS when the score at baseline in the parental study in that eye was one or more

The base 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 protocol-defined relapse.

4.5.7 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. It is a well-established scale that has been used in most major MS clinical trials for many years (Kurtzke 1983). Based on a standard neurological examination, the EDSS quantifies disability in functional systems and allows neurologists to assign an FSS in each of these. Each of the FSS is an ordinal clinical rating ranging from 0 to 5 or 6. These functional ratings are then used in conjunction with observations and information concerning gait and the use of assisting devices to rate the EDSS. The EDSS is an ordinal scale with values from 0 points (normal neurological examination) up to 10 points (death), increasing in increments of 0.5 points.

In addition to those FSS, the single eye FSS (see the material for EDSS/FSS scoring) is assessed to confirm whether a relapse has occurred.

The EDSS/FSS assessment (see Appendix 2) should be performed by the same qualified assessor, whenever it is feasible.

4.5.8 Visual Acuity/Function Testing

Visual function testing will be performed with eye charts.

Visual acuity will be measured by a Snellen 20-foot wall chart. The test will be performed monocularly and patients may use their habitual distance glasses or contact lenses.

The same visual acuity testing method is to be employed for all study visits for each patient.

Other visual function (e.g., visual fields) will be assessed for EDSS/FSS assessment as well as visual acuity.

4.5.9 EQ-5D-3L

The EQ-5D-3L scale is a generic measure of health related quality of life that rates patient health state looking at five specific dimensions such as mobility, self-care, usual activity, pain/discomfort and anxiety/depression and score their general health state.

4.5.10 Columbia-Suicide Severity Rating Scale

The C-SSRS is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit, see Appendix 4). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS baseline from the parent study will be used, and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

4.5.11 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests (except urinalysis and pregnancy tests) will be sent to the Central Laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. If a patient cannot visit the study site in extraordinary circumstances like the SARS-CoV-2 (COVID-19) pandemic, laboratory tests may be performed at a local laboratory in accordance with local regulations.

- Hematology (hemoglobin, hematocrit, platelet count, INR, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells])
- Serum chemistry (sodium, potassium, chloride, calcium, phosphorous, ferritin, BUN, creatinine, total bilirubin (TBL), fibrinogen, total protein, albumin, ALT, AST, alkaline

phosphatase, gamma-glutamyl transpeptidase, LDH, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatine kinase, uric acid) complement tests (C3, C4, and CH50)

- CRP
- For patients with positive total hepatitis B core antibody status and undetectable hepatitis B viral DNA at screening in Study BN40898 or Study BN40900, hepatitis B viral DNA measurements will be continued to be performed regularly at approximately 24-weekly intervals during Study WN42349.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urinalysis (urinary glucose, urinary protein, urinary occult blood, urobilinogen) will be conducted at each site by dip stick.
- Pregnancy test

  All female patients of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at the study site at the baseline visit confirmed as negative before the administration of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During the study pregnancy tests (serum or urine) must have a sensitivity of at least 25 mIU/mL. Patients who do not meet the criteria for childbearing potential during the study (e.g., confirmed postmenopausal status) will not require further pregnancy testing. In order to qualify for and to remain in the study, the patient must have a negative pregnancy test, evidence of surgical sterility or evidence of post-menopausal status. Postmenopausal status is defined as any of the following: natural menopause with menses >1 year ago; radiation-induced with last menses >1 year ago, or bilateral oophorectomy.

The following samples will be sent to central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK and PD analysis (IL-6, sIL-6R)
- Serum samples for immunogenicity analysis (ADA)
- Serum and plasma samples for exploratory research on biomarkers and biomarker assay development

Exploratory biomarker research may include, but will not be limited to, analysis of anti-AQP4 antibodies and GFAP over time.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed

no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

- Serum samples collected for PK or 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 CSR has been completed.
- Plasma and serum samples collected for biomarker research and biomarker assay development will be destroyed no later than 10 years after the final CSR 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.

4.5.12 Electrocardiograms

ECGs should be performed prior to any blood draws. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs for each patient should be obtained from the same machine whenever possible.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. ECG characteristics, including heart rate, QRS duration, and RR, PR, and QT intervals, will be recorded on the eCRF. QT interval corrected for heart rate with use of Fridericia's formula (QTcF) will be calculated post hoc. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 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, and 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.

Leftover serum and plasma 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 adverse events or can lead to improved adverse event 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

4.5.13.2 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 ICF by each site's Institutional Review Board or Ethics Committee (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 4.5.13) will not be applicable at that site.

4.5.13.3 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, NMOSD, or the development of disease related tests or tools:

- Leftover blood (serum and plasma) samples 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 whole genome sequencing, whole exome sequencing, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing and whole exome sequencing 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.

The 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 ICF and applicable laws (e.g., health authority requirements).

4.5.13.4 Confidentiality

The 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 ICF (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.

4.5.13.5 Consent to Participate in the Research Biosample Repository

The ICF 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.

4.5.13.6 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.

4.5.13.7 Monitoring and Oversight

The 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 ICF. 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.

4.5.14 Assessments at the Treatment Discontinuation and End of Study Visit

The treatment discontinuation (EOT) visit is for patients who discontinue from satralizumab treatment in this study. At this visit, a complete set of assessments will be conducted. If the EOT coincides with a scheduled visit, the EOT visit should be completed instead of the scheduled visit. Patients will be asked to attend an End of

Study (EOS) visit 12 weeks after the last dose of satralizumab to complete the SFU period.

Patients who decide to continue treatment with satralizumab outside of this study have to complete the EOT visit, but they will not have to complete the SFU.

After the final study visit, AEs should be reported and followed as outlined in Section 5.5 and Section 5.6.

See Appendix 1 for the schedule of activities performed at the EOT and EOS visits.

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
- Pregnancy
- Meet the discontinuation criterion in the risk mitigation strategy (see Section 5.1).
- Continuation of treatment should be carefully assessed in case of multiple or severe relapses that are not in keeping with the patients NMOSD history or trajectory.

  The investigator should consult with the Medical Monitor if these relapses meet this criterion.
- Malignancy or a severe allergic or anaphylactic reaction to satralizumab.

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

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
- Adverse event
- 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. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

When participants complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed. Patients will return to the clinic for a study discontinuation/EOS visit 12 weeks after the final dose of satralizumab.

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:

- 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 current satralizumab Investigator's Brochure 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 AEs. 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 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. In the double-blind period of Phase III Studies BN40909 and BN40900, the rates of overall infections and serious infections in patients treated with satralizumab monotherapy or in combination with IST were not higher than the placebo groups.

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.
- The administration of satralizumab should be delayed until the active infection is controlled.
- If a patient develops a serious infection, administration of satralizumab is to be interrupted until the infection is resolved. The treating physician should conduct a benefit-risk assessment before resuming treatment with satralizumab.
- Live or live attenuated vaccines should not to be given during the course of the study as clinical safety has not been established.

For patients with NMOSD participating in this study, therapies used to treat NMOSD (i.e., corticosteroids, AZA, MMF) have been shown to be associated with infections, particularly serious infections.

5.1.1.2 Serious Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions are considered a potential risk for all biologic medications, including satralizumab. As of February 2020, no anaphylaxis or serious hypersensitivity reactions have been reported in clinical trials with 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:

- If an anaphylactic reaction or other serious hypersensitivity reaction occurs, satralizumab should be discontinued. 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 be instructed to seek medical attention if they experience symptoms of hypersensitivity reaction outside of the clinic.
- Administration of satralizumab prefilled syringes outside of the study site might be allowed (see Section 4.3.2) if the investigator determines that it is appropriate. 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 serious allergic 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

It has been reported that IL-6 appears to have a hepato-protective effect on various forms of liver injury and promotes hepatocyte regeneration.

In the double-blind period of Studies BN40898 and BN40900, mild and moderate elevations of liver transaminases have been observed with satralizumab treatment. Most elevations were <5×upper limit of normal (ULN) and resolved while on treatment with satralizumab. Elevations of ALT or AST >3×ULN were not associated with increases in TBL.

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 interruptions based on transaminases are shown in Table 1.

Table 1 Hepatic Enzyme Risk Mitigation

AST or ALT values	Action
>1 to 3× ULN [a]	• 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 [a].
>3 to 5× 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 3× ULN. If at least one of following associated, satralizumab should be discontinued: • TBL >2× ULN and/or • INR >1.5× ULN and/or • Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
>5× 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.
a ULN or patient's baseline value in the parent study, whichever is higher.

5.1.1.4 Neutropenia

In the completed Studies BN40898 and BN40900 double-blind period of the Phase III studies, decreases in neutrophil counts have occurred following treatment with satralizumab. These episodes of neutropenia were not associated with serious infections. The majority of neutrophil decreases were transient or intermittent.

Recommended dose interruption based on ANC results is shown in Table 2.

Table 2 Neutropenia Risk Mitigation

ANC (/µL)	Action
>1,000	Maintain dose
500–1,000	• If neutropenia persists, satralizumab should be interrupted until ANC is above 1,000/µL. • If ANC was under 1,000/µL 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

In the double-blind period of Studies BN40898 and BN40900, decreases in platelet counts have occurred following treatment with satralizumab. The majority of the decreased platelets were transient and not below 75×10^9/L. Treatment-related reduction in platelets was not associated with bleeding events in clinical trials.

Recommended dose interruption based on platelet counts are shown in Table 3.

Table 3 Thrombocytopenia Risk Mitigation

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

5.1.1.6 Elevations in Lipid Parameters

In the double-blind period of Studies BN40898 and BN40900, elevations in total cholesterol and triglycerides were observed more often in patients treated with satralizumab compared with placebo. The elevations in lipid parameters did not require dose interruption. Patients should be managed according to local guidelines.

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 CYP450 Enzyme Normalization

No interaction studies have been performed. Population PK analyses did not detect any effect of AZA, OCs, or MMF 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)

As of February 2020, gastrointestinal (GI) perforations have not been reported in clinical trials with satralizumab treatment, with the exception of one patient who developed a GI perforation as a complication of a surgery.

Gastrointestinal perforations have been reported rarely in patients with RA administered with other anti IL-6R antibodies. Anti-IL6R antibodies 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, should be evaluated (X-ray, computerized tomography [CT] scan, etc.) 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

Although malignancies have been reported in patients given other IL-6R antibodies, there have been no reports to date that there is an appreciably increase in the occurrence of malignancies. No increased risk of malignancies has been observed in clinical trials with satralizumab treatment.

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. If symptoms suggestive of a demyelination-related disease, other than NMOSD, are observed, differential diagnosis of the patient should be performed.

5.1.3 Concomitant Immunosuppressive Treatment

Patients receiving background treatment with allowed ISTs should also be informed of the risks associated with taking corticosteroids, AZA, or MMF. For additional safety data, see the local prescribing information.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Treatment Interruption

Satralizumab treatment may be temporarily suspended in patients who experience an AE 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 AEs, including SAEs and AESIs, 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 AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. Therefore, an AE can 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 Section 5.3.5.9, and Section 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., 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)

Acute, new, or worsening neurological symptoms considered to be an NMOSD relapse will not be reported as Adverse Events. NMOSD relapses will be recorded only on a pre-specified eCRF “NMOSD relapse” form.

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE 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 AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 exception to this definition of an SAE is in the rare event that a patient is hospitalized following an NMOSD relapse, as long as the reason for hospitalization is to receive standard treatment with rescue therapy for clinical relapse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe] criteria; 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 AE recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor within 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 AEs. The data should be recorded in the eCRF on the AE page and on the special form for that particular AE.

- Infections that require treatments with intravenous antibiotics, antifungals, or antivirals
- Opportunistic infections that require treatments with oral antibiotics, antifungals, or antivirals
- Injection-related reaction (IRR; an AE that occurs within 24 hours after study drug injection except where the event is not considered an allergic reaction)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (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 AE 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

Adverse Events with onset prior to the baseline visit will be reported in the eCRF of either Study BN40898 or Study BN40900.

Investigators will seek information on AEs at each patient contact. All AEs, 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 initiation of study drug, all AEs will be reported until 3 months after the final dose of study drug.

Instructions for reporting AEs that occur after the AE 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 AE 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

Table 4 provides guidance for assessing AE severity.

Table 4 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see 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 AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Injection Related Reactions

Injection-related reaction is defined as the event that occurs within 24 hours after study drug injection. An IRR should be recorded on the IRR page of the eCRF as "injection-related reaction", and individual signs and symptoms should also be captured on the IRR page of the eCRF.

But exceptive conditions are as follows:

- Anaphylaxis or anaphylactic shock:

  If the event is judged as anaphylaxis or anaphylactic shock by Investigator's discretion, it will be recorded on the Adverse Event page of the eCRF.

- Obviously not allergic reaction (e.g., infection):

  If the event is judged not to be an allergic reaction or injection related reaction, it will be recorded on the Adverse Event page of the eCRF

5.3.5.2 Diagnosis versus Signs and Symptoms

For AEs, 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, AEs 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

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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 or 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 TBL (>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 TBL >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 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 AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization because of 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 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 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

The contact details for the Emergency Medical Contacts will be provided in the Investigator (Site) File. Medical Monitor names and contact information will be included.

Contact Information for All Sites

Medical Monitor [redacted] M.D.

Telephone No.: [redacted]

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

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 3 months 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 with use of 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 >3 months after the final dose of study treatment 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 with use of 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 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes 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 with use of the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 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.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male 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). Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male 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, a PFS with an 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; see 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 3 months [see Section 5.3.1] 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 with use of 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 document listed below:

- Satralizumab Investigator's Brochure

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 purpose of this study is to assess safety and efficacy of long-term administration of satralizumab. Patients who are on treatment with satralizumab and ongoing in the OLE period of Study BN40898 or BN40900 can be enrolled in this study. For analysis

purposes, data of both parental studies and this study will be combined, where appropriate.

This section outlines the statistical analysis strategy and procedures for the study. A detailed methodology for statistical analyses of the data collected in this trial and the analyses in conjunction with the parental trials will be documented in a Statistical Analysis Plan (SAP).

6.1 ANALYSIS POPULATIONS

6.1.1 Efficacy Analysis Populations

The intent-to-treat (ITT) population, which will serve as the primary population for the analysis of efficacy, consists of all randomized patients in the double-blind period of the parent Studies BN40898 and BN40900. The ITT population will encompass all patients from the parent studies, even if they do not participate in this study. Patients will be analyzed as randomized for analysis purposes in the ITT, even if patients randomized to placebo received satralizumab in the OLE period of the parent study.

In addition, all efficacy analyses will be conducted from the first dose of satralizumab in the parent studies. This analysis population is in line with the All-Patients-Treated (All satralizumab [ALLSA]) Population. Patients that were directly enrolled in the extension period of the parental studies will also be included in these analyses.

6.1.2 All-Patients-Treated Population

The ALLSA population will be defined as all enrolled patients who received at least one dose of satralizumab at any time either during the parent studies or this study.

6.1.3 Safety Analysis Populations

All safety variables will be analyzed on the basis of the Safety Population (SAF). The SAF population will include all randomized or enrolled patients who have received at least one dose of study drug either during the parental studies or this study. It will encompass all patients from the parent studies, even if they do not participate in this study. Patients will be analyzed as treated for analysis purposes in the SAF.

6.1.4 Pharmacokinetics Per-Protocol Set and Pharmacodynamics Analysis Population

The Pharmacokinetics Per-Protocol (PK-PPS) and immunogenicity (ADA) Set will include all patients in the SAF with at least one valid post-dose concentration or ADA titer result with a dosing record and sampling time. Pharmacodynamics variables (e.g., IL-6, sIL-6R, CRP) will be analyzed with use of the SAF population.

6.2 DETERMINATION OF SAMPLE SIZE

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 127 patients but will be

determined by the number of patients who complete Studies BN40898 and BN40900 and enroll in this study.

6.3 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, region, race, AQP4-IgG serostatus, and EDSS) will be summarized with use of means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented for all enrolled patients. In addition, descriptive summaries for the demographic and baseline characteristics at the baseline of the parental trials and at the time point of the first satralizumab dose for all originally randomized or enrolled patients will be presented.

6.5 EFFICACY ANALYSES

All efficacy analyses will be based on the ITT population and the ALLSA population. For both populations, data from Study WN42349 will be combined with data from the Studies BN40898 and BN40900.

All efficacy endpoints are secondary endpoints. The definitions are in line with Studies BN408989 and BN40900 to investigate long-term efficacy by summarizing the data of the parental studies and this Study WN42349.

Time to First Relapse

The time to first relapse (TFR) efficacy endpoint is based on several endpoint definitions to accommodate different estimand strategies. The most important intercurrent event is the use of therapy for the treatment of an acute NMOSD relapse (rescue therapy).

For the treatment policy strategy, the use of rescue therapy is ignored. Therefore, in the analysis for the treatment policy estimand the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the first protocol-defined relapse as assessed by the investigator (iPDR).

The time point of relapse onset is defined as the time at which the patient experiences any new or worsening neurological symptoms representing NMOSD clinical relapse(s). For patients who have not relapsed at the time of analysis, the TFR will be censored at the clinical cutoff date (CCOD) or at time of withdrawal from study. There are no other censoring reasons.

For the composite strategy estimand, the use of rescue therapy (as defined in Section 4.4.1) for the treatment of acute relapses will be considered as an event in addition to the iPDR. Therefore, in the analysis for the composite estimand, the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the iPDR or first use of rescue therapy, whatever comes first. Patients are either censored at the CCOD or at the time of withdrawal from study if they did not have an iPDR or did not receive rescue therapy. There are no other censoring reasons.

In addition, four further definitions of relapse are also analyzed:

- For the time to first clinical relapse, the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the first clinical relapse. Clinical relapses are all relapses that occurred during the parental studies or this study, even if they did not meet the PDR definition. Patients are censored at the CCOD or at the time of withdrawal from study if they did not have a clinical relapse. There are no other censoring reasons.
- For the time to first treated clinical relapse, the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the first treated clinical relapse. Treated clinical relapses are all relapses that occurred during the parental studies or this study and that were treated with rescue therapy. The relapses do not need to meet the PDR definition. Patients are censored at the CCOD or at the time of withdrawal from study if they did not have a treated clinical relapse. There are no other censoring reasons. This definition is similar to the time to iPDR or rescue therapy definition and another way of incorporating the intercurrent event of rescue therapy.
- For the time to first clinical relapse with EDSS change from randomization/first dose of satralizumab, the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the first clinical relapse that has an EDSS change from baseline in line with the change definition for the PDR. For the PDR definition, the EDSS at relapse is compared with the EDSS at the last regular visit. In this definition the EDSS at relapse is compared with the EDSS at the time of randomization in ITT or at the time of first dose of satralizumab in ALLSA. Patients are censored at the CCOD or at the time of withdrawal from study if they did not have a clinical relapse that fulfills the EDSS change criteria. There are no other censoring reasons.
- For the time to first treated clinical relapse with EDSS change from randomization/first dose of satralizumab, the TFR is defined as the time from randomization in ITT or first dose of satralizumab in ALLSA to the first treated clinical relapse that has an EDSS change from baseline in line with the change definition for the PDR. For the PDR definition, the EDSS at relapse is compared with the EDSS at the last regular visit. In this definition the EDSS at relapse is compared with the EDSS at the time of randomization in ITT or at the time of first dose of satralizumab in ALLSA. Patients are censored at the CCOD or at the time of withdrawal from study if they did not have a clinical relapse that fulfills the EDSS change criteria. There are no other censoring reasons.

In the analyses from randomization, the goal is to test the equality of the TFR distribution in the satralizumab (SA237) and Placebo arms:

$$H_0: TFR_{SA237}=TFR_{placebo} \text{ versus } H_1: TFR_{SA237} \neq TFR_{placebo}$$

A stratified two-sided log-rank test with use of strata of study ID of the parental study and geographical region will be used.

The Kaplan–Meier method will be used to estimate the TFR distribution for each treatment group. The Kaplan–Meier curve will provide a visual description of the differences across treatment groups. In addition, estimates of the treatment effect will be expressed as HR and 95% confidence intervals (CIs) with use of a stratified study ID of the parental study and geographical region) Cox proportional-hazards model. The Median TFR is not expected to be reached in this study at the time of the primary analysis; hence, every 6-months, relapse-free rates and their 95% CI will be used to describe TFR distribution in addition to the HR.

In the analyses from first dose of satralizumab no comparator is available to the satralizumab arm. Therefore only the Kaplan–Meier curves will be provided together with relapse-free rates and corresponding 95% CI at every 6 months.

Annualized Relapse Rate

All relapses for each eligible patient in the parental studies and in this study will be recorded throughout all study periods (parent study DB and OLE periods and this study).

The ARR will be analyzed from randomization in ITT and from first dose of satralizumab in ALLSA. In both analyses the ARR is calculated as the total number of relapses experienced divided by the person-years of the whole study period. The unadjusted 95% CI will be presented based on the Poisson distribution.

For comparing the difference between the two treatment arms, negative binomial regression model will be used with ARR as response variable and treatment group, study ID of the parental study, and geographical region as covariates. In the ALLSA analyses, treatment group will not be included because all patients will receive satralizumab in this analysis.

In addition, the ARR by year of exposure will be estimated with use of a GEE Poisson regression model with repeated measurements and an unstructured covariance matrix, adjusted by Study Identifier of the parental study, and exposure year. Log-transformed patient years are included as an offset variable. In these analyses the overall ARR for the whole period is additionally estimated by a Poisson regression model. When comparing the difference between the randomized treatment arms of the parental studies, treatment is included as an additional covariate and the adjusted ARR and corresponding 95% Cis are presented for each arm and year.

All ARR analyses will be conducted for iPDRs, clinical relapses and treated clinical relapses.

Change in Expanded Disability Status Scale Score

The EDSS score will be assessed on scheduled visits during the study. The mean change in EDSS scores from randomization/first dose of satralizumab to every 24 weeks after the randomization/first dose of satralizumab visit will be analyzed.

Time to EDSS worsening based on the definition for PDR is estimated with a Cox regression with treatment group, and Study Identifier of the parental study as covariates. The HR and 95% CI for the treatment groups are estimated in this model, the p value is calculated on the basis of the stratified log rank test. In addition, Kaplan-Meier estimate of event-free rates will be provided for every 24 weeks and Kaplan-Meier curved will be estimated.

These analyses are done for the double-blind period and the combined double-blind and OLE periods. When all randomized patients of both periods are analyzed together, patients are analyzed as randomized, even if patients randomized to placebo receive satralizumab in the OLE period. In addition, all patients are analyzed from first dose of satralizumab. In this case, only Kaplan–Meier estimate of event-free rates will be provided for every 24 weeks and Kaplan–Meier curved will be estimated since no comparison can be made.

In the same way, time to severe EDSS worsening is analyzed. Severe EDSS worsening is defined as a change of at least 2 points on the EDSS scale from randomization/first dose of satralizumab.

Change in Visual Acuity (Snellen Chart)

Visual acuity will be measured by a Snellen 20-foot wall chart. The test will be performed monocularly and patients may use their habitual distance glasses or contact lenses.

The same visual acuity testing method is to be employed for all study visits for each patient.

The mean change in logMAR Visual Acuity scores from randomization/first dose of satralizumab to every 24 weeks after the randomization/first dose of satralizumab visit will be analyzed.

Use of Acute Relapse/Rescue Therapy

The use of rescue therapy is based on treated clinical relapses. If a patient has at least one treated clinical relapse, then this patient is counted as a patient with rescue therapy use. The use of rescue therapy will be analyzed with a logistic regression model with treatment group, Study Identifier of the parental study and geographical region as covariates. The odds ratio, corresponding 95% CI, and p value for the treatment group

will be reported. This analysis will be conducted for the entire study period of each patient and also for the period after the first dose of satralizumab. In the analysis from first dose of satralizumab, treatment group will not be included as a covariate.

6.5.1 Further Analyses

6.5.1.1 Subgroup Analysis

The subgroup summary tables for TFR based on iPDRs will be presented by AQP4-IgG serostatus at screening (positive/negative), age (adolescents/adults) at randomization, geographical region (Asia, Europe, North America), weight at randomization, first dose of satralizumab, ARR at randomization (less than one/one/more than one), most recent attack at randomization (first attack vs relapse), prior therapy at randomization (B-cell depleting therapy/immunosuppressants/others), EDSS at randomization/first dose of satralizumab (≤2.5: no or minimal disability/>2.5), race, and Study Identifier of parental study. ARR was a stratification factor in Study BN40898 and is calculated on the basis of the relapses entered in the medical history for Study BN40900. Most recent attack and prior therapy were stratification factors in Study BN40900 and are only available for patients enrolled from this trial.

Further details will be described in the SAP.

6.6 SAFETY ANALYSES

All safety analyses will be performed on the SAF. Safety variables to be assessed are AEs, AESIs, SAEs, selected AEs, injection site reactions, patient withdrawals due to AEs, change in 12-lead ECGs, measurements of laboratory parameters, and vital signs (including body weight).

Summary tables for number and percentage of patients and rate of AEs per 100PY with adverse drug reactions (i.e., AEs related to study drug as assessed by the investigator) will be generated.

Adverse events will be summarized by System Organ Class (SOC) and Preferred Term (PT), on the basis of Medical Dictionary for Regulatory Activities (MedDRA) coding, and grade of severity. The incidence of treatment emergent AEs will also be displayed by severity and relationship to the study drug, respectively. In addition, the incidence of AEs leading to withdrawal from treatment and SAEs will be tabulated.

Incidence of Selected AEs (see Section 5.2.4) will be tabulated. AEs will be further analyzed according to whether they meet Sampson's criteria for diagnosis of anaphylaxis (Sampson et al. 2006).

Laboratory values (including hematology, blood chemistry, and urinalysis), frequencies of laboratory abnormalities, vital signs (temperature, blood pressure, and pulse rate), 12-lead ECG, and suicidality (C-SSRS) will be summarized. Measurement and change from baseline in continuous laboratory parameters (hematology, clinical chemistry, and

urinalysis), continuous ECG, vital signs (blood pressures and pulse rate), and body weight will be summarized with use of descriptive statistics. Body weight by change from randomization/first dose of satralizumab of more than/less than 7% and 15% will also be analyzed descriptively. 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 with their baseline status. Numbers of patients who meet the marked abnormality criterion will also be presented.

6.7 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

The PK analysis population is described in Section 6.1. The trial will evaluate the PK characteristics of satralizumab treatment by summary statistics and non-linear mixed effects analysis (population PK).

The serum concentration at each sampling timepoint will be described irrespective of whether patients receive acute relapse/rescue therapy, change background (baseline) treatment for NMOSD, miss a dosing or if the study drug administration is delayed. Individual and mean serum–concentration-versus-time curves will be plotted.

Descriptive statistics, such as geometric mean, geometric coefficient of variance and the 95% CI for the geometric mean for the serum satralizumab concentration, as well as arithmetic mean, standard deviation, median, minimum, and maximum on the measured serum satralizumab concentration, IL-6, sIL-6R, and CRP will be calculated by visit and per defined time window post-dose for the PK-PPS.

An exploratory analysis to identify any potential relationship among serum satralizumab concentration and PD (CRP, IL-6, sIL-6R) will be performed. These results will be described and reported in a separate analysis report.

Non-linear mixed effects analysis will be performed to analyze the satralizumab concentration–time data collected in the trial. The model to be used was previously developed on the basis of PK data from adult healthy volunteers and adult/adolescent patients with NMOSD (Satralizumab Simulation Report; available upon request). Further model development may be undertaken if needed in order to achieve a satisfactory description of the data, and the data from this study may be pooled with data from other studies with satralizumab. Population and individual PK and exposure parameters will be generated on the basis of the model. The results of the population PK analysis will be reported separately from the CSR.

Further details are described in a separate Data Analysis Plan.

6.8 IMMUNOGENICITY ANALYSES

The percentage of patients who have positive or negative ADA results will be tabulated. PK/PD, efficacy parameter and safety will be summarized by anti-drug antibody status.

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than fourfold of the titer of the baseline sample (treatment-boosted ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples that is greater than fourfold than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.9 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.10 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-3L health utility index-based will be calculated at specified timepoints.

The EQ-5D-3L is a participant-answered questionnaire measuring 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 3 possible response categories: 1) no problems; 2) some problems; 3) severe problems. Therefore, EQ-5D-3L is able to represent 243 (3^5) distinct health states. These states may then be converted into a single index value by with use of the time trade-off (TTO) based tariff methods. The best possible answer would be (1,1,1,1,1) and the worst possible answer would be (3,3,3,3,3). A shift table will be used to evaluate the number and percentage of patients having a different post-baseline status when compared with their baseline status. The mean change in EQ-5D-3L score will be analyzed from randomization/first dose of satralizumab to every 24 weeks after the randomization/first dose of satralizumab visit.

6.11 INTERIM ANALYSES

No formal confirmatory effectiveness or safety interim analyses are planned. Exploratory analyses of selected endpoints and in particular periodic analyses of safety data are planned to be performed during the course of the study.

6.12 HANDLING OF MISSING DATA

For TFR, patients who have not experienced relapses according to the respective relapse definition, the TFR will be censored at the CCOD or study withdrawal.

For all other efficacy endpoints missing data will not be imputed.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for 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 Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central and specialty laboratory data will be sent directly to the Sponsor, with use of 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, patient-reported outcomes, 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 (if applicable), ICFs, 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 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 ICF (and ancillary sample ICFs such as an Assent Form or Mobile Nursing ICF, 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 ICFs 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 ICF 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 with use of 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 ICFs, 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 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events 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 ICF (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 9.5).

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 CSRs and other summary reports will be provided upon request (see Section 9.5).

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, ICFs, 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. 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., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. 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 and managed by F. Hoffmann–La Roche Ltd; Chugai Pharmaceutical Co., Ltd. is co-sponsor in Taiwan and Japan. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 56 sites globally will participate to enroll approximately 127 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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 CSRs and other summary reports will be made available upon request. For more information, see 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 CSR. 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

		Treatment Period [b]								Safety follow-up period
	Screening [a]	BL [a]	Every 4 weeks [c]	Every 12 weeks	Every 24 weeks	Delayed dosing [d]	Relapse assessment	Unscheduled assessments [e]	End of treatment [f]	End of study [g]
Week (Window in days)	**While in parent study to –1**	**Day 1**	**(±7)**	**(±7)**	**(±7)**	**-**	**-**	**-**	**-**	**(±7)**
Informed consent	x									
Inclusion/exclusion criteria	x	x								
Demographic data		x								
Satralizumab injection (SC)		x	x [h]	x [h]	x [h]	x [h]				
Body weight and height [i]		x			x				x	x
Physical examination		x		x	x	x	x	x	x	x
Vital signs [j]		x		x	x	x	x	x	x	x
ECG [k]		x			x			x	x	x
Pregnancy test [l]		x		x	x			x	x	x
Laboratory tests [m]		x		x	x			x	x	x
Hepatitis B viral DNA [n]		x			x			x	x	x
C-SSRS		x			x			x	x	x
EQ-5D		x			x			x	x	x
EDSS/FSS		x			x		x	x	x	x
Adverse events	Monitor and record throughout the study									

Appendix 1: Schedule of Activities (cont.)

		Treatment period [b]								Safety follow-up period
	Screening [a]	BL [a]	Every 4 weeks [c]	Every 12 weeks	Every 24 weeks	Delayed dosing [d]	Relapse assessment	Unscheduled assessments [e]	End of treatment [f]	End of study [g]
Week (Window in days)	While in parent study to –1	Day1	(±7)	(±7)	(±7)	-	-	-	-	(±7)
Concomitant medications	Monitor and record throughout the study									
Relapse Assessment	Monitor and record throughout the study									
Visual acuity/ function [o]		x			x			x	x	x
PK sample		x			x		x	x	x	x
PD sample [p]		x			x		x	x	x	x
ADA sample		x			x		x	x	x	x
Biomarker sample [q]		x			x		x	x	x	x

ALP=alkaline phosphatase: BL=baseline; BUN=blood urea nitrogen; CK=creatine kinase; C-SSRS=Columbia-Suicide Severity Rating Scale; DBP=diastolic blood pressure; ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; FSS=functional status scale; γ-GTP=gamma glutamyl transpeptidase; Hb=hemoglobin; hCG=human chorionic gonadotropin; HCT=hematocrit; HBcAb=total hepatitis B core antibody; HBsAb=antibody to hepatitis B surface antigen; HBV=hepatitis B virus; CRP=C-reactive protein; IL-6=Interleukin-6; INR=international normalized ratio; IU=International Units; NMOSD=neuromyelitis optica spectrum disorder; PK=pharmacokinetics; PLT=platelet; sIL-6R=soluble IL-6 receptor; SBP=systolic blood pressure; SC=subcutaneous; SFU=safety follow-up;.

[a] Patients ongoing on treatment with satralizumab in Studies BN40898 and BN40900 will have their study completion in Study BN40898 or BN40900 on the same day as the BL visit in this study to allow continuous treatment. Patients will complete the BL visit and complete the next following visit on the visit schedule the patient was on in the parent study prior to study entry. To reduce the burden on patients and sites, the optimal timepoint to transition the patient is when the patient's visit schedule in the parental study falls on either a 12 or 24 week visit.

[b] If patients cannot physically attend a visit at the study site, e.g. in extraordinary circumstances such as the SARS-CoV-2 (COVID-19) pandemic, all efforts should be made to follow up with patients around the time of the scheduled visit by phone to collect any information on safety and/or neurological worsening the patient might experience and to confirm patient compliance with study treatment. Any issues occurring during the dosing period outside of the study site should be reported.

[c] In accordance with local regulations, administration of satralizumab outside of the study site (home dosing) is allowed. Patients will be followed up by study site personnel through phone calls to monitor compliance and perform safety assessments.

[d] Delayed dosing visit, in the event that the study drug cannot be administered at the scheduled visit but all other planned assessments are performed at the scheduled visit. Minimum dosing interval should be 14 days.

[e] Unscheduled assessments performed at unscheduled (non-dosing) visits will depend on the clinical need of the patient. Tests/assessments may be done as appropriate.

[f] A treatment discontinuation (EOT) visit will be performed for patients who permanently discontinue from satralizumab treatment in this study. At this visit a complete set of assessments will be conducted, if the EOT coincides with a scheduled visit, the EOT visit should be completed instead of the scheduled visit.

[g] SFU: Patients will be asked to attend an EOS Visit 12 weeks after the final dose of satralizumab to complete the safety follow up period. Patients who decide to continue treatment with satralizumab outside of this study will not have to complete the SFU.

[h] In accordance with local regulations, administration of satralizumab prefilled syringes outside of the study site (e.g., self-administration or administration by a caregiver after completing training, administration by the patient's [local] general physician) will be allowed at all dosing visits in extraordinary circumstances such as the SARS-CoV-2 (COVID-19) pandemic.

[i] Body weight is to be determined to the nearest 0.1 kg. For body weight measurements, the patient should wear clothes, without any shoes, outerwear, or accessories. Height will be recorded at baseline only.

[j] Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and while the patient is in a seated position for at least 5 minutes

[k] ECG should be performed prior to blood draws.

[l] For females of child-bearing potential urine dipstick pregnancy test [sensitivity of at least 25 mIU/mL β-hCG] will be performed.

[m] RBC, Hb, Ht, WBC, WBC differentiation, PLT, INR, fibrinogen, total protein, albumin, total bilirubin, ALP, AST, ALT, γ-GTP, LDH, total cholesterol, LDL, HDL, triglyceride, ferritin, BUN, creatinine, CK, Na, Cl, K, Ca, P, complement (CH50, C3, C4), uric acid, urinary glucose, urinary protein, urinary occult blood, urobilinogen. If patients cannot physically attend a visit at the study site for safety blood draw in extraordinary circumstances such as the SARS-CoV-2 (COVID-19) pandemic, safety lab tests should be performed, in accordance with local regulations, at a local laboratory when possible and any clinically significant abnormal laboratory values reported as AEs in the eCRF as described in Section 5.4.

[n] Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb was not clearly associated with vaccination against hepatitis B virus and HBV DNA was negative at screening or for whom HBcAb was positive and HBV DNA was negative at screening in BN40898 or BN40900.

[o] Separate visual function testing is not required if it is implemented with FSS assessment.

[p] IL-6, sIL-6R, CRP

[q] Biomarker sample (e.g., including, but not limited to, anti-AQP4-Ab)

Appendix 2
EDSS/FSS Assessment Form

The actual forms will be provided to the sites and should be used for assessment.

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION

Patient

Date of Birth (04-Jun-1980)

Centre Nr/Country

Name of EDSS rater

Date of Examination

SYNOPSIS

1. Visual
2. Brainstem
3. Pyramidal
4. Cerebellar
5. Sensory
6. Bowel/Bladder
7. Cerebral

Ambulation Score

EDSS Step

Signature

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity CC SC		
Visual fields		

Scotoma

* Disc pallor

FUNCTIONAL SYSTEM SCORE

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION

Extraocular movements (EOM) impairment

Nystagmus

Trigeminal damage

Facial weakness

Hearing loss

Dysarthria

Dysphagia

Other cranial nerve functions

FUNCTIONAL SYSTEM SCORE

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			

LIMB STRENGTH	R	L
Deltoid		
Biceps		
Triceps		
Wrist/finger flexors		
Wrist/finger extensors		
Hip flexors		
Knee flexors		

Knee extensors

Plantar flexion (feet/toes)

Dorsiflexion (feet/toes)

* Position test UE, pronation

* Position test UE, downward drift

* Position test LE, sinking

* Able to lift only one leg at a time (grade in °)

* Walking on heels

* Walking on toes

* Hopping on one foot

SPASTICITY

Arms

Legs

Gait

OVERALL MOTOR PERFORMANCE

FUNCTIONAL SYSTEM SCORE

CC = corrected
SC = without correction

* = optional part of the examination
! = converted FS Score

SPECIMEN

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION					
Head tremor			Rapid alternating movements UE impairment		
Truncal ataxia			Rapid alternating movements LE impairment		
	R	L	Tandem walking		
Tremor/dysmetria UE			Gait ataxia		
Tremor/dysmetria LE			Romberg test		
			Other, e. g. rebound		
			FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L			
Superficial sensation UE			Position sense UE		
Superficial sensation trunk			Position sense LE		
Superficial sensation LE			* Lhermitte's sign		
Vibration sense UE			* Paraesthesiae UE		
Vibration sense LE			* Paraesthesiae trunk		
			* Paraesthesiae LE		
			FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention			Bowel dysfunction		
Urinary urgency/incontinence			* Sexual dysfunction		
Bladder catheterisation			FUNCTIONAL SYSTEM SCORE		→	

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION			
° Depression		Decrease in mentation	
° Euphoria		' Fatigue	
		FUNCTIONAL SYSTEM SCORE	

AMBULATION

Distance reported by patient (in meters)		Assistance	
Time reported by patient (in minutes)		Distance measured (in meters)	
		AMBULATION SCORE	

* = optional part of the examination
! = converted FS Score
° Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
' Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

UE = upper extremities
LE = lower extremities

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

Appendix 3
EuroQol-5D (EQ-5D)

The actual forms will be provided to the sites and should be used for assessment.

Health Questionnaire

English version for the UK
(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

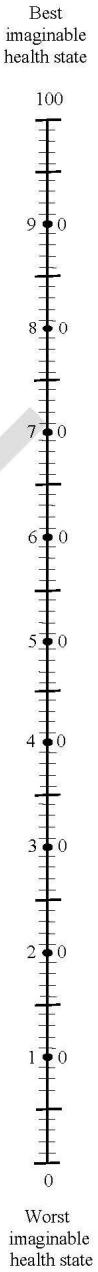
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



EQ-5D questionnaire references:

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.
EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.
Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Appendix 4
C-SSRS since Last Visit

The actual forms will be provided to the sites and should be used for assessment.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Prior to Study Entry: Time He/She Felt Most Suicidal**	**Since Study Start:**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal. Prior to Study Entry - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*) Since Study Start - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	

Version 1/14/09