Official Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy and Safety, of Satralizumab (SA237) as Monotherapy in Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)

NCT Number: NCT02073279

Document Date: Protocol Version 10: 03-April-2020

PROTOCOL

TITLE:	**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY, OF SATRALIZUMAB (SA237) AS MONOTHERAPY IN PATIENTS WITH NEUROMYELITIS OPTICA (NMO) AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)**
PROTOCOL NUMBER:	BN40900 (SA-309JG)
VERSION NUMBER:	10
EUDRACT NUMBER:	2015-005431-41
IND NUMBER:	118183
TEST PRODUCT:	Satralizumab (SA237) (RO5333787)
MEDICAL MONITOR:	[redacted], M.D.
CO-SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd. *
DATE FINAL:	Version 1.0: 14 November 2013
DATES AMENDED:	Version 2.0: 18 February 2014 Version 3.0: 26 May 2014 Version 4.0: 2 September 2014 Version 5.0: 5 November 2015 Version 6.0: 1 March 2016 Version 6.1AB (Korea, Ukraine, Bulgaria, Others): 23 March 2016 Version 7.0: 13 July 2017 Version 7.1AB (Korea, Ukraine, Bulgaria, Others): 13 July 2017 Version 8.0: 14 June 2018 Version 8.1AB (Korea, Ukraine, Bulgaria, Others): 14 June 2018 Version 8.2AB (Korea, Ukraine, Bulgaria): 25 October 2018 Version 9: 5 March 2019 Version 10: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
03-Apr-2020 23:11:18	Company Signatory	[redacted]

* 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.

PROTOCOL AMENDMENT, VERSION 10:
RATIONALE

Protocol BN40900 (SA-309JG) has been amended to reflect a change in Sponsor for South Korea and to increase the duration of the open-label extension (OLE) period until 31 December 2021. In addition, specific measures were implemented to allow continuation of treatment and ensure patients' safety during the SARS-CoV-2 (COVID-19) pandemic.

Changes to the protocol for all sites, along with a rationale for each change, are summarized below:

- The open-label extension treatment period has been extended up to 31 December 2021. The management of neuromyelitis optica spectrum disorder (NMOSD) with satralizumab requires long-term treatment. Extending the OLE treatment period to the end of December 2021 will ensure the continuation of treatment and provide additional long-term safety and efficacy data (Sections 1.3, 3.1.1, 4.3.2.2, and 4.5.2.2).
- The risks for satralizumab were updated based on the current available clinical trial data with satralizumab (Section 5.1).
- F. Hoffmann-La Roche Ltd has taken over the future development of study drug satralizumab (SA237) in South Korea from Chugai Pharmaceutical Co., Ltd. (Chugai). Chugai will remain the Sponsor in Taiwan and Japan (Section 9.3).
- Specific measures during emergency situations such as the SARS-CoV-2 (COVID-19) pandemic were added to ensure treatment continuation and patient safety (Sections 4.3.2.2, 4.3.3, 4.5.1.10, 4.5.2.2, 4.5.3.2, and 5.1.1.7, and Appendix 1, Table 8):
  - In the open-label extension period after Week 48, 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, home administration by a mobile nurse) will be allowed.
  - If patients cannot physically attend a visit at the study site for safety blood draw, 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 adverse events (AEs) in the eCRF.
  - All efforts should be made to follow up with patients around the time of the scheduled visit by phone if they cannot physically attend a visit at the study site 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.

- Following the implementation of Protocol Version 10 and in accordance with local regulations, administration of satralizumab outside of the study site may be allowed to reduce the burden on patients traveling to study sites at defined visits. Patients will be followed up by study site personnel through phone calls (Sections 4.3.2.2, 4.3.3, 4.5.2.2, and 5.1.1.7, and Appendix 1, Table 8).

The following additional clarifications have also been made:

- Medical History will include the first attack and date of diagnosis of neuromyelitis optica (NMO) or NMOSD to further characterize the enrolled patient population (Section 4.5.1.1).
- Due to drifts in the Anti-AQP4 antibody cell-based assay over time confounding longitudinal assessment of anti-AQP4 antibody titers, samples will be analyzed by ELISA (Sections 4.5.3.2 and 6.7, and Appendix 1, Table 6).
- Language has been added to clarify permitted and prohibited medications during the OLE period (Sections 4.4.1 and 4.4.2).
- Patients who do not meet the criteria for childbearing potential during the OLE period of the study (e.g., confirmed post-menopausal status) will not require further pregnancy testing (Section 4.5.1.10).
- Patients who complete the OLE period with the last study drug administration on or before 31 December 2021 and decide to continue treatment with satralizumab outside of this study will not have to complete the Last Observation Visit (Section 4.5.2.3).
- Reporting requirements for pregnancies in female patients have been clarified and aligned with the reporting requirements for pregnancies in female partners of male patients (Section 5.4.3.1).
- The statistical considerations section has been updated to provide information on efficacy analyses done for the OLE period (Section 6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY, OF SATRALIZUMAB (SA237) AS MONOTHERAPY IN PATIENTS WITH NEUROMYELITIS OPTICA (NMO) AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)**
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CO-SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.

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

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY, OF SATRALIZUMAB (SA237) AS MONOTHERAPY IN PATIENTS WITH NEUROMYELITIS OPTICA (NMO) AND NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)**
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VERSION NUMBER:	10
EUDRACT NUMBER:	2015-005431-41
IND NUMBER:	118183
TEST PRODUCT:	Satralizumab (SA237) (RO5333787)
PHASE:	Phase III
INDICATION:	Neuromyelitis optica and neuromyelitis optica spectrum disorder
CO-SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.

Objectives

Primary Objective

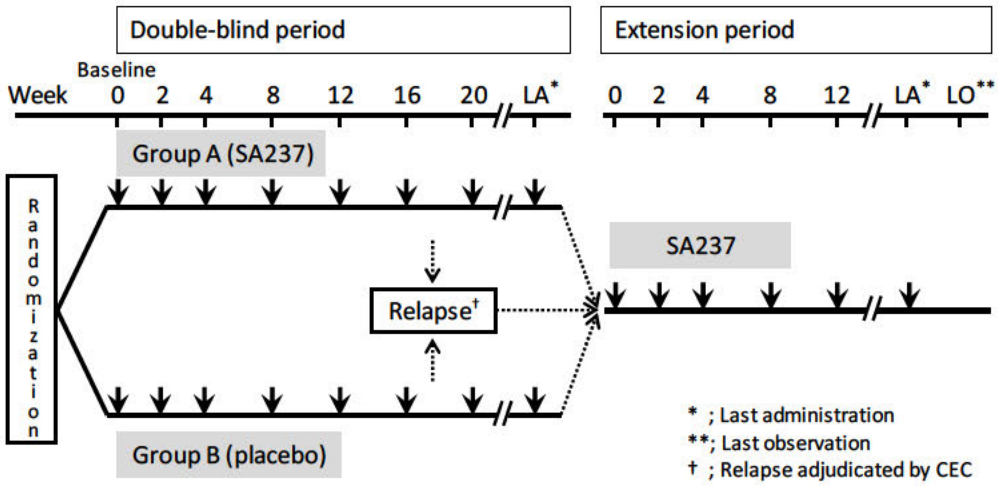
The primary objective for this study is as follows:

- To evaluate the efficacy and safety of satralizumab (also known as SA237) monotherapy in patients with neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD).

Study Design

Description of Study

This is a multicenter randomized, double-blind, placebo-controlled, parallel assignment study followed by an open-label extension period. Patients will be randomized to two groups (2:1, Group A or B) and will receive subcutaneous (SC) satralizumab 120 mg (Group A) or placebo (Group B) at weeks 0, 2 and 4, and every 4 weeks (Q4W) thereafter. The randomization will be stratified by prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse). Patients who complete the double-blind period or experience a protocol-defined relapse which is adjudicated by Clinical Endpoint Committee (CEC) in the double-blind period can enter the open-label extension period and will receive subcutaneous satralizumab. In the extension period, patients can receive open-label treatment with 120 mg satralizumab SC at Weeks 0, 2 and 4 and Q4W thereafter, *with the last study drug administration on or before 31 December 2021*. For patients who experienced a protocol-defined relapse which is adjudicated by CEC, satralizumab should start in the stable disease condition (Day 31 or later, where Day 1 is defined as the day of onset of a protocol-defined relapse which is adjudicated by CEC). For patients who completed the double-blind period, satralizumab should start after 4 weeks from the last dosing in the double-blind period.



CEC = Clinical Endpoint Committee; SA237 = satralizumab.

Patients who withdraw from the study treatment in the double-blind period due to a clinical relapse should be asked to continue into the Safety Follow-Up (SFU) period, which will last for 24 weeks from the last dose of satralizumab or placebo.

Number of Patients

Approximately 90 patients will be recruited.

Target Population

This study includes patients with NMO or NMOSD. The proportion of patients who are negative for anti-AQP4 antibody at screening will be capped at 30% of total number of patients.

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Patients must be diagnosed as either
   a. NMO as defined by Wingerchuk 2006 criteria, or
   b. NMOSD as defined by either of *the* following criteria with anti-aquaporin-4 (AQP4) antibody seropositive status at screening.
      i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord magnetic resonance imaging [MRI] lesion)
      ii. Optic neuritis, single, recurrent or simultaneous bilateral
2. Clinical evidence of at least 1 documented relapse (including first attack) in last 12 months prior to screening.
3. Expanded disability status scale (EDSS) score from 0 to 6.5 inclusive at screening.
4. Age 18 to 74 years, inclusive at the time of informed consent.
5. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

Exclusion Criteria

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

Exclusion Criteria Related to NMO:

1. Clinical relapse onset (including first attack) within 30 days prior to baseline.

Exclusion Criteria Related to Previous or Concomitant Therapy:

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

Exclusions for General Safety:

6. Pregnancy or lactation.
7. For patients of reproductive potential, a positive result from a serum pregnancy test at screening, or not willing to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug.
8. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
9. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
10. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, as described;
    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.
11. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
12. Evidence of chronic active hepatitis B or C.
13. History of drug or alcohol abuse within 1 year prior to baseline.
14. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
15. Evidence of active tuberculosis (excluding patients receiving chemoprophylaxis for latent tuberculosis infection).
16. Evidence of active interstitial lung disease.
17. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
18. History of malignancy within the last 5 years, including solid tumors, hematologic malignancies and *in situ* carcinoma (except basal cell and squamous cell carcinomas of the skin, or *in situ* carcinoma of the cervix uteri that have been completely excised and cured).
19. History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).

20. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.
21. History of Stevens-Johnson syndrome.

Laboratory Exclusion criteria (at screening):

22. Following laboratory abnormalities at screening*.
    a. White blood cells < 3.0 $x10^3/\mu L$
    b. Absolute neutrophil count < 2.0 x $10^3/\mu L$
    c. Absolute lymphocyte count < 0.5 x $10^3/\mu L$
    d. Platelet count < 10 x $10^4/\mu L$
    e. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal.

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

Length of Study

The end of the double-blind period is defined as the date of primary analysis when the total number of relapses reaches 44 or 1.5 years after the date of randomization of the last patient enrolled, whichever comes first. The extension period is expected to last until the Last Observation Visit.

End of Study

The end of the study is defined as the date when the last patient's last visit occurs; this is expected to be 12 weeks after the last dosing in the extension period.

Efficacy Outcome Measures

Primary endpoint

i. Time to first protocol-defined relapse (TFR) in the double-blind period

Secondary endpoints

i. Change in Visual Analogue Scale (VAS) score for pain
ii. Change in Functional Assessment Of Chronic Illness Therapy (FACIT) Fatigue score
iii. Change in Short Form Generic Health Survey (SF-36) score
iv. Change in EQ-5D score
v. Change in Timed 25-Foot Walk (T25W)
vi. The proportion of relapse-free patients
vii. Annualized relapse rate (ARR)
viii. Change in modified Rankin Scale (mRS) score
ix. Change in Zarit Burden Interview (ZBI) score
x. Change in EDSS scores
xi. Change in visual acuity (Snellen chart)
xii. Change in low-contrast visual acuity (low-contrast Sloan letter chart [LCSLC])

Exploratory endpoint

i. MRI scans of the brain, optic nerve and spinal cord
   MRI for exploratory evaluation is optional and will be conducted at selected sites.

Safety Outcome Measures

i. Incidence and severity of adverse events (AE), serious AEs (SAEs) and AEs of special interest (AESIs).

ii. Vital signs (temperature, systolic and diastolic blood pressure and pulse rate), physical examination, clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead electrocardiogram (ECG), suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]).

Pharmacokinetic/Pharmacodynamic Outcome Measures

i. Serum satralizumab concentration, IL-6, soluble IL-6 receptor (sIL-6R), high sensitivity C-reactive protein (hsCRP), anti-AQP4 antibody, plasmablast

Immunogenicity Outcome Measures

i. Incidence of anti-drug antibodies

ii. PK, PD, clinical response, and safety during the study by anti-drug antibody status

Investigational Medicinal Products

Test Product

Satralizumab 120 mg/mL

Dose and Mode of Administration: 120 mg SC at Weeks 0, 2 and 4, and Q4W thereafter in the double-blind period and extension period, respectively.

Comparator

Placebo

Dose and Mode of Administration: Single-dose of placebo SC at Weeks 0, 2 and 4, and Q4W thereafter in the double-blind period.

Concomitant medication/therapy for NMO and NMOSD

Permitted medication/therapy

Double-blind period

1. Rescue therapy for clinical relapse; pulse IV corticosteroids, oral corticosteroids for tapering, intravenous immunoglobulin (IVIG) and/or apheresis (including plasma exchange and plasmapheresis)
2. Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).
   Starting of pain medications is permitted; however, the dose should be stable during the double-blind period. In case pain control is insufficient, dose increase or change of pain medication is permitted. Dose decrease and temporary treatment suspension are permitted for only safety reasons.

Extension period

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

Statistical Methods

Primary Analysis

A stratified two-sided log-rank test using strata of prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse) will be used. The Kaplan-Meier method will be used to estimate the TFR in the double-blind period distribution for each treatment group. Relapse-free rates and their 95% confidence intervals (CI), in addition to the hazard ratio, will be used every 6 months to describe TFR distribution.

Determination of Sample Size

The sample size considerations are based on the following assumptions: (1) A two-sided log-rank test; (2) At least 80% power at the 5% significance level; (3) The hazard ratio of satralizumab over placebo for an initial 2 months from randomization is 1.0. The hazard ratio after an initial 2 months from randomization is 0.25; (4) TFR in the placebo arm following an exponential distribution, with hazard rate for 1 year $h(t) = 1.1295$; (5) A 2-year dropout rate of 10%.

Based on these assumptions, 44 TFR events are needed for the primary analysis. The 90 patients enrolled over 33 months and followed an additional 5 months will provide 44 TFR events.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-Drug (Satralizumab) Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AQP4	Aquaporin-4
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
AUC	Area Under The Serum Concentration-time Curve
BAFF	B-cell Activating Factor
BOCF	Baseline Observation Carried Forward
BUN	Blood Urea Nitrogen
Ca	Calcium
CCSR	Chugai Clinical Sample Repository
CD	Cluster of Differentiation
CEC	Clinical Endpoint Committee
CK	Creatinine Kinase
Cl	Chloride
CL/F	Clearance
CNS	Central Nervous System
CRO	Contract Research Organization
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	Average Trough Serum Concentration
DBP	Diastolic Blood Pressure
DNA	Deoxyribose Nucleic Acid
DOW	Dose Outside The Visit Window
EC	*European Commission*
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
ELISA	Enzyme Linked Immunosorbent Assay

Abbreviation	Definition
EQ-5D	EuroQol
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	*Food and Drug Administration*
Fc	Fragment Crystallizable
FPI	First Patient In
FSS	Functional System Score
GCP	Good Clinical Practice
γ-GTP	Gamma Glutamyl Transpeptidase
Hb	Hemoglobin
HBcAb	Total Hepatitis B Core Antibody
HbsAb	Antibody To Hepatitis B Surface Antigen
HbsAg	Hepatitis B Surface Antigen
HCVab	Hepatitis C Virus Antibody
HBV	Hepatitis B virus
β-hCG	Beta Human Chorionic Gonadotropin
HCT	Hematocrit
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
hsCRP	High Sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ID	Identification (number)
IDCC	Independent Data Coordinating Center
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IL-6	Interleukin-6
IL-6R	Interleukin-6 Receptor
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Injection-related Reaction

Abbreviation	Definition
IST	*Immunosuppressive Therapy*
ITT	Intent-To-Treat
IV	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
IxRS	Interactive Voice or Web Response System
K	Potassium
LCSLC	Low-contrast Sloan Letter Chart
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LPLV	Last Patient Last Visit
MMRM	Mixed-effects Model Repeated Measures
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MS	Multiple Sclerosis
Na	Sodium
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
NSD	Needle Safety Device
OLE	*Open-Label Extension*
P	Phosphorous
PD	Pharmacodynamic
PDR	*Protocol Defined Relapse*
PFS	Prefilled Syringe
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PML	Progressive Multifocal Leukoencephalopathy
PLT	Platelets
PPS	Per-Protocol Set
Q4W	Every 4 Weeks
QTcF	QT Interval Corrected For Heart Rate using Fridericia's Formula
RA	Rheumatoid Arthritis
RBC	Red Blood Cell(s)
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan

Abbreviation	Definition
SBP	Systolic Blood Pressure
SC	Subcutaneous (Ly)
SD	Standard Deviation
SF-36	Short Form Generic Health Survey
SFU	Safety Follow-Up
SJS	Stevens-Johnson Syndrome
sIL-6R	Soluble Interleukin-6 Receptor
SOC	System Organ Class
Study treatment	Satralizumab or Placebo
T25W	Timed 25-Foot Walk
TB	Tuberculosis
TBL	Total Bilirubin
TNF	Tumor necrosis factor
TFR	Time To First Protocol-defined Relapse
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
V/F	Distribution Volume
WBC	White Blood Cell(s)
ZBI	Zarit Burden Interview

1. INTRODUCTION

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

1.1.1 Introduction to NMO and NMOSD

Neuromyelitis optica (NMO), originally named Devic's disease, is a severe demyelinating inflammatory autoimmune disorder. NMO and NMO spectrum disorder (NMOSD) are clinically characterized by optic neuritis and/or transverse myelitis (Wingerchuk et al. 2007), leading to various disabilities, such as visual impairment (including blindness), disturbance of motility and sensory deficit. NMO usually has a worse prognosis than multiple sclerosis (MS). Optic neuritis may present as a unilateral or bilateral event depending upon the portion of the visual pathway that is affected. Visual impairment is often severe with a poor recovery. In addition, the severe relapses often lead to difficulty walking, para/tetraparesis and pan-sensory loss. Disability in NMO is usually more severe than that in MS and is usually related to the severity of NMO relapses. Most disabilities arise from the often devastating discrete acute attacks and secondary progression is uncommon. Fatigue and pain are common and affect a broader body area than those in MS and significantly impact the patient's quality of life.

NMO is distinct from MS, radiologically, and prognostically, and has a pathophysiology unresponsive to typical MS treatment (Weinshenker 2007; Oh and Levy 2012). Other distinguishing features of NMO include a strong female preponderance, longitudinally extensive spinal cord lesions and absence of oligoclonal immunoglobulin G (IgG) bands in the cerebral spinal fluid (CSF).

Currently, there is one licensed medication for NMOSD (eculizumab; approved by the Food and Drug Administration [FDA] on 27 June 2019 and by the European Commission [EC] on 27 August 2019). There are four aspects of NMO treatment in the current treatment algorithm, including: 1) acute treatment of relapses, 2) prevention of relapses, 3) symptom management and 4) rehabilitation.

Historically the distinction between NMO and MS has been extensively debated but following the discovery of NMO-IgG or aquaporin-4 (AQP4) antibody, which is a circulating antibody which targets the dominant water channel in the central nervous system (Lennon et al., 2005), separate classifications have been developed. The 2006 Wingerchuk NMO diagnostic criteria have been established and shared globally (Wingerchuk et al 2006). NMOSD includes individuals manifesting *with* recurrent myelitis or recurrent optic neuritis or with a variety of signature brain syndromes, such as intractable vomiting and hiccups, and is diagnosed by 'Criteria 2007' (Wingerchuk et al., 2007). *In the most recently published diagnostic criteria, the overarching term*

NMOSD was selected to unify traditional NMO and modern NMOSD definitions (Wingerchuk et al. 2015).

In light of the non-reversibility of the neurological deficit associated with relapses, maintenance immunosuppression has become standard practice. The current standard in the United States (US), European Union (EU), Canada and Pacific Rim countries outside of Japan, is to achieve and maintain remission with corticosteroids and then gradually withdraw them in favor of a non-steroid immunosuppressant, although some patients need a low dose of oral steroids to maintain remission. Treatment with a variety of different agents has been described although no randomized comparisons of different therapies exist. Treatment approaches for prevention of attacks include systemic immunosuppression with azathioprine or mycophenolate mofetil. Methotrexate use has also been reported, as is use of mitoxantrone chemotherapy. In terms of biologic agents, rituximab, which is not approved for treatment of MS or NMO, is widely used by clinicians in some countries. The use of tocilizumab (Araki et al. 2012, Ayzenberg et al. 2013, Kieseier et al. 2013) in NMO *has* also been reported.

Limited observational evidence suggests that typical MS treatments, including interferon (IFN)-β, natalizumab and fingolimod, are not effective in NMO and may be harmful when used to treat these patients. Unlike MS, disability in NMO is directly tied to the number and severity of relapses. There *remains* an unmet medical need to develop *additional* therapeutic *options to reduce the likelihood* of relapses.

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

One of the key features of NMO is the presence of NMO-IgG, specific antibodies against AQP4, a major water channel protein in the central nervous system (CNS). Transfer of anti-AQP4 antibody has been shown to exacerbate experimental autoimmune encephalomyelitis in animal models (Lennon et al. 2005; Hinson et al. 2012). From this observation, the role of the humoral arm of the immune system in disease pathology for NMO has been developed. Yamamura and coworkers have identified a CD19intCD27hiCD38hiCD180- (and CD20-) plasmablast B-cell subset, which is associated with production of anti-AQP4 antibodies) (Chihara et al. 2011). Cell surface expression of cluster of differentiation 19 (CD19) in plasmablasts is lower than other B-cells. Survival of plasmablasts is promoted by interleukin-6 (IL-6), but not by other B-cell survival factors such as a proliferation including ligand (APRIL), the related or tumor necrosis factor (TNF) family B-cell activating factor (BAFF, known as BLyS). IL-6, but not BLyS was suggested to enhance antibody production by these plasmablasts, and anti-IL-6 receptor (IL-6R) blockade selectively inhibited survival of AQP4

antibody-producing plasmablasts *in vitro*. Based on these *ex vivo* studies, there are also now reports from several different global Investigators that have used anti-IL-6R blockade to treat patients with NMO.

This suggests that immunomodulatory agents that specifically target the humoral immune system could potentially have an effect in treatment of patients with NMO. Complement activation by NMO-IgG binding to AQP4 has been suggested. An agent that targets production of AQP4-Ab, would be upstream of the complement activation step.

IL-6 which is secreted by T-cells and macrophages during infection and trauma acts as both a pro-inflammatory and anti-inflammatory cytokine, Anti-IL-6R blockade may have a direct effect on B cells in NMO. Survival of plasmablasts is promoted by IL-6, and IL-6 was suggested to enhance antibody production by the selective plasmablasts, and anti-IL-6R blockade selectively inhibited survival of AQP4 antibody-producing plasmablasts *in vitro*.

Araki et al. 2013, reported initial positive results with IL-6R blockade in a 36-year-old female patient with NMO and multiple relapses, who had been previously diagnosed with MS. The patient experienced relapses with two different treatment regimens (IFN-β plus low-dose oral prednisolone and subsequently prednisolone plus azathioprine). Following treatment with intravenous (IV) tocilizumab 8 mg/kg monthly for 6 months, relapses ceased (apart from one minor case) and the patient's Expanded Disability Status Scale (EDSS) score improved to 2.0 from 3.5.

Kieseier et al. 2013 reported a case study of a 34-year old female who was diagnosed with NMO. Therapy with rituximab and alemtuzumab did not prevent relapses. After starting IV treatment with tocilizumab 8 mg/kg body weight every 4 weeks, EDSS score was reduced from 8.0 to 4.0 within 2 months, and the patient was ambulatory with an EDSS score of 2.5 after 1 year.

Ayzenberg et al. 2013 reported a case series of three patients with aggressive NMO unresponsive to rituximab therapy. The patients continued to experience relapses despite complete cluster of differentiation CD20-cell depletion. After starting treatment with tocilizumab 6 mg/kg every 4 or 6 weeks, the median annualized relapse rate (ARR) decreased from 3.0 (range 2.3-3.0) to 0.6 (range 0–1.3).

1.2 BACKGROUND ON SATRALIZUMAB

Satralizumab is a humanized anti-human IL-6R neutralizing monoclonal antibody that was designed by application of recycling antibody technology to the approved anti-IL6 receptor antibody, tocilizumab, which is currently marketed as a treatment for

rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis and Castleman's disease. 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, imparting a longer plasma half-life. In addition, satralizumab is an IgG2 isotype which reduces fragment crystallizable (Fc) receptor effector functions compared with tocilizumab (which is an IgG1 antibody). The longer plasma half-life of satralizumab compared with tocilizumab was confirmed based on the result of non–clinical study and Phase 1 study in healthy volunteers (SA-001JP).

Like tocilizumab, satralizumab achieves its pharmacological effects by inhibiting IL-6 signaling. Compared with tocilizumab, satralizumab was designed to have:

1) A longer plasma half-life due to pH-dependent binding to the IL-6R, a lower antibody molecule isoelectric point and stronger binding to neonatal Fc receptor, and
2) Lower effector activities (e.g., antibody dependent cellular cytotoxicity and complement-dependent cytotoxicity) owing to its lower binding affinity to Fcγ receptor and the adoption of an IgG2 backbone.

The pharmacological effects and safety of satralizumab are expected to be comparable or superior to those of tocilizumab, and because of its longer plasma half-life, it is expected to show pharmacological efficacy at a lower dosing frequency.

The safety, tolerability, pharmacokinetics and bioavailability of subcutaneously (SC) administered satralizumab were investigated in Japanese and Caucasian healthy adult male volunteers (SA-001JP) in Japan. In this Phase 1 (single-dose) study, 48 Japanese subjects were given satralizumab by SC injection or IV, and 24 Caucasian subjects were given satralizumab by SC. This study demonstrated comparable safety and pharmacokinetic (PK) profiles with a single administration of satralizumab within no ethnic effects observed other than body weight. A single SC dose of satralizumab up to 240 mg and an IV dose of satralizumab up to 120 mg were safe and well tolerated.

SA-105JP is a Phase 1b, open-label, randomized, parallel group, multiple dosing study in patients with RA. The objectives of the study are to assess safety, immunogenicity, PK/pharmacodynamics (PD), and efficacy of satralizumab as a monotherapy. All patients were given 120 mg of satralizumab as a loading dose at Week 0, 2 and 4 to induce high dose tolerance at the beginning of the study. Patients were then randomized to satralizumab 120 mg (Group A; 11 patients), 60 mg (Group B; 11 patients) or 30 mg (Group C; 11 patients) and received 3 doses of randomized treatment at Weeks 8, 12 and 16. In total, during the primary evaluation period, 45 adverse events (AEs) were

reported in 22 patients, 17 events in Group A, 14 in Group B and 14 in Group C. The most frequent AEs by system organ class (SOC) were infections and infestations (15 AEs in 12 patients), and most frequently reported individual AE was upper respiratory tract infection (4 events). The next most frequent AEs by SOC were skin and subcutaneous tissue disorders (7 AEs in 5 patients). The majority of AEs were mild in severity and there was no apparent difference in incidence of AEs between the groups. Two serious adverse events (SAEs) were reported in the primary evaluation period: one patient in Group A developed interstitial pneumonia after the second injection and discontinued due to this SAE. Following treatment in hospitalization, this event resolved. One patient in Group B developed bronchopneumonia after the first injection. Injection at Week 2 was interrupted due to the SAE. Following treatment in hospitalization, this event resolved. See the Investigator's Brochure for details on nonclinical and clinical studies with satralizumab.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Satralizumab is being developed for the treatment of NMO and NMOSD, which is a serious condition that has substantial impact on day-to-day functioning of the patient. Satralizumab has the potential to treat this serious disease and fulfills an unmet medical need. Patients diagnosed with NMO and NMOSD remain poorly served by existing treatments and experience a series of catastrophic relapses culminating in worsening disability including paraplegia and blindness. Treatment options are limited to the use of high dose corticosteroids at the time of relapse and chronic immunosuppression most commonly with azathioprine, mycophenolate, low dose oral corticosteroids and B-cell depleting agents, but none of these are approved. The evidence supporting the use of these therapies is limited to small single arm studies. More recently there have been small series of patients who experienced a dramatic reduction in relapse rate following inhibition of IL-6 signaling following treatment with the humanized antibody tocilizumab. Satralizumab is the first of a new class of monoclonal antibodies which following its uptake is recycled from within the cell permitting infrequent dosing. Satralizumab binds potently to the alpha-subunit of the IL-6 receptor preventing signaling via this receptor. Satralizumab has been studied in healthy volunteers and subjects with rheumatoid arthritis.

In addition to the safety information for satralizumab, the safety information obtained for tocilizumab is considered to be useful in predicting the safety of satralizumab since tocilizumab has essentially the same mechanism of action as satralizumab. The following risks have been identified following treatment with tocilizumab: serious infections; gastrointestinal perforation; hypersensitivity.

In order to address the potential risks for the patients, the following safety precautions are included in the study design:

In addition to regular standard safety evaluations (laboratory measures, physical examinations, vital signs and electrocardiogram [ECG]), a special focus will be placed on the above-noted risks.

An Independent Data Monitoring Committee (IDMC) will periodically review AEs *during the double-blind period* in an un-blinded manner. The study will be stopped prematurely if there are any critical safety concerns.

An independent Clinical Endpoint Committee (CEC) will review all cases of relapses and adjudicate each to see if it meets the protocol-defined relapse in the double-blind period. In order to ensure that no relapse events are missed by the Investigator, the adjudication process will include a concurrent review of all cases to determine if a possible relapse event has been missed.

In summary, treatment with satralizumab is an approach for a specific therapeutic strategy in NMO with possible advantages for patients. All necessary measures are taken to closely monitor the safety of the treatment and thus to protect the patients enrolled in this study. The possible benefits are deemed to outweigh the potential risks involved in participation in this study.

The Clinical Development Program of satralizumab in NMOSD currently consists of two ongoing pivotal placebo-controlled randomized, double-blind Phase 3 studies. The double-blind periods of both studies have been completed (please refer to the latest Investigator's Brochure for a summary of the study results), and the studies are currently ongoing in their open-label extension (OLE) periods.

A multicenter, open-label, uncontrolled study to evaluate the pharmacokinetics, safety, tolerability, and pharmacodynamic effects of satralizumab in children from 2 to less than 12 years of age is planned to start in Q4 2020.

The first study described here (Study BN40900, also known as Study SA-309JG, the monotherapy study) is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of satralizumab monotherapy for treatment of *NMOSD* that was recommended by FDA at the meeting of 11 July 2013.

In addition, the Sponsor *is conducting* a second study (Study BN40898, also known as Study SA-307JG, the add-on study), a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of satralizumab as an add-on to widely used baseline *immunosuppressive* therapies *(ISTs) for the treatment of NMOSD*.

To date, *a* Phase 1 single ascending dose study in healthy subjects (SA-001JP), and *a* Phase 1 multiple dose study in patients with rheumatoid arthritis (SA-105JP) have been conducted.

Long-term safety information and data supporting durability of efficacy *in patients with NMOSD* will be derived from the open-label extension period of *the ongoing* Phase 3 studies. Additional long-term safety information is supplied from Phase 1 multiple dose study in Japanese patients with rheumatoid arthritis (SA-105JP).

2. OBJECTIVES

2.1 EFFICACY OBJECTIVE

The efficacy objective for this study is:

- To evaluate the efficacy of satralizumab monotherapy compared with placebo in patients with NMO and NMOSD

The primary efficacy endpoint:

i. Time to first protocol-defined relapse (TFR) in the double-blind period

The secondary efficacy endpoints are:

i. Change in visual analog scale **(**VAS) score for pain
ii. Change in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score
iii. Change in Short Form generic health survey (SF-36) score
iv. Change in EQ-5D score
v. Change in Timed 25-Foot Walk (T25W)
vi. The proportion of relapse-free patients
vii. Annualized relapse rate (ARR)
viii. Change in modified Rankin Scale (mRS) score
ix. Change in Zarit Burden Interview (ZBI) score
x. Change in EDSS score
xi. Change in visual acuity (Snellen chart)
xii. Change in low-contrast visual acuity (Low-contrast Sloan letter chart [LCSLC])

Exploratory endpoints

i. Magnetic resonance imaging (MRI) scans of the brain, optic nerve and spinal cord

   MRI for exploratory evaluation is optional and conducted at selected sites.

2.2 SAFETY OBJECTIVE

The safety objective for this study is:

- To evaluate the safety of satralizumab monotherapy compared with placebo in patients with NMO and NMOSD.

Safety outcome measures:

- Incidence and severity of AEs, adverse events of special interest (AESIs) and SAEs, vital signs (temperature, systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate), physical examinations, clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead ECGs, suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]).

2.3 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic objective for this study is as follows:

- To examine the PD of satralizumab

Pharmacodynamics Endpoints:

- IL-6, soluble IL-6R (sIL-6R), high-sensitivity C-reactive protein (hsCRP), anti AQP4 antibodies and plasmablasts.

2.4 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic objective for this study is as follows:

- To examine the pharmacokinetics (PK) of satralizumab

Pharmacokinetics Endpoint:

- Serum satralizumab concentration

2.5 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is as follows:

- To examine the immunogenicity of satralizumab.

Immunogenicity Endpoint:

- Incidence of anti-drug antibodies.
- PK, PD, clinical response, and safety during the study by anti-drug antibody status.

Study endpoints relating to these objectives are described in Section 3.3.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This Phase 3 pivotal study is a multicenter randomized, double-blind, placebo-controlled parallel assignment study followed by an open-label extension period. Patients will be randomized to two groups (2:1, Group A or B) and will receive subcutaneous satralizumab (Group A) or placebo (Group B) at Weeks 0, 2 and 4, and Q4W thereafter. The number of patients who are negative for anti-AQP4 antibody at screening will be limited to 30% of total study population. The randomization will be stratified by prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse).

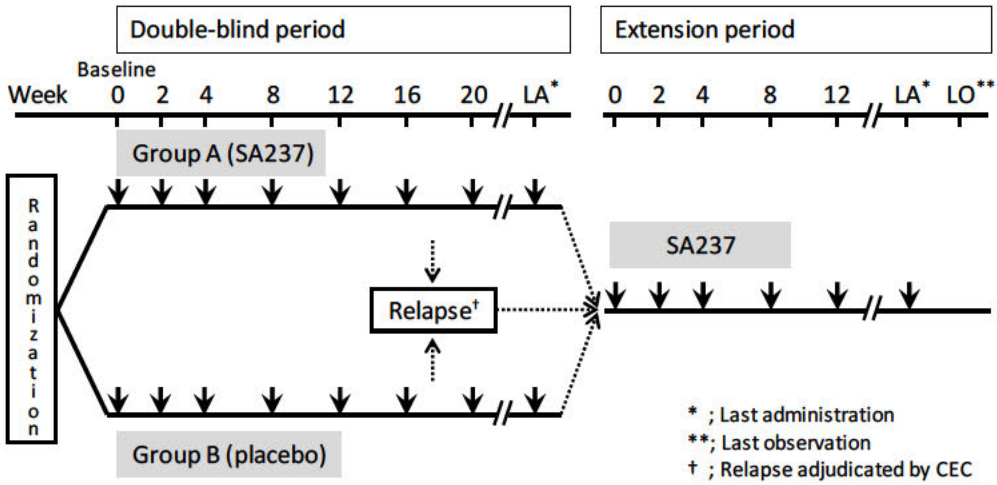
Patients who experience a protocol-defined relapse which is adjudicated by the CEC in the double-blind period or complete the double-blind period (see the section "Length of Study" in PROTOCOL SYNOPSIS) can enter the open-label extension period. In the extension period, patients will receive open-label treatment with 120 mg satralizumab SC at Weeks 0, 2 and 4 and every 4 weeks (Q4W) thereafter, *with the last study drug administration on or before 31 December 2021*. For patients who experience a relapse in the double-blind period, appropriate rescue therapy for relapse will be conducted. For patients who experienced a protocol-defined relapse which is adjudicated by CEC, satralizumab should start in the stable disease condition (Day 31 or later, where Day 1 is defined as the day of onset of a protocol-defined relapse which is adjudicated by CEC). For patients who completed the double-blind period, satralizumab should start after 4 weeks from the last dosing in the double-blind period.

The extension period is expected to last until the Last Observation Visit.

Those patients who experience 2 relapses in the extension period, both with a more severe intensity than the last relapse prior to baseline must be discontinued from treatment (See Section 4.7.1.1). It is the Investigator's decision whether the patient can continue in the extension period. If the relapses aren't as severe as the relapse prior to baseline they can remain in the extension period without being limited to the total number of relapses.

Study design is summarized in Figure 1.

Figure 1 Study Design



CEC = Clinical Endpoint Committee; SA237 = satralizumab.

Patients who withdraw from the study treatment in the double-blind period due to a clinical relapse should be asked to continue Safety Follow-Up (SFU) lasting for a period of 24 weeks from the last dose of satralizumab or placebo.

3.1.2 Investigational Patients and Sites

It is planned to recruit approximately 90 patients from multinational sites across North America and rest of the world.

3.1.3 Independent Data Monitoring Committee

An IDMC will be used *during the double-blind period* to perform periodic un-blinded safety reviews and to recommend if the trial should be stopped early. All summaries and analyses will be prepared by the Independent Data Coordinating Center (IDCC) and presented by treatment group for IDMC's review. Members of the IDMC and IDCC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities. Personnel who have operational responsibilities for the study will remain blinded during the *double-blind period* and will not be involved with the IDMC.

The IDMC was disbanded in December 2018, after the end of the double-blind period of both ongoing Phase 3 studies.

3.1.4 Clinical Endpoint Committee (CEC)

A CEC will be used to review all cases of relapse to determine if the case meets the protocol definition of a relapse in the double-blind period. Details regarding the CEC

responsibilities and the process of adjudication of relapses are described on in detail in the CEC charter.

Screening for a Possible Relapse During the Study

During the screening period patients will be trained on the possible symptoms and signs of a potential relapse of optic neuritis or myelitis, or a relapse involving other locations. A Relapse Assessment Form, including the time and content of every report of a possible event, will be prepared. All reports of potential relapses from patients regardless of the time of the report will be described in the Relapse Assessment Form. Patients will be instructed to remember accurately the time and content of every symptom of a possible relapse and to contact the study site if they have such symptoms. During the double-blind period, the site will contact the patient weekly by phone calls between the scheduled site visits, to query any change in symptoms or other signs of a potential relapse. Additionally, the site will contact the patient, at the discretion of the Investigator, between the scheduled site visits if necessary.

The site staff will also be trained on signs and symptoms that may be indicative of a potential relapse.

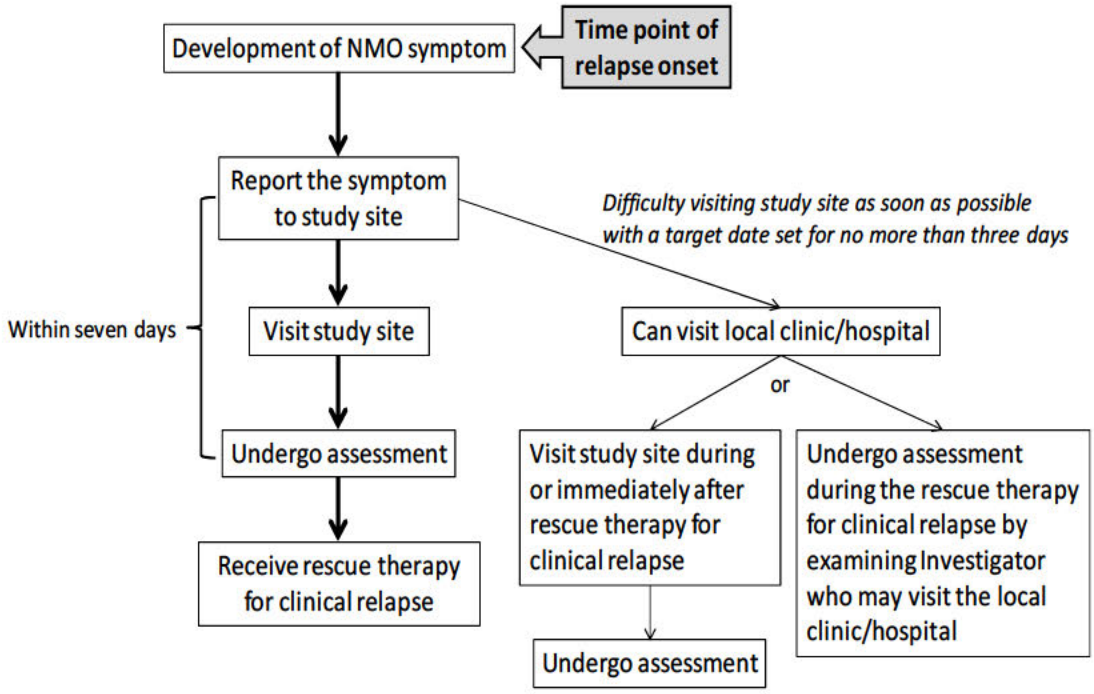
If a patient becomes aware of signs or symptoms which might indicate relapse, the patient will return to the site for an extra visit as soon as possible with a target date set for no more than three days after reporting the symptoms to the site. The examining Investigator must perform an EDSS/FSS assessment within seven days after the patient reports the symptoms to the site. The list of assessments to be obtained at the extra visit at relapse 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. MRI findings might be supportive for evaluation of relapse.

If a patient has difficulty visiting the study site within three days, the patient can visit a local clinic/hospital to receive rescue therapy for clinical relapse, and then visit the study site during or immediately after rescue therapy for clinical relapse. Alternatively, the examining Investigator may visit the local clinic/hospital to conduct the EDSS/FSS assessment during rescue therapy for clinical relapse.

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 must make every effort to obtain medical records from the facility, including information on treatment administered and the nature of the symptoms and signs observed.

Assessment of relapse is summarized in Figure 2.

Figure 2 Assessment of Relapse



Each extra visit following relapse will be captured in the electronic case report form (eCRF) and a separate Relapse Assessment Form will be completed by the site and sent (e.g., by fax, e-mail) with the accompanying necessary data, into PAREXEL immediately regardless of the assessment of the site staff about whether potential relapse meets protocol-defined relapse and regardless of the time when EDSS/FSS assessment was performed. During the double-blind period, the form and the data will be reviewed by a CEC. The CEC will be able to request additional information to assist in the determination of a relapse if necessary. The CEC will review all cases of relapse and adjudicate each to see if it meets the protocol definition of a relapse. In order to ensure that no relapse events were missed by the Investigator, the adjudication process will include a concurrent review of all cases for potential relapses that may be missed. The relapse which is regarded as a protocol-defined relapse by the CEC followed by confirmation that the EDSS/FSS assessment was performed within seven days after the patient reported the symptoms to the site, will be treated as an event.

The CEC will be comprised of physicians with expertise in NMO and NMOSD. The committee will be responsible for validating each reported relapse event, in a blinded fashion, to determine the event as to whether it meets the criteria of a protocol-defined relapse. Further details regarding the CEC responsibilities and the process of adjudication are described in the CEC charter.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Choice of Study Design Elements

A Phase 3 study with a sample size of 90 evaluable patients is considered to be adequate to demonstrate efficacy for this rare disease population. As no proof-of-concept Phase 2 studies have been conducted for satralizumab in NMO or NMOSD, the magnitude of the treatment effect is not known *a priori*, although there are some case reports of treatment with tocilizumab reducing the relapse rate.

The proportion of patients who are negative for anti-AQP4 antibody is expected to increase because this study allows enrolling such patients. In order to avoid a big difference between the study population and population in real world, percentage of the patients who are negative status for anti-AQP4 will be capped at 30% based on published data (Jarius et al. 2012, Lennon et al. 2004, Marignier et al. 2013, Takahashi et al. 2007).

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur 12 weeks after the last dosing in the extension period.

3.2.2 Rationale for Time to First Relapse Endpoint

There are currently no validated endpoints to evaluate the efficacy of agents for the treatment of NMO or NMOSD. In the absence of such endpoints, TFR was selected as the primary efficacy measure in this study. TFR is proposed rather than ARR because of the devastating nature of relapses and standard clinical approach of changing therapy following a relapse which prevents a more prolonged study period. TFR is alternative to ARR, of which is precedent for selection as the primary endpoint in MS clinical trial, as a statistical measure of the frequency of relapse and has been used as the secondary endpoint in several large MS studies (Giovannoni et al. 2010, Cohen et al 2010, Kappos et al 2010, O'Connor et al 2011). Furthermore, for NMO, the natural history of the disease is such that any relapse is potentially catastrophic to the patient and is often accompanied by long lasting neurological impairment.

One of the primary advantages of using TFR is from the ethical perspective, particularly dealing with the clinical consequences of relapse experienced by NMO and NMOSD patients. Time to first relapse allows patients who experience a relapse during the double-blind period to receive acute therapy. This mitigates the ethical concern of keeping patients with NMO/NMOSD on a potentially ineffective therapy for a fixed period of time and reflects current clinical practice in NMO/NMOSD, that when a patient experiences a relapse, treatment choice is often changed.

3.2.3 Rationale for Test Product Dosage

Based on PK and PD assessments in Phase I studies with satralizumab and anecdotal efficacy data from investigational studies of tocilizumab, 120 mg Q4W will be used as the maintenance dose of satralizumab in this study.

The mean trough level of satralizumab 120 mg SC Q4W in steady state in study SA-105JP was 20.3 ±6.13 µg/mL and the computed mean trough level of tocilizumab 8 mg/kg IV Q4W in steady state was 9.7 ±11 µg/mL (Frey N et al. 2010). Based on these data, the PK of satralizumab 120 mg SC Q4W was higher than that of tocilizumab 8 mg/kg IV Q4W. However, the patients enrolled to the Phase 1b (SA-105JP) were all Japanese RA patients and mean body weight of the patients was 54.1 ±10.8 kg. On the other hand, the mean body weight of patient in the Phase 3 studies of tocilizumab was 67 to 73 kg. The computed PK of satralizumab 120 mg SC Q4W in RA patients (based on a body weight of 75 kg) is 8.2 µg/mL, which is comparable to tocilizumab 8 mg/kg IV Q4W.

This dose is appropriate based on the following considerations:

Results from Phase 1 single-dose study in healthy subjects and multiple dose study in patients with rheumatoid arthritis showed that satralizumab 120 mg Q4W inhibited IL-6 signaling completely, whereas lower doses (30, 60 mg Q4W) did not.

Systemic inflammatory condition is not expected in patients with NMO and NMOSD compared to RA patients, therefore, inflammatory parameter such as C-reactive protein (CRP) and IL-6 is within normal range in patients with NMO and NMOSD.

Therefore, satralizumab 120 mg Q4W is expected to inhibit IL-6 signaling completely in patients with NMO and NMOSD.

IV tocilizumab 8 mg/kg Q4W, trough level of which is comparable to satralizumab 120 mg Q4W, showed preliminary clinical efficacy in the investigational case reports in patients with NMO and NMOSD. In addition, the PK/PD correlation between tocilizumab and satralizumab is comparable.

Satralizumab has been investigated in 2 studies, including one Phase 1 single ascending dose study in Caucasian and Japanese healthy volunteer (SA-001JP) and one Phase 1b multiple dose study in Japanese RA patients (SA-105JP).

For the NMO Studies BN40890 and BN40900 (SA-307JG and SA-309JG), satralizumab 120 mg SC Q4W was selected based on the assumptions below.

- The sIL-6R complex in plasma, which is a PD marker of satralizumab's mechanism of action increased in a dose dependent manner in the Phase 1 study in healthy subjects. However the increase reached a plateau at higher doses, which suggesting that sIL-6R was saturated and trans-signaling of sIL-6R was completely inhibited.
- The sIL-6R increased also in RA patients and the increase reached a plateau following satralizumab 120 mg SC Q4W. In addition, CRP, which is a PD marker of classical signaling of IL-6, showed sustained decreases, meaning that trans-signaling and classical signaling of IL-6 was completely inhibited by satralizumab 120 mg SC Q4W.
- Based on the hypothesis that the quantity of sIL-6R in NMO is not apparently different from that in, healthy volunteer and RA patients, the elimination rate of satralizumab from circulating blood in NMO patients is not expected to be different from healthy volunteer or RA patients. Therefore, PK in NMO patients is expected to be comparable to healthy volunteer and RA patients.
- The mean trough of satralizumab 120 mg SC in steady state was comparable to tocilizumab 8 mg/kg IV Q4W. Furthermore, the inhibition effect of IL-6 signaling was also comparable between both.
- The exposure dependent safety issues of satralizumab are not expected as long as IL-6 signaling is completely inhibited. Satralizumab 120 mg SC Q4W is the dose which completely inhibits IL-6 signaling in RA patients. In fact, dose-dependent safety issue was not observed in Phase 1b study in RA patients.

Based on above, satralizumab 120 mg Q4W is expected to be an optimal dose in patients with NMO and NMOSD.

PD Response

The assay of sIL-6R can measure free sIL-6R and satralizumab-sIL-6R complex. Therefore, the value of sIL-6R was measured as total of free sIL-6R and the sIL-6R complex (Nishimoto et al., 2008). The sIL-6R complex which is a PD marker of the mechanism of action of satralizumab increased with dose dependent manner in Phase 1 in healthy subjects. However the increase reached to plateau in higher dose, meaning that sIL-6R was saturated and trans-signaling of sIL-6R was completely inhibited. Validation data indicates that the assay for sIL-6R is not inhibited by satralizumab (drug on board).

3.2.4 Justification for Upper Age Limit

For the NMO study BN40900 (SA-309JG), the inclusion criteria allow enrollment of patients 18-74 years inclusive. The upper age limit is based on safety data from patients enrolled in the Phase 1b RA Study SA-105JP. In that study, 13 of 33 patients enrolled in the study were 65 years or older. Preliminary analysis of data from that study suggests that the overall safety profile of satralizumab in patients age 65 or older may be similar to that of patients younger than 65 years.

3.2.5 Justification for Placebo-Controlled Trial

A placebo-controlled superiority trial comparing satralizumab monotherapy to placebo has been designed in this study. There are several key points to justify design of a placebo-controlled monotherapy study for approval of satralizumab:

- One of the primary rationales for a placebo-controlled study is the risk of mandating exposure of patients to unapproved drugs with safety profiles that are not well characterized based on results of randomized studies.
- Patients will be randomized in a 2:1 ratio to active treatment and placebo groups. This study design decreases the probability that on randomization a patient will receive placebo.
- The results of comparing satralizumab monotherapy to placebo would enable the evaluation of the safety and efficacy of satralizumab itself.

The need for placebo for scientific reasons:

A control treatment is generally considered necessary to demonstrate efficacy in various types of clinical trials, including NMO trials.

Placebo controls are needed to differentiate the pharmacologic and PD effects of a drug from the nondrug effects that patients experience in clinical trials. For example, the systematic attention by repeated examinations and frequent visits in a clinical study may lead to noteworthy placebo effects that patients are not exposed to in routine medical practice. Without a placebo group, these non-pharmacologic effects in the artificial environment of a clinical study cannot be distinguished from a real drug effect. Furthermore, many AEs seen in clinical trials are complaints that patients experience independent of drug therapy (e.g., headache, respiratory infections). Thus, the real safety and tolerability profile of a drug can best be evaluated by comparing the incidence of reported AEs with a placebo group.

Placebo controls offer a clear reference point, and they increase the likelihood of attaining statistical significance with a smaller sample size; this means that trials may be done more quickly and with a smaller number of patients.

Finally, the validity of the whole study as a measurement instrument can be proven by showing the difference of active drug versus placebo. If a study that has only active treatment arms does not show a difference between treatments, it cannot be known whether there actually was no treatment difference or if the study just failed to detect the difference (e.g., by poor design or conduct).

Protocol features to minimize the risk of placebo exposure:

- To further reduce the risk of harm to the patients in the placebo group, the following safety measures will be implemented in this study:
- Patients who have conditions indicating a higher risk as per exclusion criteria (e.g., cardiovascular, CNS disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency, known active infection, history of diverticulitis, active tuberculosis (TB), malignancy) will be excluded from participation in the study.
- The study design uses TFR rather than ARR to minimize the number of risk events; important when using a placebo.
- Proactive screening for potential relapses will include a contact with the patient between the scheduled site visits, if required in the judgment of the Investigator. The site staff will query the patient for any change in symptoms or other signs of a potential relapse. If such a symptom is reported, the patient will be instructed to return to the site as soon as possible for an extra visit following relapse.

During the screening period patients will be trained on the possible symptoms and signs of a potential relapse of optic neuritis or myelitis, or a relapse involving other locations. Patients will be instructed to contact the site if they have symptoms or signs of a potential relapse. The patient will be instructed to return to the site as soon as possible for an extra visit following relapse, but no more than three days after reporting the symptoms to the site. This is to allow for a rapid decision on rescue therapy.

- Resources will be put in place to focus on blinding, proactive screening for relapses, and minimizing drop-out. To ensure patients can conveniently return for visits, appointments would be scheduled according to the patient's schedule as much as possible, and objective independent clinical measures of global disability (see Appendix 6). The effectiveness of blinding procedures will be monitored during the trial.

- A process for proactive screening for possible attacks, documentation of the time and content of every report of a possible event by a patient, and a list of sequential tests and procedures to be followed when a patient reports a potential event described above (see Section 3.1.4).
- The adjudication process includes concurrent systematic ongoing data review of all cases to determine if a possible relapse event is missed.

3.3 STUDY ENDPOINTS/OUTCOME MEASURES

3.3.1 Efficacy Outcome Measures

3.3.1.1 Primary Endpoint

i. TFR in the double-blind period

3.3.1.2 Secondary Endpoints

i. Change in VAS score for pain
ii. Change in FACIT fatigue score
iii. Change SF-36 score
iv. Change in EQ-5D score
v. Change in T25W score
vi. The proportion of relapse-free patients
vii. ARR
viii. Change in mRS score
ix. Change in ZBI score
x. Change in EDSS score
xi. Change in visual acuity (Snellen chart)
xii. Change in low-contrast visual acuity (by LCSLC)

3.3.2 Safety Outcome Measures

i. Incidence and severity of AEs, SAEs and AESIs
ii. Vital signs (temperature, SBP and DBP and pulse rate), physical examinations, clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead ECG, suicidality (C-SSRS)

3.3.3 Exploratory Endpoints

i. MRI scans of the brain, optic nerve and spinal cord
MRI for exploratory evaluation is optional and will be conducted at selected sites.

3.3.4 Pharmacodynamic Outcome Measures

i. IL-6
ii. sIL-6R
iii. hsCRP
iv. Anti-AQP4 antibodies

v. Plasmablasts

3.3.5 Pharmacokinetic Outcome Measures

i. Serum satralizumab concentration

3.3.6 Immunogenicity Outcome Measures

i. Incidence of anti-drug antibodies

ii. PK, PD, clinical response, and safety during the study by anti-drug antibody status

4. MATERIALS AND METHODS

4.1 PATIENTS

This study includes patients with NMO or NMOSD. The proportion of patients who are negative for anti-AQP4 antibody at screening will be capped at 30% of total number of patients.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Patients must be diagnosed as either:
   a. NMO as defined by Wingerchuk 2006 criteria*, or
   b. NMOSD as defined by either of *the* following criteria with anti-AQP4 antibody seropositive status at screening.
      i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion)
      ii. Optic neuritis, single, recurrent or simultaneous bilateral
2. Clinical evidence of at least 1 documented relapse (including first attack) in the last 12 months prior to screening.
3. EDSS score from 0 to 6.5 inclusive at screening.
4. Age 18 to 74 years, inclusive at the time of informed consent.
5. Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.

*According to Wingerchuk et al. 2006, a diagnosis of NMO requires all of following criteria:

I. Optic neuritis

II. Acute myelitis

III. At least two of three supportive criteria:

- Contiguous spinal cord lesion identified on an MRI scan extending over 3 vertebral segments
- Brain MRI not meeting diagnostic criteria for multiple sclerosis

- NMO-IgG seropositive status

4.1.2 Exclusion Criteria

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

Exclusion Criteria Related to Neuromyelitis Optica:

1. Clinical relapse onset (including first attack) within 30 days prior to baseline.

Exclusion Criteria Related to Previous or Concomitant Therapy:

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

Exclusions for General Safety:

6. Pregnancy or lactation.
7. For patients of reproductive potential, a positive result from a serum pregnancy test at screening, or not willing to use reliable means of contraception (physical barrier [patient or partner] in conjunction with a spermicidal product, contraceptive pill, patch, injectables, intrauterine device or intrauterine system) during the treatment period and for at least 3 months after the last dose of study drug.
8. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
9. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
10. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, as described;
    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.
11. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
12. Evidence of chronic active hepatitis B or C.
13. History of drug or alcohol abuse within 1 year prior to baseline.
14. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.

15. Evidence of active TB (excluding patients receiving chemoprophylaxis for latent TB infection).
16. Evidence of active interstitial lung disease.
17. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
18. History of malignancy within the last 5 years, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured).
19. History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
20. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.
21. History of Stevens-Johnson syndrome (SJS).

Laboratory exclusion criteria (at screening):

22. Following laboratory abnormalities at screening*.
    a. White blood cells (WBC) < 3.0 $x10^3$/µL
    b. Absolute neutrophil count (ANC) < 2.0 x 10^3/µL
    c. Absolute lymphocyte count < 0.5 x 10^3/µL
    d. Platelet count < 10 x 10^4/µL
    e. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN).

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be stratified by prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse). If a patient was administered B-cell depleting therapies (e.g., anti-CD20 antibody [e.g., rituximab], anti-CD19 antibody) at least once in the year prior to baseline, the patient will be stratified into “B-cell depleting therapy group” and otherwise into the “immunosuppressants/others group” (e.g., oral corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus). Patients will be randomized in a 2:1 ratio to one of the two treatment groups. Administration of study treatment should occur on same day as randomization. For the randomization of patients, the Investigator will use Interactive Web Response and Voice Response Systems (IxRS). Details can be found in the study manual The IxRS will assign patients to a treatment group based on the pre-defined randomization list.

During the double-blind period, the study is performed in a double-blind manner. Study treatments (satralizumab and placebo) are supplied in identical vials and are similar in color and appearance, thereby enabling double-blind conditions.

Patients and all study site personnel are blinded to treatment assignment until all patients have either completed the double-blind period, discontinued early from the study or as described below regarding un-blinding.

Patients, Investigator staff, persons performing the assessments, and data analysts remain blinded to the identity of the treatment, from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of un-blinding, and are not accessible by anyone else involved in the study, (2) The identity of the study treatments (i.e., satralizumab and placebo) is concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration and appearance, (3) Relapse is assessed separately from the treating Investigator, who is responsible for the patient care.

There will be a treating Investigator and an examining Investigator at each site – the treating Investigator responsible for the patient care and the examining Investigator responsible for the administration of the EDSS/FSS. The examining Investigator must be appropriately qualified to assess EDSS/FSS. The treating Investigator will have access to both safety and efficacy data and will make treatment decisions based on the patient's clinical response and laboratory findings. The examining Investigator will have access via the paper form only to the EDSS/FSS data (including Relapse Assessment Form) except in an emergency (such as there is no physician other than for EDSS/FSS assessment in study site) and will not consult the patient medical records. Patients will be instructed not to discuss any symptoms with the examining Investigator in order to avoid potential un-blinding of the examining Investigator; the examining Investigator should remind the patient at the start of the examination. At the protocol-specified study visit that includes an EDSS/FSS assessment (see Appendix 1) from baseline in the double-blind period, the examining Investigator will complete and sign a form which includes the kind of assessment form examining Investigator used for assessment and the confirmation of blinding the patient medical record, the study-related data apart from EDSS/FSS and information apart from neurological findings since the last EDSS/FSS assessment visit.

In addition, site personnel, study monitor, the Sponsor and the study team will be blinded for some of the laboratory results (including serum satralizumab concentration, hsCRP, IL-6, sIL-6R, anti-drug antibody [ADA], anti-AQP4 antibodies [except screening], plasmablasts and complement [C3, C4, and CH50]) before the primary analysis.

The study blind should not be broken except in a medical emergency (where knowledge of the study treatment received would affect the treatment of the emergency), due to regulatory requirement (e.g., for SAE reporting), IDMC/IDCC or sample management at laboratory for pharmacokinetic and immunogenicity objectives.

The blind for each patient must only be broken following discussion between the Investigator and the PAREXEL Medical Monitor on a case-by-case basis.

The Investigator should notify the Medical Monitor prior to contacting IxRS for un-blinding. All calls resulting in an un-blinding event will be recorded and reported by the IxRS to the Medical Monitor. If an Investigator, site personnel performing assessments, or patient, is un-blinded, this must be listed as major protocol violation. The medical monitor and Investigator should consult each other to decide whether a patient who had his/her emergency key code broken can enter the open-label extension period.

Serious unexpected suspected adverse reactions (SUSARs), which are subject to expedited reporting, should be un-blinded by authorized personnel of the Sponsor who are not involved in the satralizumab clinical trial program before submission to the Regulatory Authorities.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging and Handling

4.3.1.1 Satralizumab and Placebo

Satralizumab

Investigational product name:	Satralizumab (also known as SA237-120)
Appearance:	Colorless to slightly yellow liquid
Formulation	Liquid for SC injection
Manufacturing process:	The drug substance manufacturing process consists of a cell culture process and a purification process. The cell line used for the cell culture process is generated from a Chinese Hamster Ovary cell line using recombinant deoxyribose nucleic acid (DNA) technology
Manufacturer:	Drug product in vial: Chugai Pharma Manufacturing Co., Ltd. 5-1, Ukima, 5-Chome, Kita-ku Tokyo, 115-8543, Japan Drug product in plastic prefilled syringe (PFS) with needle safety device (NSD): Chugai Pharma Manufacturing Co., Ltd. 16-3 Kiyohara-Kogyodanchi, Utsunomiya Tochigi, 321-3231, Japan
Composition:	The drug product is a vial or a plastic PFS with NSD filled with 1.0 mL of solution, which contain 120 mg of satralizumab. As excipients, it contains L-histidine, L-arginine, L-aspartic acid and polyoxyethylene (160) polyoxypropylene (30) glycol, and it has a pH of 5.5 to 6.5.
Storage conditions:	The drug product is stored at 2-8°C, protected from light until use

Satralizumab PFS with NSD can be used in the extension period.

For further details on satralizumab, see the current Investigator's Brochure.

Placebo

Satralizumab placebo vial is identical in composition to satralizumab vial, but does not contain the satralizumab active ingredient. It is identical in appearance and packaging to satralizumab.

Kit ID, lot number and expiry date will be labeled. Local labeling may be different in some countries according to local regulatory guidelines. Packaging will be the same for

all countries. All satralizumab vials, placebo vials and satralizumab PFS with NSD must be stored at a controlled temperature of 2-8°C, and handled according to Good Manufacturing Practice and Good Clinical Practice (GCP) procedures. A temperature log must be kept recording the storage temperature of the satralizumab vials, placebo vials and satralizumab PFS with NSD, and be available for regular review by the study monitor.

Please refer to the pharmacy section of the study manual for details.

4.3.2 Dosage, Administration, and Compliance

All study centers will be provided with a supply of satralizumab and placebo after all the necessary documentation is in place for the study but before the first administration of study treatment. If a patient is found to be eligible for the study, the Investigator or designated person will be informed via the IxRS as to which coded study treatment to use for injection.

Satralizumab 120 mg or placebo 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 for that visit. Choice of needle and syringe sizes is left to the discretion of the Investigator. This will be performed at the study center in a setting where medications for treatment of anaphylaxis and resuscitation facilities are available. Patients should remain at the study center for at least 1 hour in order to receive medication immediately if anaphylaxis occurs.

If study drug is not 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). Site staff should consult with the Medical Monitor if in doubt as to how to schedule dosing in such circumstances.

4.3.2.1 Satralizumab and Placebo: Double-blind period

The patient will receive an SC injection of satralizumab or placebo at Weeks 0, 2 and 4, and Q4W thereafter during the double-blind period. The double-blind period ends when either the patient has a protocol-defined relapse which is adjudicated by CEC, the total number of registered relapses is 44 or 1.5 years after the date of randomization of the last patient enrolled, whichever comes first.

Patients who experienced a relapse during the double-blind period should continue the double-blind period regardless of rescue therapy unless the patient experiences a relapse which is adjudicated by CEC as a protocol-defined relapse, and will continue administration of study treatment at the discretion of the Investigator.

4.3.2.2 Satralizumab: Extension period

Patients who complete the double-blind period (see the section "Length of Study" in PROTOCOL SYNOPSIS) or experience a protocol-defined relapse which is adjudicated by the CEC in the double-blind period can enter the open-label extension period. In the open-label extension period, the patient will receive an SC injection of satralizumab at Week 0, 2 and 4, and Q4W thereafter, *with the last study drug administration on or before 31 December 2021.*

For patients who experienced a protocol-defined relapse which is adjudicated by CEC, satralizumab should start in the stable disease condition (Day 31 or later, where Day 1 is defined as the day of onset of a protocol-defined relapse which is adjudicated by CEC). For patients who completed the double-blind period, satralizumab should start after 4 weeks (± 7 days) from the last dosing in the double-blind period.

Patients who experience a relapse during the extension period will continue administration of satralizumab at the discretion of the Investigator.

In the OLE period after Week 48, and 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, or home administration by a mobile nurse) will be allowed in emergency situations such as the SARS-CoV-2 (COVID-19) pandemic.

Following the implementation of Protocol Version 10 and 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, or home administration by a mobile nurse) may be allowed on scheduled study drug administration days that do not require additional assessments that must be performed on site (Appendix 1).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (satralizumab or placebo) will be provided by the Sponsor or its designee. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. See the study manual for details of procedures for handling temperature excursions. Any damaged shipments will be replaced.

IMP may be disposed of at the study site according to the study site's institutional standard operating procedure. The site's method of IMP destruction must be agreed upon by the Sponsor or its designee. The site must obtain written authorization from the Sponsor or its designee before any IMP is destroyed and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at site, dispensed from site, and returned to the Sponsor or designee, or disposed of by the study site should be recorded.

If patients are administered satralizumab outside of the study site, IMP may be shipped to the patient's home from the study site (only in emergency situations such as the SARS-CoV-2 [COVID-19] pandemic) or given to the patient to take home during a study site visit. Patients will be asked to return all IMP boxes at their next on-site visit.

Please refer to the pharmacy section of the study manual for details regarding IMP dispensation, return and destruction.

4.4 CONCOMITANT THERAPY

Data on details of prior and concomitant medications (e.g., prescription drugs and over-the-counter drugs) should be reported to the Investigator and recorded in the Concomitant Medications section of the eCRF as follows:

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="3">Prior to and throughout the study</th></tr>
<tr><th>More than 4 weeks prior to baseline</th><th>Within 4 weeks prior to baseline</th><th>From baseline to the end of study</th></tr>
<tr><td rowspan="4">NMO/ NMOSD treatments</td><td>Relapse prevention</td><td colspan="2">indication, drug name*, dose, frequency, route, first administration (date), last administration (date)/continuing at the end of the study</td><td></td></tr>
<tr><td rowspan="2">Rescue therapy</td><td colspan="3">indication, drug name*, route, first administration (date), last administration (date)/continuing at the end of the study</td></tr>
<tr><td></td><td colspan="2">dose, frequency</td></tr>
<tr><td>Pain</td><td>-</td><td colspan="2">indication, drug name*, route, dose, frequency, first administration (date), last administration (date)/continuing at the end of the study</td></tr>
<tr><td colspan="2">Other treatments</td><td>-</td><td colspan="2">indication, drug name*, route, first administration (date), last administration (date)/continuing at the end of the study</td></tr>
</table>

*Trade name is preferred.

4.4.1 Major Permitted Therapies for NMO

Permitted Medication/Therapy During the Double-Blind Period

1. Rescue therapy for clinical relapse; pulse IV corticosteroids, oral corticosteroids for tapering, intravenous immunoglobulin (IVIG) and/or apheresis (including plasma exchange and plasmapheresis)
2. Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).
   Starting of pain medications is permitted; however, the dose should be stable during the double-blind period. In case pain control is insufficient, dose increase or change of pain medication is permitted. Dose decrease and temporary treatment suspension are permitted for only safety reasons.

Permitted Medication/Therapy During the Extension Period

1. Rescue therapy for clinical relapse; pulse IV corticosteroids, oral corticosteroids for tapering, IVIG and/or apheresis (including plasma exchange and plasmapheresis)
2. Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen)
3. *During the OLE period: Treatment with corticosteroids (e.g., oral, nasal) for AEs (i.e., indications other than a relapse) is permitted; the treatment duration should be kept as short as possible*

Rescue therapy should proceed at the discretion of the treating Investigator after the examining Investigator or rater has completed EDSS/functional system score (FSS) assessment except in an emergency. Rescue therapy can be started based on Investigator's decision.

4.4.2 Prohibited Therapy

1. Prior to and throughout the study
   - IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation, bone marrow transplantation.
2. From 2 years prior to baseline to the end of the study.
   - Anti-CD4, cladribine, cyclophosphamide, mitoxantrone.
3. From 6 months prior to baseline to the end of the study.
   - Eculizumab, anti-BLyS monoclonal antibody (e.g., belimumab), anti-CD20 treatment (e.g., rituximab, ocrelizumab, ofatumumab), any other treatment for prevention of MS relapse (e.g., interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate).
4. From 3 months prior to baseline to the end of the study.
   - Treatment with any investigational agent (other than satralizumab).

5. From 6 weeks prior to baseline to the end of the study.
    - Immunization with live or live attenuated vaccine.
6. From baseline to the end of the study.
    - Immunosuppressants (e.g., cyclosporine, methotrexate, tacrolimus)*, and during the double-blind period, azathioprine and mycophenolate mofetil.*
    - *Treatment with azathioprine or mycophenolate mofetil in the OLE period should only be initiated after consultation with the Medical Monitor.*
    - Corticosteroids, IVIG excepting for rescue therapy for clinical relapse. *For treatment with corticosteroids for indications other than relapse therapy in the OLE period, see Section 4.4.1.*

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history refers to clinically significant diseases, including but is not limited to medication allergies, anaphylaxis, cancer, demyelinating disease other than NMO and NMOSD, neurologic disorders, psychiatric disorders, rheumatologic disorders, musculoskeletal diseases, cardiovascular disease, pulmonary disease, gastrointestinal diseases including hepatic diseases, hematologic disorders and renal disease.

Demographic data will include age (date of birth), sex and race/ethnicity. These data are required in order to perform subgroup analyses to evaluate the consistency of the results across race/ethnic groups. Previous relapse (including first attack) *and date of NMO or NMOSD diagnosis* will be recorded in the eCRF. Height will be recorded at baseline and body weight will be recorded at baseline and every 24 weeks thereafter.

4.5.1.2 Hepatitis B screening

Patients who are hepatitis B surface antigen (HBsAg) positive will be excluded from the study.

Patients for whom a positive result for antibody to HbsAg (HBsAb) is clearly associated with hepatitis B virus (HBV) vaccination can be enrolled. If not, hepatitis B viral DNA will be measured at a central laboratory.

If total hepatitis B core antibody (HBcAb) status is positive, hepatitis B viral DNA will be measured at a central laboratory.

If hepatitis B viral DNA is detectable, the patient must be excluded. If undetectable, the patient may be enrolled. In these cases hepatitis B viral DNA measurements must be performed regularly at approximately 12 weekly intervals during the study.

4.5.1.3 Hepatitis C screening

Patients with negative hepatitis C serology can be enrolled. Patients with positive hepatitis C serology will be excluded from the study. However, if hepatitis C virus (HCV) ribonucleic acid (RNA) is undetectable 12 weeks after HCV treatment completion, the patient can be enrolled.

4.5.1.4 Screening for Tuberculosis

For entry into this study, patients should be screened for TB at site according to local guidance (or instruction for TB screening if none exist). Result of screening tests will be reported on the eCRFs. If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 3 weeks prior to initiating study treatment administration.

For further details on screening for TB, see Appendix 12.

4.5.1.5 Magnetic Resonance Imaging

During the screening period, patients who are classified as PML based on the local imaging assessment will be excluded. If patients who show lesions suspicious for PML by brain MRI, JC virus in the CSF will be measured - if “detectable” or “undetectable with high clinical suspicion”, the patient must be excluded. Patients who are anti-AQP4 antibody negative and have an MRI with classic MS features on T2 weighted imaging with Dawson’s fingers, adjacent to lateral ventricles, juxtacortical and/or cortical lesions must also be excluded.

4.5.1.6 Vital Signs

Vital signs will include measurements of pulse rate, temperature and SBP and DBP while the patient is in a seated position for at least 5 minutes. At the injection visit, vital signs will be measured before and after study treatment administration. Measurement of pulse rate, temperature, SBP and DBP should take place immediately before and then at 15 (±5) and 60 (±5) minutes after study treatment administration.

4.5.1.7 Physical Examination

A complete physical examination should include an evaluation of the head, neck, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal and respiratory, gastrointestinal and genitourinary systems. There should be a detailed examination of neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event page of the eCRF.

4.5.1.8 Efficacy Assessments

Relapse Assessment

All new or worsening neurological events compatible with NMO representing a clinical relapse are to be reported in the eCRF. 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 clinical relapse has occurred or not. Clinical relapse should be confirmed whether it meets the criteria for protocol-defined relapse or not. There will be a treating Investigator and an examining Investigator at each site to keep blindness of relapse assessment – the treating Investigator responsible for the patient care and the examining Investigator responsible for the administration of the EDSS/FSS. The examining Investigator must be appropriately qualified to assess EDSS/FSS. The treating Investigator will have access to both safety and efficacy data and will make treatment decisions based on the patient's clinical response and laboratory findings. The examining Investigator will have access via the paper form only to the EDSS/FSS data (including Relapse Assessment Form) except in an emergency (such as there is no physician other than for EDSS/FSS assessment in study site) and will not consult the patient medical records. The EDSS assessment should always be performed by the same examining Investigator from baseline whenever it is feasible and, in the double-blind period, will be performed with the assessor blinded to the patient's treatment assignment. The examining Investigator must perform EDSS/FSS assessment within seven days after the patient reports the symptoms to the site.

The separation of the role of the treating and examining Investigator should be maintained during the OLE extension period whenever possible.

Patients will be instructed not to discuss any symptoms, other than those to EDSS/FSS assessment, with the examining Investigator; the examining Investigator should remind the patient at the start of the examination to discuss any symptoms, other than those to EDSS/FSS assessment, with the treating Investigator. Please see Section 3.1.4 for procedure of screening for a possible relapse.

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

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

The base of comparison for the increase is the score in the most recent EDSS/FSS assessment visit. 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. All patients with new neurological symptoms suggestive of relapse should have EDSS/FSS performed during an unscheduled visit. In addition to eCRF, a separate Relapse Assessment Form and accompanying necessary data will be completed by the site and sent to the PAREXEL Pharmacovigilance department (please refer to the instructions in the study manual) *during the double-blind period*. Relapse Assessment Form will be completed in case of the occurrence of any new or worsening neurologic symptoms or EDSS/FSS change shown above at EDSS/FSS assessment visit. During the double-blind period, the form and the data will be reviewed by a CEC. Details regarding the CEC responsibilities and the process of adjudication are described in the CEC charter (see Section 3.1.4).

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 NMO, and is included as a secondary endpoint in this study. 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 assisted 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.

A reference to the EDSS/FSS is included in Appendix 2.

Health Status Measurements Using Short Form-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile (vitality, physical functioning, bodily pain, general health, role-physical, role-emotional, social role functioning and mental health) of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a disease, or treatment group.

A reference to the SF-36 questionnaire is included in Appendix 3.

Visual Analogue Scale for Pain

The VAS for pain is a scale 100 mm in length that the patient uses to rate the intensity of the pain they experience, from no pain to pain as bad as it could be.

A reference to the VAS for pain is included in Appendix 4.

Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale

The FACIT fatigue scale is a short, 13-item tool that measures and individual's level of fatigue during their usual daily activities over the past 7 days (Webster et al. 2003). The level of fatigue is measured on a five-point scale (0 = not at all to 4 = very much).

A reference to the FACIT Fatigue questionnaire is included in Appendix 5.

Visual Function Testing

Visual function testing will be performed with eye charts. Visual acuity will be measured by a Snellen chart and LCSLC.

Visual acuity measured using a Snellen chart will be assessed monocularly. Visual acuity of LCSLC will be binocularly assessed using 100%, 2.5% and 1.25% contrast charts, from a distance of 2 meters.

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.

Disability Testing using Modified Rankin Scale

The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The mRS is scored from 0 (no symptoms at all) to 6 (death).

A reference to the mRS is included in Appendix 6.

Zarit Burden Interview

The ZBI is a popular caregiver self-report measure that originated as a 29-item questionnaire (Zarit et al, 1980). The revised version contains 22 items. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale.

The ZBI should be conducted for the patient's caregiver (e.g., family, relative) (when there is one), if the Investigator considers the caregiver to be reliable by in supporting the patient's daily life. The caregiver has knowledge of the patient's condition and symptoms, and is acting in an informal or unpaid capacity. Caregivers will be asked to sign a separate written informed consent for the collection of data using the ZBI. If a caregiver withdraws from the study, the assessment of ZBI is terminated.

A reference to the ZBI questionnaire is included in Appendix 7.

EQ-5D

The EQ-5D scale is a generic measure of health related quality of life that rates subject 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.

A reference to the EQ-5D questionnaire is included in Appendix 8.

Timed 25-Foot Walk (T25W)

The T25W is a quantitative measure of lower extremity function and is the component of the Multiple Sclerosis Functional Composite (MSFC) (Fischer et al., 1999). The patient is directed to one end of a clearly marked 25-Foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. The 25-foot lane will be certified by the study coordinator or nurse.

4.5.1.9 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used to assess the lifetime suicidality of a patient and to track suicidal events through the treatment. The scale will be administered at the time points indicated in the Schedule (see Appendix 1) for prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential

lethality. The “C-SSRS at baseline” should be collected at baseline and the “C-SSRS since last visit” should be collected at subsequent visits.

References to the C-SSRS form are included in Appendix 10 (C-SSRS at baseline) and Appendix 11 (C-SSRS since last visit).

4.5.1.10 Laboratory Assessments

Samples for the following laboratory tests will be sent to the Central Laboratory for analysis (except urinalysis and pregnancy tests). Instruction manuals and supply kits will be provided for all central laboratory assessments. *If a patient cannot visit the study site in emergency situations 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, international normalized ratio (INR), red blood cell (RBC) count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells]).
- Serum chemistry (sodium, potassium, chloride, calcium, phosphorous, ferritin, blood urea nitrogen (BUN), creatinine, total bilirubin, fibrinogen, total protein, albumin, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, creatine kinase (CK), uric acid).
- 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 serum pregnancy test at the study site at the screening visit. During the study, serum or urine pregnancy tests will be performed at site, and confirmed as negative before the administration of study treatment (except Week 2 of double-blind and extension period). 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 OLE period of the study (e.g., confirmed* post–menopausal status*) will not require further pregnancy testing. Post–*menopausal status is defined as any of the following: natural menopause with *last* menses > 1 year ago; radiation induced with last menses > 1 year ago*, or due to bilateral oophorectomy.*
- Complement tests (C3, C4 and CH50).
- Plasmablasts.

- hsCRP.

Samples for the following laboratory tests will be sent to Sponsor's designee for analysis.

- Pharmacokinetic/Pharmacodynamic assessments.
  - Serum satralizumab concentration, IL-6, sIL-6R, anti-AQP4 antibody.
- *Immunogenicity* assessments.
  - Anti-drug antibodies.
- Chugai Clinical Sample Repository (CCSR) (blood/serum/plasma).

The maximum blood volumes that may be taken at each visit, depending upon the assessments the patient has opted into, are summarized in Table 1.

Table 1 Maximum Blood Volumes

Visit(s)	Maximum blood volume taken (mL) [1]
Double-blind period	
Screening	35.5
Week 0	46
Week 2	32.5
Weeks 4 & 8	44
Weeks 5 & 6, Dose outside the visit window	3.5
Weeks 12, 24 & 48, every 24 weeks after Week 48 and at the withdrawal visit	47
Weeks 16, 20, 28, 32, 40, 44, every 4 weeks after Week 48	26.5 [2]
Week 36	29.5
At extra visit on relapse	42
Extension period	
Weeks 0, 24, 48	32.5
Week 2	16
Weeks 4, 8, 16, 20, 28, 32, 40, 44	26.5
Every 12 weeks after Week 48	21
Weeks 12, 36 & every 24 weeks after Week 48	29.5
Dose outside the visit window	3.5
At extra visit on relapse	27.5
Last observation visit and withdrawal visit	29.5

[1] Blood volumes of TB test with using blood sample and serum pregnancy test are calculated as 3.0 and 2.0 respectively. These values are depending on the study site.

[2] 29.5 mL every 12 weeks after Week 48.

Assessment of hsCRP, PK, IL-6, sIL-6R, anti-drug antibody, anti-AQP4 antibodies (except screening), plasmablasts and complement (C3, C4, and CH50) will be performed in a blinded manner during the double-blind period of the study.

For details on name and address of laboratory, sampling procedures, sample storage and shipment, see the materials in the Site Laboratory Binder.

4.5.1.11 Electrocardiograms

For all patients who consent to the study, 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 those patients who consent to additional PK testing, triplicate digital ECG recordings will be obtained with approximately 2–5 minutes between each ECG recording at each specified time point from baseline. The average of the three readings will be used to determine ECG intervals (e.g., PR, QT and QT intervals).

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 using 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.

For those patients who consent to additional PK testing, triplicate digital ECG should be also performed at Weeks 5 and 6, and copies of ECG tracings will be collected at baseline and Weeks 5, 6, 24 and 48 by PAREXEL and sent to the Sponsor.

4.5.1.12 Adverse Events

The reporting of AEs is detailed in Section 5.3.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Signed Informed Consent Forms (ICFs) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to baseline, unless otherwise specified. All screening evaluations must be completed and reviewed to confirm that patient meets all eligibility criteria before randomization. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a patient fails any laboratory inclusion/exclusion criteria at screening, the test can be repeated within 28 days of screening period.

If a patient has not met all inclusion/exclusion criteria within 28 days of the original screening visit, rescreening which refers to repeating whole screening process can be conducted twice. Each patient must be re-consented before rescreening occurs. As part of the rescreening process, a TB test, an X-ray, hepatitis tests, MRI and anti-AQP4 antibodies testing are not required if each of them are conducted within 12 weeks prior to baseline. Patients may be eligible for rescreening up to two additional times. A retest is defined as any assessment repeated within 28 days of screening.

If relapse occurs during screening period, the patient should be treated as a screening failure and should receive the site-specific acute relapse treatment. The patient can be rescreened with a new ICF.

Please see Appendix 1 for the schedule of screening assessments.

4.5.2.2 Assessments During Treatment

Assessment during treatment applies to both double-blind and extension period. All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

If study drug cannot be administered on the scheduled dosing day, 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 the scheduled study visit assessments.

Following the implementation of Protocol Version 10, administration of satralizumab prefilled syringes outside of the study site may be allowed, in accordance with local regulations, only if no on-site assessments are scheduled for that dosing day (Appendix 1). 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 during the OLE period after Week 48 (Appendix 1). 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 5.3.5.

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Last Observation Visit/Withdrawal Visit

The Withdrawal Visit is for patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks after the last dosing. At the Withdrawal Visit of the double-blind period, a complete set of the assessments performed every 24 weeks after Week 48 of the double-blind period is to be performed including a chest X-ray. At the Withdrawal Visit of the extension period, a complete set of the assessments performed every 24 weeks from Week 0 to Week 48 of the extension period is to be performed (including a chest X-ray) with the exception of the anti-AQP4 antibody assay.

Patients who complete the double-blind period or experience a protocol-defined relapse which is adjudicated by CEC in the double-blind period can enter the open-label extension period. Patients completing the open-label extension period will attend a Last Observation Visit 12 weeks after the last dose of satralizumab.

The Last Observation *Visit* will be conducted 12 weeks after the last dose of satralizumab for patients who complete the *open-label* extension period. At this visit, a complete set of the assessments performed at Week 0 of the extension period is to be performed (including a chest X-ray) with the exception of the anti-AQP4 antibody assay. *Patients who complete the OLE period with the last study drug administration on or before 31 December 2021 and decide to continue treatment with satralizumab outside of this study will not have to complete the Last Observation Visit.*

After the Last Observation Visit or Withdrawal Visit, AEs should be followed as outlined in Sections 5.5 and 5.6.

Please see Appendix 1 for the schedule of assessments performed at the Withdrawal Visit and the Last Observation.

4.5.2.4 Follow-Up Assessments

Safety Follow-Up will be conducted for patients who withdraw from the study in the double-blind period due to clinical relapse and will last for 24 weeks from the last dosing. A telephone interview will be conducted by site personnel every 4 weeks from last dosing to record details of any medications and treatments NMO/NMOSD the patient is

taking and to identify any new or worsening neurological symptoms and data will be entered into the relevant pages of the eCRF.

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Extra Visits due to Relapse

If patients develop new or worsening neurological symptoms they will attend for an extra visit within the shortest reasonable timeframe to have a relapse assessment at the investigational site. Please see Appendix 1 for assessments that are required to be performed in case of such extra visits.

4.5.2.6 Unscheduled Visits

Any unscheduled visits during the study apart from those mentioned above should be captured in the unscheduled visits module in the eCRF.

Regular phone calls to patients will be conducted in order to ensure that relapses are not missed.

4.5.3 Study Schedule

The observation and tests listed in Table 6 (Observation and Test Schedule in the Double-Blind Period), Table 7 and Table 8 (Observation and Test Schedule in the Extension Period) will be performed.

4.5.3.1 Screening Period (Day -27 to 0 [Week -4 to -1])

All participants must sign an informed consent form before any study-specific procedures are performed. All screening procedures are to be conducted within 28 days of first drug administration, except as noted below:

Day -27 to 0 (Week -4 to -1)

- Complete informed consent [Informed consent must be obtained prior to first screening assessment, but if informed consent is obtained before the 28-day screening period (i.e., before Day -27), all screening assessments must be completed within 28 days prior to baseline (i.e., from Day -27 to 0).
- Review the study inclusion/exclusion criteria
- Record medical history
- Physical examination
- Record vital signs including body temperature, systolic and diastolic blood pressure and pulse rate
- ECG should be performed prior to blood draws.

- TB test (e.g., tuberculin test and or/ Quantiferon® test) should be conducted according as local guidance.
- Perform Chest X-ray
- Perform pregnancy test for females of child-bearing potential. Serum beta human chorionic gonadotropin (β-hCG) must be performed at screening. During the study, serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Perform laboratory test: RBC, hemoglobin (Hb), hematocrit (HCT), WBC, WBC differentiation, platelets (PLT), INR, fibrinogen, total protein, albumin, total bilirubin, alkaline phosphatase (ALP), AST, ALT, γ-GTP, LDH, total cholesterol, LDL, HDL, triglyceride, ferritin, BUN, creatinine, CK, sodium (Na), chloride (Cl), potassium (K), calcium (Ca), phosphorus (P), complement (CH50, C3, C4), uric acid, urinary glucose, urinary protein, urinary occult blood, urobilinogen.
- Hepatitis test includes HBsAg, HBcAb, HBsAb, hepatitis C virus antibody (HCVAb). If a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus or HBcAb status is positive, hepatitis B viral DNA will be measured.

Efficacy

- Conduct EDSS
- Brain MRI for screening is required for excluding PML or MS. If PML cannot be excluded by MRI, JC virus in the CSF will be measured. Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent.

Exploratory Biomarker

- Collect sample for Anti-AQP4 antibody (enzyme linked immunosorbent assay [ELISA]).

4.5.3.2 Treatment Period

Safety including adverse events and concomitant medications and efficacy including relapse assessment will be monitored and recorded throughout the treatment period of the study. During the double-blind period, the site will contact the patient weekly by phone calls between the scheduled site visits, to query any change in symptoms or other signs of a potential relapse.

Day 1 (Week 0-Baseline)

- Review the study inclusion/exclusion criteria
- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Record body height and weight

- Physical exam
- Record vital signs including body temperature, systolic and diastolic blood pressure and pulse rate which are to be measured before dosing and 15 min (±5 min) and 60 min (±5 min) after dosing in case of study treatment injection visit
- Perform ECG (PAREXEL will collect copies of ECG tracings of those patients who provided informed consent for additional PK sampling). ECG should be performed prior to blood draws.
- Perform pregnancy test
- Perform laboratory test: RBC, Hb, HCT, 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
- Perform C-SSRS (C-SSRS at baseline scale should be used)

Efficacy

- Perform EDSS/FSS, Visual Function Testing (Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR-this sampling is optional and will require a separate signature on the informed consent

- Blood samples for DNA analysis, 2 mL blood samples will be taken from the patients who consent to the procedure and to CCSR project prior to the first injection on Day 1 (Baseline).
- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Day 15 (Week 2)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Laboratory test: RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Day 29 (Week 4)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test: RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Day 36 (Week 5) and Day 43 (Week 6)

These visits are optional and will require a separate signature on the informed consent

- Perform ECG-the copies of ECG chart should be collected for only patients who consent to additional PK sampling. ECG should be performed prior to blood draws.

PK

- Obtain PK sample

Day 57 (Week 8)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test: RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Day 85 (Week 12)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Efficacy

- Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent (Window in days is within ±28 days).

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Day 113 (Week 16)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam

- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 141 (Week 20)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 169 (Week 24)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.

- Record body weight
- Physical exam
- Record vital signs
- Perform ECG - the copies of ECG chart should be collected only for patients who consent to additional PK sampling. ECG should be performed prior to blood draws.
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Efficacy

- Perform EDSS/FSS, Visual Function Testing (Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- Perform ZBI (Window in days is within ±28 days)
- Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent (Window in days is within ±28 days).

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Day 197 (Week 28)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 225 (Week 32)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 253 (Week 36)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 281 (Week 40)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test

- Laboratory test: RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Study Day 309 (Week 44)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Physical exam
- Record vital signs
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Perform C-SSRS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Day 337 (Week 48)

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Record body weight
- Physical exam

- Record vital signs
- Perform ECG-the copies of ECG chart should be collected for only patients who consent to additional PK sampling. ECG should be performed prior to blood draws.
- Perform pregnancy test
- Laboratory test RBC, Hb, HCT, 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
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Efficacy

- Perform EDSS/FSS, Visual Function Testing (Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- Perform ZBI (Window in days is within ±28 days)
- Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent (Window in days is within ±28 days).

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

After Day 337 (Week 48), the following assessments to be performed:

Every 4 Weeks

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Perform physical exam
- Record vital signs
- Perform pregnancy test for females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.
- Laboratory test: RBC, Hb, HCT, 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
- Hepatitis B viral DNA must be monitored every 12 weeks in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- Adverse events and concomitant medications will be monitored and recorded throughout the study

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody

Every 24 Weeks

- Administer study treatment injection (SC) after all other study-related procedures have been performed.
- Record body weight.
- Perform physical exam.
- Record vital signs.

- ECG should be performed prior to blood draws.
- Perform pregnancy test for females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.
- Laboratory test RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- Adverse events and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- EDSS/FSS.
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample.
  - Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
  - Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

During the double-blind period, when an extra visit at relapsing occurs, the following assessments are to be performed:

- Perform physical exam
- Record vital signs
- Laboratory test RBC, Hb, HCT, 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

Safety

- Adverse events and concomitant medications will be monitored and recorded throughout the study

Efficacy

- EDSS/FSS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Withdrawal visit (WD)

This visit should be performed for patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks after the last dosing. Assessments to be performed at this visit are:

- Record body weight
- Perform physical exam
- Record vital signs
- ECG should be performed prior to blood draws.

- Perform Chest X-ray
- Perform pregnancy test for females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.
- Laboratory test RBC, Hb, HCT, 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
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- EDSS/FSS
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.
- Obtain plasmablasts sample.

Immunogenicity

- Collect sample for anti-drug antibody.

CCSR- this sampling is optional and will require a separate signature on the informed consent

- Serum and plasma blood samples will be taken from the patients who consent to the procedure. 5 mL of serum blood and 4.5 mL for plasma blood.

Safety Follow-up (SFU)

SFU will be conducted for patients who withdraw from the study in double-blind period due to clinical relapse and will last for 24 weeks from the last dosing. A telephone interview will be conducted by site personnel every 4 weeks from last dosing to identify any new or worsening neurological symptoms. The following assessments will be performed at these visits:

Safety

- Information on concomitant medication/therapy for NMO and NMOSD will be collected.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

Observation and Test Schedule in the Extension Period
Week 0

Patients who experienced a protocol-defined relapse which is adjudicated by CEC can visit the study site in the stable disease condition (Day 31 or later, where Day 1 is defined as the day of onset of a protocol-defined relapse which is adjudicated by CEC). Patients who completed the double-blind period can visit the study site after 4 weeks (± 7 days) from the last dosing in the double-blind period. The following procedures will be performed:

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Record body weight.
- Perform physical exam.
- Record vital signs.
- Perform ECG prior to blood draws.
- Perform pregnancy test for females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Laboratory test: RBC, Hb, HCT, 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.

- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBsAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.
- Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent (Window in days is within ±28 days). Only for patients who end the double-blind period by Week 48 of the double-blind period.

PK-PD

- Obtain PK sample.
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.

Immunogenicity

- Collect sample for anti-drug antibody.

Week 2

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Perform physical exam.
- Vital signs.

- Laboratory test: RBC, Hb, HCT, 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.
- Perform C-SSRS

Safety

- AE and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

From Week 0 to Week 48, the following procedures will be performed in the Extension Period:
Every 4 weeks

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Perform physical exam.
- Record vital signs.
- Perform pregnancy test for females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored every 12 weeks in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

PK-PD

- Obtain PK sample.
- Obtain PD sample includes IL-6, sIL-6R and hsCRP.

Immunogenicity

- Collect sample for anti-drug antibody.

Every 24 Weeks

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Record body weight.
- Perform physical exam.
- Record vital signs.
- ECG should be performed prior to blood draws.
- Perform pregnancy test for females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AE and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS.
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.

- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.
- Performing an MRI scan for exploratory evaluation is optional, will be conducted at selected sites, and will require a separate signature on the informed consent (Window in days is within ±28 days. Week 48 only.). Only for patients who end the double-blind period by Week 48 of the double-blind period.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP and anti-AQP4 antibody.

Immunogenicity

- Collect sample for anti-drug antibody

After Week 48, the following procedures will be performed in the Extension Period:

Every 4 weeks

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- *In accordance with local regulations, patients may have study drug administered outside of the study site for these visits. In such cases, patients should be followed up through phone calls from the study site to monitor treatment compliance and perform safety and efficacy assessments as described below.*

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

Every 12 Weeks

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Perform physical exam.
- Record vital signs.
- Perform pregnancy test for females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.
- Laboratory test: RBC, Hb, HCT, 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.

- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.

Every 24 Weeks

- Administer satralizumab injection (SC) after all other study-related procedures have been performed.
- Record body weight.
- Perform physical exam.
- Record vital signs.
- ECG should be performed prior to blood draws.
- Perform pregnancy test for females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AE and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS.
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample

Immunogenicity

- Collect sample for anti-drug antibody

During the Extension Period, when extra visits at relapsing occur, the following procedures will be performed:

- Perform physical exam
- Record Vital signs
- Laboratory test: RBC, Hb, HCT, 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

Safety

- Adverse events and concomitant medications will be monitored and recorded throughout the study

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP until Week 48 and anti-AQP4 antibody.

Immunogenicity

- Collect sample for anti-drug antibody after Week 48.

Last Observation Visit

This visit will be conducted 12 weeks after the last dose of satralizumab for patients who complete the extension period. The following procedures will be performed:

- Record body weight.
- Perform physical exam.
- Record vital signs.
- ECG should be performed prior to blood draws.
- Perform chest X-ray.
- Perform pregnancy test for females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study.

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS
- Visual Function Testing (visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP

Immunogenicity

- Collect sample for anti-drug antibody

Withdrawal Visit

For patients who withdraw from the study, every effort should be made to conduct the visit at 12 weeks after the last dose of satralizumab. The following assessments will be performed:

- Record body weight.
- Perform physical exam.
- Record vital signs.
- ECG should be performed prior to blood draws.
- Perform chest X-ray.
- Perform pregnancy test for females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
- Laboratory test: RBC, Hb, HCT, 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.
- Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
- Perform C-SSRS

Safety

- AEs and concomitant medications will be monitored and recorded throughout the study

Efficacy

- Relapse assessment will be monitored and recorded throughout the study.
- Perform EDSS/FSS

- Visual Function Testing (Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment), SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D and T25W.
- ZBI which is optional and will be performed (window in days is within ±28 days) for caregiver who signed informed consent to caregiver burden assessment.

PK-PD

- Obtain PK sample
- Obtain PD sample includes IL-6, sIL-6R and hsCRP

Immunogenicity

- Collect sample for anti-drug antibody

4.6 CHUGAI CLINICAL SAMPLE REPOSITORY (CCSR)

The CCSR project is an independent and optional sub-study of the main study BN40900 (SA-309JG). The CCSR for this study is run by Chugai Pharmaceutical Co., Ltd. on behalf of the Sponsor.

Should a site opt to participate in the CCSR sub-study, their patients will be given the option to participate in CCSR project.

For blood samples for DNA analysis, 2 mL blood samples will be taken from the patients who consent to the procedure and to CCSR project prior to the first injection on Day 1 (Baseline). The blood samples will be stored by the Sponsor for up to 15 years after the end of the associated main study (database closure) at which time they will be destroyed.

For the CCSR, serum and plasma samples will be taken from the patients who consent to the procedure. Blood for serum and plasma samples (each 5 mL for serum and 4.5 mL for plasma) will be taken at the time points indicated in the Schedule of Assessments (see Appendix 1). The serum and plasma samples will be stored by the Sponsor for up to 5 years after the end of the associated main study. The samples will be used for analysis of proteins such as, but not limited to, cytokines and chemokines.

These samples will be used only for purpose of retrospective CCSR research analysis to understand inter-individual variability in satralizumab efficacy, safety and pharmacokinetics as will be explained in the Informed Consent Form. The Informed Consent for an optional specimen donation will be incorporated as a specific section into the main Clinical Trial ICF. A second, separate, specific signature consenting to specimen donation will be required to document the study participant's agreement to provide an optional specimen; if the participant declines, he/she will check a "no" box in

the appropriate section and not provided a second signature. The blood, serum and plasma sampling for CCSR will be contingent on a site's Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) approval of sampling for the CCSR and the Informed Consent Form. If a site's IRB and/or IEC does not approve the sampling, this section of CCSR project will not be applicable.

4.6.1 Schedule of Assessments and Procedures

4.6.1.1 Study Procedures

After written informed consent for the associated main clinical study has been obtained from a patient, the blood, serum and plasma sampling will be explained. The patient will be asked if they wish to participate in CCSR project, and written informed consent will be obtained specifically for CCSR project.

The blood, serum and plasma samples are scheduled to be collected at the time points detailed in the Schedule of Assessments (Appendix 1).

Dates of consent and sample collection should be recorded on the CCSR section of the study eCRF.

4.6.1.2 Sampling Procedures

Blood samples for DNA analysis:

A 2 mL venous blood sample will be collected into a blood collection tube containing ethylenediaminetetraacetic acid as anti-coagulant. The blood will be transferred to a storage tube. Samples will then be stored at approximately -20°C. Details on sample handling procedures, sample storage, and shipment are described in the supplemental laboratory manual.

Serum samples:

A 5 mL venous blood sample will be collected into a blood collection tube. The blood will be placed to clot at room temperature (30 min, not more than 60 min after blood collection) and then be centrifuged for 10 min at 4°C at 1700 g. The serum will be collected and transferred to storage tubes. Details on sample handling procedures, sample storage and shipment are described in the laboratory manual.

Plasma samples:

A 4.5 mL venous blood sample will be collected into a blood collection tube containing sodium citrate as anti-coagulant. The blood will be centrifuged for 10 min at 4°C at 1700 g. The plasma will be collected and transferred to storage tubes. Plasma separation should be carried out immediately after blood draw. If this is not possible, blood should be kept on an ice bath until centrifugation (not more than 30 minutes after

blood collection). Details on sample handling procedures, sample storage and shipment are described in the supplemental laboratory manual.

4.6.1.3 CCSR

These samples will be transferred to and stored in the CCSR on behalf of the Sponsor.

4.6.1.4 Biomarker Research Analysis Protocol

When the schedules or contents of a biomarker analysis using CCSR samples are specified, “Biomarker Research Analysis Protocol” will also be prepared before the research will be performed.

The samples and results of anti-AQP4 antibody may be used for development of a companion diagnostic for satralizumab in the future.

4.6.2 Sample Confidentiality and Sample Destruction

It is the intent of Sponsor to assure that pharmacogenomic and biomarker information obtained from patient blood, serum, and plasma samples remains confidential. The Sponsor already maintains rigorous confidentiality standards for clinical studies by “coding” (i.e., assigning a unique patient identification (ID) number at the Investigator site) all patients enrolled in the Sponsor’s clinical studies. This means patient names are never revealed to anyone at the Sponsor. Given the sensitive nature of pharmacogenomic data, the Sponsor has implemented a number of additional processes to assure patient confidentiality. All samples taken for blood samples for DNA analysis undergo a second level of “coding”. At the Sponsor, the new label with a new random number referred to as the double-coded ID is placed over the original label of the blood sample. Identified only by the double-code ID, the samples will be forwarded to storage and DNA analysis.

Both the patient ID number and the double-coded ID number will co-exist as a table in a sample repository code manager. This allows patients to withdraw their sample from the blood samples for DNA analysis during their participation in the associated main clinical study if they change their mind after signing the ICF.

The blood samples for DNA analysis and serum/blood samples for protein analysis will be stored by the Sponsor for up to 15 years and 5 years respectively after the end of the associated main study (database closure) at which time they will be destroyed.

4.6.3 Withdrawal of Patients from the CCSR Project

Patients who give consent to the CCSR project have the right to withdraw their consents from the CCSR project at any time for any reason. If a patient wishes to withdraw his/her consent from the CCSR project, the Investigator must inform the Sponsor in writing of the patient’s wishes using the CCSR Subject Withdrawal Form (Appendix 9). If a patient

wishes to withdraw his/her consent to the testing of his/her specimen(s) during their participation in the clinical study, the Investigator must enter the date of the withdrawal in the patients eCRF. Within the Sponsor, the request for sample withdrawal will be forwarded to the biomarker operation. A patient's withdrawal from the main study does not, by itself, constitute withdrawal from the CCSR project. Likewise, a patient's withdrawal from the CCSR project does not constitute a withdrawal from the main study.

In the case of blood sample for DNA analysis, if a patient wishes to withdraw the consent to use the sample, then the sample must be destroyed. In the case of serum and plasma samples, if a patient wishes to withdraw the consent both to collect subsequent samples and to use the samples already collected, then the samples already collected must be destroyed. If a patient wishes to withdraw only the consent to collect subsequent samples, the Sponsor can use samples and the data from the samples already collected. If DNA, proteins, and other substances have already been analyzed at the time the Sponsor receives a CCSR Subject Withdrawal Form, the data from those analysis will not be destroyed. If the blood sample for DNA analysis, serum sample and plasma sample to be destroyed are at the Sponsor or central laboratory, the biomarker operation will issue confirmation of the withdrawal, which will be forwarded to the Investigator. If the blood samples for DNA analysis, serum sample and plasma sample to be destroyed are still at the Investigator site at the time a patient wishes to withdraw his/her sample, the Investigator must inform the Sponsor as before, destroy the sample and sign the CCSR Subject Withdrawal Form to confirm that this has been done. The Sponsor will forward confirmation of the destruction, recorded on the Subject Withdrawal Form, to the biomarker operation.

4.6.4 Benefits to Donors

Donors will not benefit personally from the biomarker research because the aim is to evaluate potential patient-selection and efficacy/safety markers and to generate or test hypotheses by analyzing the data and compiling the overall results. However, the findings may contribute to future medical treatment with satralizumab.

4.7 PATIENT, STUDY AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from study treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason. Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.

- Any medical condition that the Investigator or Sponsor/Medical Monitor determines may jeopardize the patient's safety if he or she continues in the study.

Investigator or Sponsor/Medical Monitor determines it is in the best interest of the patient.

Additionally, the patient may be discontinued from the study for the following reasons:

- Major protocol violation.
- Administrative reasons.
- Lost to follow-up.

If a patient wishes to discontinue from study treatment or withdraw from the study, the Investigator should conduct an interview with the patient using uniform procedures with scripted questions to evaluate potential relapse (e.g., any new symptoms of a potential relapse or adverse events) and minimize dropout or discontinuation from the study due to reasons such as misunderstanding of the study design.

The withdrawal visit will be performed as noted in Section 4.5.3.2 and Appendix 1.

4.7.1.1 Discontinuation of Study Treatment

In addition to the criteria listed above, reasons for withdrawal of the study treatment but which do not preclude the patient remaining in the study include, but are not limited to, if the patient:

- Meets the discontinuation criteria in the risk mitigation and dose modification strategy (see Section 5.1).
- Misses three consecutive doses of study drug on scheduled visits in the double-blind period.
- Experiences two relapses in the open-label extension period with a more severe intensity compared with the last relapse prior to baseline.
  Investigator should consult with the Medical Monitor if these relapses meet this criterion.
- Experiences malignancy or a severe allergic or anaphylactic reaction to satralizumab.
- Pregnancy.
- Unacceptable toxicity.

If the patient is unwilling to continue in the study, he/she will be asked to return to the clinic for a Withdrawal visit (see Section 4.5.2.3) and may undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study treatment

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

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.7.2 Study and Site 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 or its designee will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for GCP

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Important Identified and Potential Risks of Satralizumab

On the basis of mechanism of action, key non-clinical and clinical safety findings, experience with similar molecules, an Integrated Summary of Safety Information is included in the current Investigator's Brochure for satralizumab. *Please refer to the current satralizumab Investigator's Brochure for an up-to-date summary of available safety information.*

There have been no important identified or potential risks for satralizumab. The safety management plan for other potential risks and laboratory abnormalities associated with satralizumab, and risks for drugs in the same drug class are outlined below.

- Serious Infections
- Neutropenia and Potential Risk of Infection
- Thrombocytopenia and Potential Risk of Bleeding
- Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity
- Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
- Immunogenicity
- Serious Hypersensitivity Reactions
- CYP450 Enzyme Normalization
- Complications of Diverticulitis
- Malignancies
- Demyelinating Disorders

In order to address the risks for the patients, the following safety precautions are included in the study design:

- In addition to regular standard safety evaluations (laboratory measures, physical examinations, vital signs and ECG), a special focus will be placed on the above risks.
- *An* IDMC will evaluate the safety *of patients* every six months *during the double-blind period of the study*.
- A patient ID card which includes information about the study, investigational drug and Investigator's contact information will be provided to the patient. Patients should be instructed to show this card to healthcare professionals in case they contact any other hospital/clinic, etc. In addition, a Dear Doctor Letter which includes information about the study and investigational drug should be provided to healthcare professionals, in case patients contact any other hospital/clinic etc.

Recommendation for vigilance with regards to sign and symptoms of particular safety events are summarized in the following sections.

5.1.1.1 Serious infection

In a Phase I multiple dose study of satralizumab in patients with rheumatoid arthritis (SA-105JP), one case of serious infection, bronchopneumonia (1of 33 patients), was reported. Serious infection is an identified risk of tocilizumab. In the all-exposure population of tocilizumab, the most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis.

Treatment with satralizumab 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. As a result, it may potentially make the infection more serious.

In the completed double-blind periods of the Phase 3 studies (BN40898 and BN40900), the rates of infections and serious infections in the satralizumab group were not higher than in the placebo group.

Patients with an active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline will be excluded from this study.

Patients with evidence of active TB (excluding patients receiving chemoprophylaxis for latent TB) will be excluded from this study.

Patients with chronic active hepatitis B or C will be excluded from this study.

Patients who received any live or live attenuated vaccine within 6 weeks prior to baseline will be excluded from this study.

- Satralizumab should not be initiated or administered in patients with active infections.
- Patients should be closely monitored for the development of signs and symptoms of infection, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants.
- Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to *ensure* rapid evaluation and appropriate treatment.
- If a patient develops 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 within 6 weeks prior to baseline and during the course of the study as clinical safety has not been established.

5.1.1.2 Neutropenia and Potential Risk of Infection

Reversible neutropenia was reported in 1 of 33 patients with rheumatoid arthritis in the Phase I multiple dose study (SA-105JP).

In the completed double-blind period of the Phase 3 studies, decreases in neutrophil counts have occurred following treatment with satralizumab, which was not associated

with serious infections. The majority of neutrophil decreases were transient or intermittent.

Patients with a low neutrophil count <2 x10^3/uL will be excluded from this study.

Caution should be exercised in patients with a low neutrophil count and appropriate measures (such as interruption of satralizumab) should be considered if neutropenia persists.

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

Table 2 Neutropenia Risk Mitigation

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

ANC = absolute neutrophil count.

5.1.1.3 Thrombocytopenia and Potential Risk of Bleeding

Treatment-related reduction in platelet count has been observed in the Phase I multiple dose study with rheumatoid arthritis (SA-105JP), although these were within normal range.

In the Phase 3 studies, decreases in platelet counts have been observed following treatment with satralizumab.

Treatment-related reduction in platelets was not associated with bleeding events in clinical trials.

Patients with a platelet count below 10 x10^4/μL will be excluded from this study.

Caution should be exercised in patients with a low platelet count and appropriate measures (such as interruption of satralizumab) should be considered if thrombocytopenia persists.

Recommended dose interruption based on PLT count is shown in Table 3.

Table 3 Thrombocytopenia Risk Mitigation

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

5.1.1.4 Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity

Reversible elevations of AST and total bilirubin were each observed in 2 healthy subjects and reversible elevation of ALT in 1 healthy subject out of 72 healthy subjects in the Phase 1 single ascending dose study (SA-001JP).

In the Phase 3 studies, mild and moderate elevations of liver transaminases have been observed with satralizumab treatment. Most elevations were $< 5 \times$ ULN and resolved while on treatment with satralizumab. Elevations of ALT or AST $> 3 \times$ ULN were not associated with increases in total bilirubin.

It has been reported that IL-6 appears to have a hepatoprotective effect on various forms of liver injury and promotes hepatocyte regeneration. Patients with elevated transaminases ALT or AST > 1.5x ULN will be excluded from this study.

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

Recommended dose interruption based on transaminases is shown in Table 4.

Table 4 Hepatic Enzyme Risk Mitigation

AST or ALT values	Action
>1 to 3x ULN*	• Reduction (if necessary, interruption) of hepatotoxic drugs could be considered. • For persistent increases in this range, satralizumab could be interrupted until AST and ALT is below ULN*.
>3 to 5x ULN	Laboratory tests (ALT, AST, ALP and TBL) should be repeated within 72 hours to confirm value. The presence of clinical symptoms should be queried. Patients who are far away from the trial site may be retested locally if prompt return to the trial site is difficult. If close monitoring is not possible, the drug should be discontinued. Satralizumab should be interrupted until AST and ALT is below 3x ULN. If at least one of following associated, satralizumab should be discontinued. • Total bilirubin >2x ULN and/or • INR >1.5x ULN and/or • Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
>5x ULN	Laboratory tests (ALT, AST, ALP, and TBL) should be repeated within 72 hours as soon as possible to confirm value. If continued, satralizumab should be discontinued immediately and gastroenterology expert should be contacted. 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.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

* ULN or patient's baseline whichever is higher.

5.1.1.5 Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events

The slight increases in lipid levels (3 AEs of hyperlipidemia [mild] were observed in 3 out of 33 patients in Phase Ib [SA-105P]) or and no cardiovascular/cerebrovascular events have been observed in Phase 1 trials of satralizumab.

Increases in total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides due to administration of tocilizumab have been observed. However, it is unknown whether these changes were associated with cardiovascular events.

In the Phase 3 studies, elevations in total cholesterol and triglycerides were observed. The elevations in lipid parameters did not require dose interruption.

Patients should be managed according to the guideline such as the National Cholesterol Education Program Adult Treatment Panel III or Japan Atherosclerosis Society guideline.

5.1.1.6 Immunogenicity

In a Phase 1 single-dose study (SA-001JP) of satralizumab in healthy Japanese and Caucasian adult male volunteers, ADA were detected in 39 of the 72 subjects who received satralizumab. Most of ADAs were characterized as neutralizing antibody. In a Phase 1 multiple dose study (SA-105JP) of satralizumab in patients with rheumatoid arthritis, ADA were detected in 2 of the 33 patients who received satralizumab. These ADAs were also characterized as neutralizing antibody, and in these 2 patients, elevation of serum level of satralizumab was not observed.

In the double-blind periods of the Phase 3 studies, ADAs were observed in 41% (Study BN40898) and 71% (Study BN40900) of patients receiving satralizumab. Exposure was lower in ADA positive patients; however, there was no impact of ADAs on safety and no clear impact on efficacy or pharmacodynamic markers indicative of target engagement.

5.1.1.7 Serious Hypersensitivity Reactions

Anaphylaxis and serious hypersensitivity reactions have not been reported in clinical trials with satralizumab treatment; however, anaphylaxis and hypersensitivity reactions are considered a potential risk with all biologic medications, including satralizumab.

Patients with a history of a severe allergic reaction to a biologic agent are excluded from study participation.

The symptoms/signs of hypersensitivity include, but 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.

- *Up to Week 48 in the OLE period of the study:*
  - The SC injections should be administered under close supervision in a setting where medications (e.g., corticosteroid, antihistamine and epinephrine) and resuscitation facilities are available
  - Patients should stay in the clinic/hospital at least 1 hour after study treatment administration in order to receive medication immediately if anaphylaxis occurs.

- Patients should be instructed to seek medical attention if they experience symptoms of hypersensitivity reaction outside of the clinic.
- If an anaphylactic reaction or other serious hypersensitivity reaction occurs, satralizumab should be discontinued.
- *Administration of satralizumab prefilled syringes outside of the study site might be allowed (see Section 4.3.2.2) 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.*

5.1.1.8 CYP450 Enzyme Normalization

Drug interaction studies have not been conducted with satralizumab. In patients with rheumatoid arthritis who were administered tocilizumab, increased expression of CYP3A4, CYP2C19 and CYP2D6 has been suggested. Reports have suggested that overproduction of IL-6 in patients with inflammatory response inhibits the expression of CYPs. Satralizumab administration may normalize CYP expression and the beneficial effects of concomitant drugs may decrease as the inflammatory reaction improves.

- Patients taking medicinal products which are individually adjusted and are metabolized via CYP450 3A4, 1A2, 2C9 or 2C19 should be monitored as doses may need to be *modified*.

5.1.1.9 Complications of Diverticulitis

To date, gastrointestinal perforations have not been reported in clinical trials with satralizumab treatment.

Gastrointestinal perforations have been reported rarely in patients administered tocilizumab. Although it is unknown whether gastrointestinal perforations are associated with IL-6 inhibition, satralizumab may suppress the acute symptoms (abdominal pain, pyrexia, etc.) associated with diverticulitis, etc., causing delayed diagnosis and progression to perforation.

In this *study*, patients who have a history of active diverticulitis may be precluded from participation.

- Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated (X-ray, computerized tomography 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 physician 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 inhibitor or H2 blocker should be considered

5.1.1.10 Malignancies

No increased risk of malignancies *has* been *observed* in clinical trials with satralizumab treatment.

Although malignancies have been reported in patients given tocilizumab, there have been no report to date that tocilizumab appreciably increases the occurrence of malignancies.

All patients with history of malignancy within the last 5 years, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured) will be excluded from this study.

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

5.1.1.11 Demyelinating Disorders

Demyelination-related diseases have not been reported in clinical trials with satralizumab treatment.

The impact of treatment with tocilizumab on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. PML has not been reported.

Patients with evidence of other demyelinating disease or PML will be excluded from this study.

If symptoms suggestive of a demyelination-related disease are observed, differential diagnosis of the cause should be performed.

5.1.2 Other Information

*Stevens-Johnson syndrome (*SJS*)* has not been reported in clinical trials with satralizumab treatment.

It is unknown whether SJS is associated with IL-6 inhibition, but SJS has been reported rarely in patients administered tocilizumab.

Patients with a history of SJS will be excluded from this study. Patients must be instructed to contact their physician immediately when any symptoms suggesting SJS appear, in order to assure early diagnosis and appropriate treatment. Satralizumab must not be administered in patients with SJS.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs, AESIs and selected AEs (see Section 5.2.4); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- 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 treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive screening procedures such as biopsies)

New or worsening neurological symptoms considered NMO-related are not AEs. Clinical relapse will be recorded only on a pre-specified eCRF “NMO 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 5.3.5.10)
- 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 treatment
- 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 NMO relapse, as long as the reason for hospitalization is to receive standard treatment with pulse IV corticosteroids and/or apheresis (including plasma exchange and plasmapheresis).

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 Non-serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious AESIs 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). Non-serious AESIs for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.
- Suspected transmission of an infectious agent by the study treatment.

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 IV antibiotics, antifungals, antivirals
- opportunistic infections that require treatments with oral antibiotics, antifungals, or antivirals
- injection-related reaction (IRR; an AE which occurs within 24 hours after study treatment 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) are recorded on the Adverse Event pages of the 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 pages in the eCRF, the Investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on 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 pages of the eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures of the protocol). These SAEs will be recorded in the Drug Safety database but not on the Adverse Event eCRF.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported on the eCRF until the Withdrawal Visit or Last Observation (12 weeks after the last dose of study treatment). After this period, Investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information. Example of non-directive questions includes 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 5 provides guidance for assessing AE severity.

Table 5 Adverse Event Severity Grading

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 SAE (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 or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with the study treatment 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 page of the eCRF. Colloquialisms and abbreviations should be avoided.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Injection-Related Reactions

Injection-related reaction is defined as the event that occurs within 24 hours after study treatment 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 as not allergic reaction, it will be recorded on the Adverse Event page of the eCRF.

Other Adverse Events

For AEs other than injection-related reactions, a diagnosis (if known) should be recorded on the Adverse Event page of the 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 page of the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring 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. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event page of the 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 subsequent 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 AEs should be recorded separately on the Adverse Event page of the eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event page of the eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event page of the eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event page of the eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

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

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

If a clinically significant laboratory abnormality cannot be related to a disease or syndrome, the abnormality itself should be recorded on the Adverse Event page of the eCRF, along with a descriptor indicating if 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 AE. 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 not be repeatedly recorded on the Adverse Event page of the eCRF, unless the etiology or severity changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 AE.

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 page of the eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event page of the eCRF, unless the etiology or severity changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens or improves.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3x ULN) in combination with either an elevated total bilirubin (>2x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an AE the occurrence of either of the following:

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

Any other reason than study treatment induced liver injury should be checked, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury in case these have any clinical probability. The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event page of the eCRF (see Section 5.3.5.1) either as an SAE or a non-serious AESI (see Section 5.4.2) and must be reported to the Sponsor within 24 hours after learning of the event.

5.3.5.7 Deaths

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

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 page of the eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to e.g., presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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 page of the

eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

If the death is attributed to progression of NMO "NMO progression” should be recorded on the Adverse Event page of the eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present prior to baseline. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

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

5.3.5.9 Lack of Efficacy or Worsening of NMO

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as elements of the 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 using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.10 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 NMO relapse
- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment 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 suffered an AE.

5.3.5.11 Overdoses

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event page of the eCRF. If the associated AE fulfills serious criteria, the event should be reported as a SAE to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The Investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious AESI
- Pregnancies

The Investigator must report new significant follow-up information for these events to the Sponsor within 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 SAE reporting to the local health authority and IRB/IEC.

5.4.1 Emergency Medical Contacts

The contact details for the Emergency Medical Contacts will be provided in the Study Manual and the Investigator (Site) File. Medical Monitor names, contact information, and country-specific toll free numbers will be included.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-serious Adverse Events of Special Interest

For reports of SAEs and non-serious AESI, Investigators should record all case details that can be gathered within 24 hours on the paper SAE form and fax the completed SAE form to PAREXEL International Pharmacovigilance. Investigators should refer to the Study Manual and the Investigator (Site) File for the current contact information (fax and telephone numbers, and email addresses) for SAE and non-serious AESI reporting.

In the event of fax transmission failure of the SAE form, the site could alternatively e-mail the SAE form to the PAREXEL Pharmacovigilance department using the e-mail address provided.

Concurrently the Adverse Event eCRF should be completed immediately (see Section 5.3.1).

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 last dose of study treatment. A paper pregnancy report form should be completed within 24 hours and submitted via fax to the PAREXEL Pharmacovigilance department, using the fax numbers provided (see Section 5.4.2). Pregnancy should not be recorded on the Adverse Event page of the eCRF. The Investigator should discontinue study treatment 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 update the paper pregnancy report form when updated information on the course and outcome of the pregnancy become available.*

In the event of the fax transmission failure of the pregnancy report form, the completed pregnancy report form could alternatively be sent by e-mail to PAREXEL Pharmacovigilance department using the e-mail address provided.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study treatment. A paper pregnancy report form should be completed within 24 hours of learning of the pregnancy and submitted via fax to the PAREXEL Pharmacovigilance department, using the fax numbers provided (see Section 5.4.2). In the event of the fax transmission failure of the pregnancy report form, the completed pregnancy report form could alternatively be sent by e-mail to the PAREXEL Pharmacovigilance department using the e-mail address provided.

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 treatment. The pregnant partner will need to sign an ICF for Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the paper pregnancy report form *when updated* information on the course and outcome of the pregnancy *become 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

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event page of the eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female or female partner of a male patient exposed to study treatment patient should be classified as an SAE, recorded both on the Adverse Event page of the eCRF and on the paper form, and reported to the Sponsor by faxing within 24 hours after learning of the event (see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, PFS with NSD is considered a medical device. The Investigator must report all medical device complaints to the Sponsor or its designee. 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 or its designee (see IMP Deviation Form).

If the medical device results in an AE to the study patient, the event must be recorded on the eCRF (see Section 5.3.5). If the event is serious, SAE form must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. If the medical device results in an AE to an individual other than the study patient, the AE should be reported as a spontaneous AE to Sponsor Drug Safety via e-mail (see IMP Deviation Form).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each AE 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 SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event page of the eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event page of the eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. Follow reporting instructions provided in Section 5.4.3.1.

5.6 POST-STUDY ADVERSE EVENTS

At the last observation/withdrawal visit, the Investigator should instruct each patient to report to the Investigator any subsequent AEs that the patient's personal physician believes could be related to prior study treatment or study procedures (e.g., infections or reactivation of previously acquired infective agents).

The Investigator should notify the Sponsor of any death, SAE (e.g., development of cancer) and non-serious AESI of concern occurring at any time after the Withdrawal Visit or last observation if the event is believed to be related to prior study treatment or study procedures. The Sponsor should also be notified if the Investigator becomes aware of a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report the event via a paper Serious Adverse Event form to the PAREXEL Pharmacovigilance department.

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

The Sponsor will promptly evaluate all SAEs and AESIs 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 AE cases, the Sponsor will assess the expectedness of these events *through use of* the *reference safety information in the* 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.

Expedited reporting to Health Authorities will follow each country's specific regulations.

An IDMC will periodically monitor the incidence of AEs (not only expedited reporting to Health Authorities but also all AEs) during the *double-blind period of the* study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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 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 will serve as the primary population for the analysis of efficacy, which consists of all randomized patients in the study. Patients will be analyzed as randomized for analysis purposes.

The Per-Protocol Set population (PPS) will include all patients in the ITT population who received at least 3 doses of study treatment, and without any major protocol deviations which are considered to have an impact on efficacy. Patients will be analyzed as treated for analysis purposes in the PPS.

6.1.2 All-Patients-Treated Population

The All-Patients-Treated (All satralizumab) population will be defined as all enrolled patients who took at least one dose of active study treatment at any time.

6.1.3 Safety Analysis Populations

All safety variables will be analyzed based on the Safety Population (SAF). The SAF population will include all randomized patients who have received at least one dose of study treatment. 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 Set (PK-PPS) and immunogenicity (anti-drug antibody) will include all patients in the SAF with at least 1 valid post-dose concentration result with a dosing record and sampling time. PD variables (IL-6, sIL-6R, hsCRP, anti-AQP4 antibodies and plasmablast) will be analyzed using the SAF population.

6.2 DETERMINATION OF SAMPLE SIZE

Approximately 90 patients need to be recruited and randomized in a 2:1 ratio to the two treatment groups (satralizumab and placebo). The sample size considerations are based on the following assumptions:

- A two-sided log-rank test.
- At least 80% power at the 5% significance level.
- The hazard ratio of satralizumab over placebo for an initial 2 months from randomization is 1.0. The hazard ratio after an initial 2 months from randomization is 0.25.
- TFR in the placebo arm following an exponential distribution, with hazard rate for 1 year $h(t) = 1.1295$.
- A 2-year dropout rate of 10%.

Based on the assumptions, 44 TFR events are needed for the primary analysis. The 90 patients enrolled over 33 months and followed for an additional 5 months will provide 44 TFR events. The primary analysis will be performed once 44 TFR events have been observed or 1.5 years after the date of randomization of the last patient enrolled, whichever comes first. The Sponsor will conduct a blind review of the data including accumulation of events during the double-blind period and may take appropriate action such as to increase the number of patients or to extend the double-blind period based on this blind review.

It has been assumed that the number of relapses will follow a Gamma-Poisson distribution and that the variance/mean ratio will be a constant value of √2. This distribution was assumed and the ratio was estimated using data from MS trials (Gold et al. 2012; Kappos et al. 2010) because there are no approved medications for NMO and no raw data from patients with this indication are available.

Because the mean ARR of NMO patients is estimated at 0.82 and eligibility criterion 2 says patients at least 1 relapse in last 12 months prior to screening are selected, we calculate the zero-truncated mean of the Gamma-Poisson distribution with the mean of 0.82 and the mean and variance ratio of √2, then the baseline ARR is estimated at 1.65. The post-treatment ARR in the placebo group in NMO patients with anti-AQP4 positive and negative is estimated as 1.5 and 1.0, respectively (Cree et al. 2015). Given that the proportion of patients who are negative for anti-AQP4 antibody at screening will be capped at 30% of the total number of patients in this study, post-treatment ARR is estimated as 1.35.

Using the proportion of zero under supposed ARR distribution, we estimate the relapse-free rate at a year in placebo group at 32.3%. The relapse-free rate is assumed to follow the exponential distribution with a constant hazard, and then we set the hazard for 1 year of 1.1295 in placebo group.

According to tocilizumab case report in NMO patients, the pre- and post- baseline relapse counts were reduced from total 4 counts per 6 months to 1 count per 6 months. Then the pre- and post- baseline ratio of 0.25 is used as the estimation of the mean ARR ratio of tocilizumab compared with placebo. Under the assumption of ARR and relapse-free rate distribution above, the mean ARR ratio is coincided with the hazard ratio. The primary rationale for the mechanism of anti-IL-6 blockade in NMO/NMOSD is the expected inhibition of the survival of plasmablast followed by a reduction in anti-AQP4 antibody. Given that the reduction in anti-AQP4 antibody is required for prevention of relapse, and considering the half-life of immunoglobulin G, sufficient effectiveness might not be expected for an initial period of a few months even if IL-6 signaling is inhibited immediately. So we have set the hazard ratio of satralizumab over placebo at 1.0 for an initial 2 months from randomization and at 0.25 after an initial 2 months from randomization.

6.3 SUMMARY OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by study site and treatment arm. Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment group. Study discontinuation as well as reasons for discontinuations will be summarized. Eligibility criteria deviations and other major protocol deviations will be summarized.

6.4 SUMMARY OF TREATMENT GROUP COMPARABILITY

Demographics (age, sex, race/ethnicity and concomitant medication) and baseline characteristics (hepatitis status, baseline annual relapse rate and number of previous episodes within one year before enrollment) of patents will be collected at screening or baseline visit before administration of first dose of study treatment.

In general, data will be summarized by treatment group and for all patients in the study (i.e., independent of treatment group). Descriptive statistics will be presented for continuous data with sample size, mean, standard deviation (SD), median, minimum, and maximum. Frequency table with percentage will be presented for discrete data.

6.5 EFFICACY ANALYSES

All efficacy analyses will be based on the ITT population. Supportive evaluations will be performed using the PPS population for primary and key secondary endpoints.

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is TFR based on CEC evaluations (see Section 4.5.1.8). TFR is defined as the time from the date of the randomization until the first occurrence of relapse throughout the double-blind period. Time point of relapse onset is defined as time at which the patient experiences any new or worsening neurological NMO/NMOSD representing clinical symptom(s). For patients who have not relapsed, the TFR will be censored on the date of end of the double-blind period (see the section “Length of Study” in PROTOCOL SYNOPSIS). Further details will be mentioned in the SAP.

The primary analysis of the study is to test the equality of the TFR distribution in the satralizumab (SA237) and placebo arms:

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

A stratified two-sided log-rank test using strata of prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others) and the most recent attack in the last one year prior to screening (first attack or relapse) will be used. If a patient was administered B-cell depleting therapies (e.g., anti-CD20 antibody [e.g., rituximab], anti-CD19 antibody) at least once in the year prior to baseline, the patient will be stratified into “B-cell depleting therapy group” and otherwise into the “immunosuppressants/others group” (e.g., oral corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus). 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 hazard ratio and 95% confidence intervals using a stratified (prior therapy for prevention of

NMO/NMOSD attack [B-cell depleting therapy or immunosuppressants/others] and the most recent attack in the last one year prior to screening [first attack or relapse]) Cox proportional-hazards model. Relapse-free rates and their 95% confidence intervals (CI), in addition to the hazard ratio, will be used every 6 months to describe TFR distribution.

6.5.2 Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are change in VAS for pain and change in FACIT fatigue scale. In order to control the rate of false positive conclusions, the serial gatekeeping methodology (fixed-sequence test) will be employed to control for multiple (primary and key secondary) endpoints in this order.

Change in VAS score for Pain

The VAS is a subjective measure of pain and it consists of a 100 mm line with two end-points representing “no pain” and “pain as bad as it could be”. Patients are asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the ‘no pain’ marker is then measured with a ruler giving a pain score out of 10.

The change in VAS for pain score from baseline to Week 24 in the double-blind period will be analyzed by analysis of covariance (ANCOVA) method with baseline observation carried forward (BOCF) imputation. The analysis will include the categorical effects for treatment, prior therapy for prevention of NMO/NMOSD attack and the most recent attack in the last one year prior to screening, as well as the continuous covariates of baseline VAS for pain score.

Change in FACIT Fatigue Score

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

The change in FACIT fatigue Scale score from baseline to Week 24 in the double-blind period will be analyzed by ANCOVA method with BOCF imputation. The analysis will include the categorical effects for treatment, prior therapy for prevention of NMO/NMOSD attack and the most recent attack in the last one year prior to screening, as well as the continuous covariates of baseline FACIT fatigue score.

Further Secondary Efficacy Endpoints

Change in Short Form Generic Health Survey (SF-36) Score

The scores will be presented and summarized for each of the 8 domains (vitality, physical functioning, bodily pain, general health, role-physical, role-emotional, social role functioning and mental health) and 2 summary components (physical and mental). The mean change in SF-36 domain scores will be analyzed from baseline to every 24 weeks after the baseline visit.

Change in EQ-5D Score

The EQ-5D 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. The EQ-5D is therefore able to represent 243 (3^5) distinct health states. These states may then be converted into a single index value by using the time trade-off 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 to their baseline status. The mean change in EQ-5D score will be analyzed from baseline to every 24 weeks after the baseline visit.

Change in Timed 25-Foot Walk (T25W)

The T25W is the measurement to assess the walking ability. The time (in seconds) that it takes the patient to walk 25 feet is measured. The mean change of the amount of time will be analyzed from baseline to every 24 weeks after the baseline visit.

The Proportion of Relapse-free Patients

The proportion of patients who are relapse-free during *the* double-blinded period and *the* entire study *(double-blind and OLE periods combined)* will be calculated for the two treatment groups. *When both periods are analyzed together, patients are analyzed as randomized, even if patients randomized to placebo receive satralizumab in the OLE period.*

The Kaplan-Meier estimates and corresponding 95% CIs for the proportion of patients who were relapse-free during the double-blind period are calculated for both treatment groups.

Relapse-free rates will be analyzed at every 24 weeks after baseline.

Annualized Relapse Rate (ARR)

The relapse episodes for each eligible patient will be recorded throughout the whole study. The ARR is calculated as the total number of relapses experienced divided by the

person-years at risk for each year of the study period. The 95% CI will be presented based on the Poisson distribution.

For comparing the difference between two treatment arms, negative binomial regression model will be used with ARR as response variable; treatment group, prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others), and the *type of the* most recent attack in the last one year prior to screening (first attack or relapse) as covariates.

Change in Modified Rankin Scale Score

The mRS is a 7-point disability scale that assesses the degree of disability in patients with neurological impairment. Possible scores range from 0 (no symptom at all) up to 6 (death). The higher scores reflect increased disability. Descriptive statistics will be calculated for the change in mRS.

The mean change in mRS score will be analyzed from baseline to every 24 weeks after the baseline visit.

Change in Zarit Burden Interview Score

The ZBI is the measurement to assess caregiver burden. The 22 items ask for the strain caregivers perceive. Responses range from 0 (never) to 4 (nearly always) with maximum score of 88. The higher the total score, the heavier the perceived burden. Descriptive statistics will be calculated for the change in ZBI.

The mean change in ZBI score will be analyzed from baseline to every 24 weeks after the baseline visit.

Change in Expanded Disability Status Scale (EDSS) Score

The EDSS will be assessed on scheduled visits during entire study. The mean change in EDSS scores from baseline to every 24 weeks after the baseline visit will be analyzed.

Time to EDSS worsening based on the definition for PDR is estimated with a cox regression with treatment group, prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others), and the type of the most recent attack in the last year prior to screening (first attack or relapse) as covariates. The hazard ratio and 95% CI for the treatment groups is estimated in this model, the p-value is calculated based on the log rank test. In addition, Kaplan-Meier estimate of event-free rates will be provided.

These analyses are done for the double-blind period and the combined double-blind and OLE period. When both periods are analyzed together, patients are analyzed as

randomized, even if patients randomized to placebo receive satralizumab in the OLE period.

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.

Change in low-contrast visual acuity (Low-contrast Sloan letter chart (LCSLC))

The LCSLC is the testing to evaluate the visual function and captures the minimum size at which individuals can perceive letters of a particular contrast level. The change in binocular visual acuity, as assessed by the number of letters read correctly from 2 meters distance on 100% (high contrast, used to measure visual acuity as a descriptor of the study cohorts), 2.5% and 1.25% contrast level Sloan letter charts, will be analyzed from baseline to every 24 weeks after the baseline visit.

A mixed-effects model repeated measures (MMRM) analysis will be used for the change from baseline in EDSS, SF-36, VAS for pain, FACIT fatigue, T25W, mRS, ZBI and EQ-5D scores, as well as visual function testing (including visual acuity tests of Snellen and low-contrast Sloan letter chart). The model will include treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements as a covariate; and visit as a repeated measure. *An* unstructured covariance matrix will be assumed in the model.

If the unstructured covariance matrix does not converge, other covariance structure will be used. If treatment-by-visit interaction is not statistically significant, we still keep the full model.

If the normality assumption for the secondary efficacy variable does not hold, a generalized estimating equation or Generalized Linear Mixed-effect model analysis will be used. The assessment will be performed prior to un-blinding and details will be mentioned in the SAP.

Use of rescue medication

The use of rescue medication 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 medication use. The use of rescue medication will be analyzed with a logistic regression model with treatment group, prior therapy for prevention of NMO/NMOSD attack (B-cell depleting therapy or immunosuppressants/others), and the type of the

most recent attack in the last year prior to screening (first attack or relapse) as covariates. The odds ratio, corresponding 95% CI, and p-value for the treatment group will be reported. This analysis is conducted for the double-blind period.

6.5.3 Further Analysis

6.5.3.1 Sensitivity Analysis for Primary Endpoint

Several sensitivity analyses are planned for the primary efficacy analysis of TFR to account for the potential impact of differences in definition of primary endpoint. In this analysis TFR will be defined as follows:

- Clinical Relapse.
- Treated Clinical Relapse.
- Treated Clinical Relapse: Optic Neuritis.
- Protocol-defined relapse based on CEC adjudication (regardless of assessment limit of seven days).

Further details will be mentioned in the SAP.

6.5.3.2 Sensitivity Analysis for Key Secondary Endpoint

Several sensitivity analyses are planned for the key secondary efficacy analysis of VAS for pain and FACIT fatigue to account for the potential impact of differences in handling of missing data. In this analysis the following analyses will be conducted:

- The change in VAS for pain score from baseline to Week 24 in the double-blind period will be analyzed by ANCOVA method with hot-deck imputation
- The change in FACIT fatigue scale score from baseline to Week 24 in the double-blind period will be analyzed by ANCOVA method with hot-deck imputation

Further details will be mentioned in the SAP.

6.5.3.3 Subgroup Analysis

The subgroup summary tables will be presented by AQP4 antibody status at screening (positive/negative) in NMO and NMO/NMOSD. In case that satralizumab does not show the effectiveness in NMO patients who are AQP4 antibody negative at all, companion diagnostics co-development will be considered by using this data. Further details will be mentioned 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, IRRs, 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 with adverse drug reactions which AEs related to study treatment will be tabulated.

Adverse events will be summarized by SOC and preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) coding, and grade of severity. In addition, the incidence of AEs leading to withdrawal from treatment and SAEs will be tabulated.

Laboratory values (including hematology, blood chemistry, and urinalysis), frequencies of laboratory abnormalities, vital signs (temperature, SBP, DBP and pulse rate), physical examination 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 using descriptive statistics. When analyzing categorical data, the number and percentage of patients in each category will be presented. In addition, shift tables may be used to evaluate the number and percentage of patients having a different post-baseline status when compared to their baseline status. Numbers of patients who meet the marked abnormality criteria will also be presented.

6.7 PHARMACOKINETIC/PHARMACODYNAMICS ANALYSES

Descriptive statistics, such as geometric mean, geometric coefficient of variance (CV) and the 95% CI for the geometric mean for the serum satralizumab concentration, as well as arithmetic mean, SD, median, minimum, and maximum on the measured serum satralizumab concentration, IL-6, sIL-6R, anti-AQP4 antibodies, and plasmablasts 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 pharmacodynamics (CRP, IL-6, sIL-6R, plasmablasts and anti-AQP4 antibodies) will be performed. These results will be described and reported in the clinical study report.

In addition, nonlinear mixed-effects modeling will be used to analyze the sparse sampling dose-concentration-time data of satralizumab. The data from this study will be pooled with data from SA-001JP study, SA-105JP study and BN40898 (SA-307JG) study to develop a population PK model for satralizumab. A covariate analysis will be conducted to evaluate the effect of covariates on satralizumab exposure. Some covariates such as body weight, age and gender will be included in the covariate analysis. Population and individual estimates of primary PK parameters [e.g., clearance (CL/F), distribution volume (V/F)] and secondary PK parameters [e.g., area under the serum concentration-time curve (AUC), average trough serum concentration (C_{trough})] will

be computed and used to explore exposure response relationship on primary and key secondary as well as PD marker and safety.

Details of this mixed-effects modeling analysis, exploration of exposure-response and the results will be described and reported in a document separated from the clinical study report.

6.8 IMMUNOGENICITY

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

6.9 HANDLING MISSING DATA

For TFR, patients who have not relapsed at the time of analysis, the TFR will be censored on the date of end of the double-blind period (see the section “Length of Study” in PROTOCOL SYNOPSIS). Further details will be mentioned in the SAP.

For key secondary endpoints, missing data at Week 24 in the double-blind period will be imputed by a BOCF and for the purpose to assess the robustness of the imputation method, we will also conduct hot-deck imputation as sensitivity analysis.

For secondary continuous endpoints, a MMRM analysis incorporating data in double-blind phase will be used to utilize data collected over time with consideration of the variance-covariance matrix of the repeated measures. This method allows a general unstructured variance-covariance matrix and will include data from patients with incomplete data from some scheduled time points.

For the FACIT fatigue questionnaire, if there are less than 7 responses recorded, then the total fatigue score will be considered missing. If there are 7 or more responses recorded, then the total fatigue score for that questionnaire will be calculated as the average of the non-missing scores multiplied by 13.

Detailed methods for handling of missing data will be mentioned in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A Contract Research Organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request

data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor or its designee will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, using the CRO'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 or its designee and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper patient- or caregiver-completed questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor or its designee 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, the Investigators and institutions must provide the Sponsor or its designee direct access to applicable source documents and reports for trial-related monitoring, Sponsor or designee audits, and IRB/IEC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the 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).

8.2 INFORMED CONSENT

The Sponsor's sample master ICF including CCSR, ICFs for ZBI and authorization for use and disclosure of pregnancy health information 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 ICF or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/IEC submission. The final IRB/IEC-approved Consent Forms must be provided to the Sponsor or its designee for health authority submission purposes according to local requirements.

The ICFs 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 ICFs 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/IEC-approved ICFs must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICF (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs 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 ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). 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/IEC by the Principal Investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC 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 9.5).

In addition to the requirements for reporting all AEs to the Sponsor or its designee, Investigators must comply with requirements for SAE reporting to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug (IND) safety reports or other safety-related communications from the Sponsor or the CRO. 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/IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor or its designee 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 only be disclosed to third parties 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.

Data generated by this study must be available for inspection upon request by representatives of the US FDA and other national and local health authorities, Sponsor or its designated monitors, auditors, representatives and collaborators, and the IRB/IEC for each study site, as appropriate.

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 (i.e., the last patient's last visit).

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/IEC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 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 or its designated monitors, representatives, and collaborators, and the IRBs/IECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This trial is co-sponsored by F. Hoffmann-La Roche Ltd and Chugai Pharmaceutical Co., Ltd. (in Taiwan and Japan). PAREXEL International LLC will provide clinical operations oversight, data management support, statistical analysis and medical monitoring. The eCRF data will be recorded via an EDC system. An IxRS will be used for study treatment inventory, management and to randomize patients to study treatment. An IDMC will be set up to monitor the safety of the study.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission per the Investigator's Clinical Research Agreement. 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.

The Sponsor will comply with the requirements for publication of study results. 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.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB/IEC of any amendments to the protocol. Approval must be obtained from the IRB/IEC 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 Expert or contact information).

10. REFERENCES

Araki M, Aranami T, MatsuokaT et al. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab. Mod Rheumatol 2013;23:827-31.

Araki M, Aranami T, Matsuoaka T et al. Clinical Efficacy of anti-IL-6 receptor antibody tocilizumab in three patients with neuromyelitis optica. ECTRIMS 2012b (Poster presentation).

Ayzenberg I, Kleiter I, Schroder A et al. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. JAMA Neurol 2013;70:394-7.

Chihara N, Aranami T, Sato W et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. Proc Natl Acad Sci USA 2011;108:3701-6.

Cohen JA, Barkhof F, Comi G et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. New Engl J Med 2010;362:402-15.

Cree BA, Bennett JL, Sheehan M et al. Placebo-controlled study in neuromyelitis optica-Ethical and design considerations. Multi Scler 2015 published online.

Fischer JS, Rudick RA, Cutter GR et al. The multiple sclerosis functional composite measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force.Mult Scler 1999;5:244-50.

Frey N, Grange S, Woodworth T. Population pharmacokinetic analysis of tocilizumab in patients with rheumatoid arthritis. J Clin Pharmacol 2010;50:754-66.

Giovannoni G, Comi G, Cook S et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New Engl J Med 2010;362:416-26.

Gold R, Kappos L, Arnold DL et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098-107.

Hinson SR, Romero MF, Popescu BF et al. Molecular outcomes of neuromyelitis optica (NMO)-IgG binding to aquaporin-4 in astrocytes. Proc Natl Acad Sci USA 2012;109:1245-50.

Jarius S, Ruprecht K, Wildemann B et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. J Neuroinflammation 2012;9:14.

Kappos L, Radue EW, O'Connor P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.

Kieseier BC, Stuve O, Dehmel T et al. Disease amelioration with tocilizumab in a treatment-resistant patient with neuromyelitis optica: implicationfor cellular immune responses. JAMA Neurol 2013;70:390-3.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.

Lennon VA, Kryzer TJ, Pittock SJ et al. IgG marker of optic-spinal cord multiple sclerosis binds to the aquaporin-4 water channel. J Exp.Med 2005;202:473-7.

Lennon VA, Wingerchuk DM, Kryzer TJ et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004;364:2106-12.

Marignier R, Bernard-Valnet R, Giraudon P et al. Aquaporin-4 antibody-negative neuromyelitis optica: Distinct assay sensitivity-dependent entity. Neurology 2013;80:2194-200.

O'Connor P, Wolinsky J, Confacreux C et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. New Engl J Med 2011;365:1293-303.

Oh J, Levy M. Neuromyelitis optica: an antibody-mediated disorder of the central nervous system. Neurol Res Int 2012 published online.

Takahashi T, Fujihara K, Nakashima I et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. Brain 2007;130:1235-43.

Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.

Weinshenker BG. Neuromyelitis optica is distinct from multiple sclerosis. Arch Neurol 2007;64:899-901.

Wingerchuk DM, Banwell B, Bennett JL et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89.

Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. Neurology 2006;66:1485-9.

Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15.

Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980;20:649-55.

Appendix 1
Schedule of Assessments

Table 6 Observation and Test Schedule in the Double-Blind Period

	Screening	Double-blind period															
Week	**-4 to -1**	**0 (BL)**	**2**	**4**	**5 [d)]**	**6 [d)]**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Study day	**-27 to 0**	**1**	**15**	**29**	**36**	**43**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Window in days	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Study treatment injection (SC)		X	X	X			X	X	X	X	X	X	X	X	X	X	X
Informed consent	X [v)]																
Inclusion/exclusion criteria	X	X															
Medical history/demographic data	X																
Body height		X															
Body weight		X									X						X
Physical examination	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Vital signs [j)]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
ECG [n)]	X	X [l)]			X [l)]	X [l)]					X [l)]						X [l)]
TB screening [k)]	X																
Chest X-ray	X																
Pregnancy test [h)]	X	X		X			X	X	X	X	X	X	X	X	X	X	X
Laboratory test [a)]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Hepatitis test [b)]	X																
Hepatitis B viral DNA	X [q)]							X [r)]			X [r)]			X [r)]			X [r)]
C-SSRS		X [t)]	X [u)]	X [u)]			X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]	X [u)]
Phone call		Every week between the scheduled visits															
Safety																	
Adverse events		Monitor and record throughout the study															
Concomitant medications		Monitor and record throughout the study															

Appendix 1: Schedule of Activities (cont.)

Table 6: Observation and Test Schedule in the Double-Blind Period (cont.)

	Screening	Double-blind period															
Week	**-4 to -1**	**0 (BL)**	**2**	**4**	**5 [d)]**	**6 [d)]**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Study day	**-27 to 0**	**1**	**15**	**29**	**36**	**43**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Window in days	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Efficacy																	
Relapse assessment		Monitor and record throughout the study															
EDSS/FSS, visual function testing [m)], SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D, T25W	X [e)]	X									X						X
ZBI [p)]		X									X [o)]						X [o)]
MRI	X [f, i)]							X [f,o)]			X [f,o)]						X [f,o)]
PK-PD																	
PK sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD sample [c)]		X	X	X			X	X	X	X	X	X	X	X	X	X	X
Plasmablast		X	X	X			X	X			X						X
Anti-AQP4 antibody [s)]	X	X	X	X			X	X			X						X
Immunogenicity																	
Anti-drug antibody		X		X			X	X	X	X	X	X	X	X	X	X	X
CCSR [d)]																	
Blood		X															
Serum		X		X			X	X			X						X
Plasma		X		X			X	X			X						X

a) RBC, Hb, HCT, 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

b) HBsAg, HBcAb, HBsAb, HCVAb.

Hepatitis B screening: If a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus or HBcAb status is positive, hepatitis B viral DNA will be measured.

Hepatitis C screening: If HCVAb is positive, HCV RNA can be measured for study entry.

c) IL-6, sIL-6R, hsCRP

d) This visit/sampling is optional and will require a separate signature on the informed consent.
e) Only EDSS is conducted
f) MRI for exploratory evaluation is optional and conducted at selected sites, and will require a separate signature on the informed consent
h) For females of child-bearing potential. Serum β-hCG must be performed at screening. During the study, serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.
i) Brain MRI for screening is required for excluding PML. If PML cannot be excluded by MRI, JC virus in the cerebrospinal fluid (CSF) will be measured.
j) Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and 15 min (±5 min) and 60 min (±5 min) after dosing in case of study treatment injection visit.
k) TB test (e.g., tuberculin test and/or Quantiferon® test) should be conducted according as local guidance.
l) For patients who consent to additional PK sampling, triplicate digital ECG recordings will be obtained with approximately 2 - 5 minutes between each ECG recording and the copies of ECG chart should be collected.
m) Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment.
n) For all patients who consent to the study, ECG should be performed prior to blood draws.
o) Window in days is within ±28 days.
p) ZBI is optional and will be performed in selected countries for caregiver who signed informed consent to caregiver burden assessment.
q) Hepatitis B viral DNA must be measured in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus or whom HBcAb is positive at screening.
r) Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.
s) Anti-AQP4 antibody at screening will be measured *only* by ELISA as an exploratory biomarker. Other points will be measured by cell-based assay *and/or ELISA* as a PD marker.
t) C-SSRS at baseline scale should be used.
u) C-SSRS since last visit scale should be used.
v) Informed consent must be obtained prior to first screening assessment, but if informed consent is obtained before the 28-day screening period (i.e., before Day -27), all screening assessments must be completed within 28 days prior to baseline (i.e., from Day -27 to 0).

BL = Baseline, CCSR = Chugai Clinical Sample Repository.

Appendix 1: Schedule of Activities (cont.)

Table 6: Observation and Test Schedule in the Double-Blind Period (cont.)

	Double-blind period				WD [g]	SFU [f]
Week	**After Week 48**		**Extra visit at relapsing**	**DOW [q]**		
	Every 4 weeks	**Every 24 weeks**				
Window in days	**±7**	**±7**	-	-	-	-
Study treatment injection (SC)	X	X		X		
Body weight		X			X	
Physical examination	X	X	X	X	X	
Vital signs [m]	X	X	X	X	X	
ECG [j]		X			X	
Chest X-ray					X	
Pregnancy test [e]	X	X			X	
Laboratory test [a]	X	X	X		X	
Hepatitis B viral DNA [n]	X [o]	X			X	
C-SSRS [p]	X	X		X	X	
Phone call	Every week between the scheduled visits					
Safety						
Adverse events	Monitor and record throughout the study		X	X	X	
Concomitant medications	Monitor and record throughout the study		X	X	X	X [k]
Efficacy						
Relapse assessment	Monitor and record throughout the study		X	X	X	X
EDSS/FSS		X	X		X	
Visual function testing [i], SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D, T25W		X			X	
ZBI [h,l]		X			X	

Appendix 1: Schedule of Activities (cont.)

Table 6: Observation and Test Schedule in the Double-Blind Period (cont.)

	Double-blind period				WD [g]	SFU [f]
Week	After Week 48		Extra visit at relapsing	DOW [q]		
	Every 4 weeks	Every 24 weeks				
Window in days	±7	±7	-	-	-	-
PK-PD						
PK sample	X	X	X	X	X	
PD sample [b]	X	X	X		X	
Plasmablast		X	X		X	
Anti-AQP4 antibody		X	X		X	
Immunogenicity						
Anti-drug antibody	X	X			X	
CCSR [c]						
Serum		X	X		X	
Plasma		X	X		X	

a) RBC, Hb, HCT, 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

b) IL-6, sIL-6R, hsCRP

c) The sampling is optional and will require a separate signature on the informed consent.

e) For females of child-bearing potential. Serum or urine β-hCG [sensitivity of at least 25 mIU/mL] will be performed.

f) Safety Follow-Up will be conducted for patients who withdraw from the study in double-blind period due to clinical relapse and will last for 24 weeks from the last dosing. A telephone interview will be conducted by site personnel every 4 weeks from last dosing to identify any new or worsening neurological symptoms.

g) For patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks after the last dosing.

h) Window in days is within ±28 days.

i) Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment.

j) For all patients who consent to the study, ECG should be performed prior to blood draws.

k) Information on concomitant medication/therapy for NMO and NMOSD will be collected.

l) ZBI is optional and will be performed in selected countries for caregiver who signed informed consent to caregiver burden assessment.

Appendix 1: Schedule of Activities (cont.)

Table 6: Observation and Test Schedule in the Double-Blind Period (cont.)

m) Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and 15 min (±5 min) and 60 min (±5 min) after dosing in case of study treatment injection visit.

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

o) Every 12 weeks.

p) C-SSRS since last visit scale should be used.

q) In the event that the study drug is not administered within the scheduled visit window and is subsequently administered outside the visit window. Minimum dosing interval should be 14 days.

DOW = dose outside the visit window, SFU = Safety follow-up, WD = Withdrawal visit, CCSR = Chugai Clinical Sample Repository.

Table 7 Observation and Test Schedule in the Extension Period (Week 0 – Week 48)

	Extension period							WD [e]
Week	0 [i]	2	From Week 0 to Week 48		Extra visit at relapsing	DOW [o]	Last observation [d]	
			Every 4 weeks	Every 24 weeks				
Window in days	-	±3	±7	±7	-	-	±7	-
Satralizumab injection (SC)	X	X	X	X		X		
Body weight	X			X			X	X
Physical examination	X	X	X	X	X	X	X	X
Vital signs [k]	X	X	X	X	X	X	X	X
ECG [h]	X			X			X	X
Chest X-ray							X	X
Pregnancy test [c]	X		X	X			X	X
Laboratory test [a]	X	X	X	X	X		X	X
Hepatitis B viral DNA [l]	X		X [m]	X			X	X
C-SSRS [n]	X	X	X	X		X	X	X
Safety								
Adverse events	Monitor and record throughout the study				X	X	X	X
Concomitant medications	Monitor and record throughout the study				X	X	X	X
Efficacy								
Relapse assessment	Monitor and record throughout the study				X	X	X	X
EDSS/FSS	X			X	X		X	X
Visual function testing [g], SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D, T25W	X			X			X	X
ZBI [f, j]	X			X			X	X
MRI [f, p]	X			X [q]				

Appendix 1: Schedule of Activities (cont.)

Table 7: Observation and Test Schedule in the Extension Period (Week 0 – Week 48) (cont.)

	Extension period							WD [e]
Week	0 [i]	2	From Week 0 to Week 48		Extra visit at relapsing	DOW [o]	Last observation [d]	
			Every 4 weeks	Every 24 weeks				
Window in days	-	±3	±7	±7	-	-	±7	-
PK-PD								
PK sample	X		X	X	X	X	X	X
PD sample [b]	X		X	X	X		X	X
Anti-AQP4 antibody	X			X	X			
Immunogenicity								
Anti-drug antibody	X		X	X			X	X

a) RBC, Hb, HCT, 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

b) IL-6, sIL-6R, hsCRP

c) For females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.

d) Last observation will be conducted 12 weeks after the last dose of satralizumab for patients who complete extension period.

e) For patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks after the last dose of satralizumab.

f) Window in days is within ±28 days.

g) Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment.

h) For all patients who consent to the study, ECG should be performed prior to blood draws.

i) Patients who experienced a protocol-defined relapse which is adjudicated by CEC can visit the study site in the stable disease condition (Day 31 or later, where Day 1 is defined as the day of onset of a protocol-defined relapse which is adjudicated by CEC). Patients who completed the double-blind period can visit the study site after 4 weeks (± 7 days) from the last dosing in the double-blind period.

j) ZBI is optional and will be performed in selected countries for caregiver who signed informed consent to caregiver burden assessment.

k) Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and 15 min (±5 min) and 60 min (±5 min) after dosing in case of study treatment injection visit.

l) Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.

m) Every 12 weeks.

n) C-SSRS since last visit scale should be used.

o) In the event that the study drug is not administered within the scheduled visit window and is subsequently administered outside the visit window. Minimum dosing interval should be 14 days.

p) MRI for exploratory evaluation is optional and conducted at selected sites, and will require a separate signature on the informed consent. Only for patients who end the double-blind period by Week 48 of the double-blind period.

q) Week 48 only.

DOW = dose outside the visit window, WD = Withdrawal visit.

Table 8 Observation and Test Schedule in the Extension Period (After Week 48)

	Extension period [o]						WD [e]
Week	After Week 48			Extra visit at relapsing	DOW [m]	Last observation [d]	
	Every 4 weeks [p]	Every 12 weeks	Every 24 weeks				
Window in days	±7	±7	±7	-	-	±7	-
Satralizumab injection (SC)	X [n]	X [n]	X [n]		X		
Body weight			X			X	X
Physical examination		X	X	X	X	X	X
Vital signs [j]		X	X	X	X	X	X
ECG [h]			X			X	X
Chest X-ray						X	X
Pregnancy test [c]		X	X			X	X
Laboratory test [a]		X	X	X		X	X
Hepatitis B viral DNA [k]		X	X			X	X
C-SSRS [l]		X	X		X	X	X
Safety							
Adverse events	Monitor and record throughout the study			X	X	X	X
Concomitant medications	Monitor and record throughout the study			X	X	X	X
Efficacy							
Relapse assessment	Monitor and record throughout the study			X	X	X	X
EDSS/FSS			X	X		X	X
Visual function testing [g], SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D, T25W			X			X	X
ZBI [f, i]			X			X	X
PK-PD							
PK sample			X	X	X	X	X
PD sample [b]						X	X
Anti-AQP4 antibody				X			
Immunogenicity							
Anti-drug antibody			X	X		X	X

Table 8: Observation and Test Schedule in the Extension Period (After Week 48) (cont.)

a) RBC, Hb, HCT, 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 emergency situations 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 5.3.5.*

b) IL-6, sIL-6R, hsCRP

c) For females of child-bearing potential. Serum or urine [sensitivity of at least 25 mIU/mL] β-hCG will be performed.

d) Last observation will be conducted 12 weeks after the last dose of satralizumab for patients who complete *the* extension period.

e) For patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks after the last dose of satralizumab.

f) Window in days is within ±28 days.

g) Visual function testing includes visual acuity tests of Snellen and Low-contrast Sloan letter chart. Visual acuity test of Snellen chart is not required if it is implemented with FSS assessment.

h) For all patients who consent to the study, ECG should be performed prior to blood draws.

i) ZBI is optional and will be performed in selected countries for caregiver who signed informed consent to caregiver burden assessment.

j) Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and 15 min (±5 min) and 60 min (±5 min) after dosing in case of study treatment injection visit.

k) Hepatitis B viral DNA must be monitored in patients for whom a positive result for HBsAb is not clearly associated with vaccination against hepatitis B virus and HBV DNA is negative at screening or whom HBcAb is positive and HBV DNA is negative at screening.

l) C-SSRS since last visit scale should be used.

m) In the event that the study drug is not administered within the scheduled visit window and is subsequently administered outside the visit window. Minimum dosing interval should be 14 days.

n) In the OLE period after Week 48, 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, or home administration by a mobile nurse) will be allowed in emergency situations such as the SARS-CoV-2 (COVID-19) pandemic.

o) *If patients cannot physically attend a visit at the study site in emergency situations 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.*

p) *Following the implementation of Protocol Version 10 and in accordance with local regulations, administration of satralizumab outside of the study site can be implemented. Patients will be followed up by study site personnel through phone calls to monitor compliance and perform safety assessments.*

DOW = dose outside the visit window, WD = Withdrawal visit.

Appendix 2
EDSS/FSS Assessment Form

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- ❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- ❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

- ❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
- ❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
- ❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
- ❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
- ❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
- ❑ 10.0 - Death due to NMO.

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.
Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Kurtzke Functional Systems Scores (FSS)

❑ **Pyramidal Functions**

0 - Normal
1 - Abnormal signs without disability
2 - Minimal disability
3 - Mild to moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4 - Marked paraparesis or hemiparesis (function is difficult), moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5 - Paraplegia, hemiplegia, or marked quadriparesis
6 - Quadriplegia
9 - (Unknown)

❑ **Cerebellar Functions**

0 - Normal
1 - Abnormal signs without disability
2 - Mild ataxia (tremor or clumsy movements easily seen, minor interference with function)
3 - Moderate truncal or limb ataxia (tremor or clumsy movements interfere with function in all shpheres)
4 - Severe ataxia in all limbs (most function is very difficult)
5 - Unable to perform coordinated movements due to ataxia
9 - (Unknown)

❑ Record #1 in small box when weakness (grade 3 or worse on pyramidal) interferes with testing.

❑ **Brainstem Functions**

0 - Normal
1 - Signs only
2 - Moderate nystagmus or other mild disability
3 - Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4 - Marked dysarthria or other marked disability
5 - Inability to swallow or speak
9 - (Unknown)

❑ **Sensory Function**

0 - Normal
1 - Vibration or figure-writing decrease only in one or two limbs
2 - Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs
3 - Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs
4 - Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5 - Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6 - Sensation essentially lost below the head
9 - (Unknown)

❑ **Bowel and Bladder Function**

(Rate on the basis of the worse function, either bowel or bladder)
0 - Normal
1 - Mild urinary hesitance, urgency, or retention
2 - Moderate hesitance, urgency, retention of bowel or bladder, or rare urinary incontinence (intermittent self-catheterization, manual compression to evacuate bladder, or finger evacuation of stool)
3 - Frequent urinary incontinence
4 - In need of almost constant catheterization (and constant use of measures to evacuate stool)
5 - Loss of bladder function
6 - Loss of bowel and bladder function
9 - (Unknown)

❑ **Visual Function**

0 - Normal
1 - Scotoma with visual acuity (corrected) better than 20/30
2 - Worse eye with scotoma with maximal visual acuity (corrected) of 20/30–20/59
3 - Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60–20/99
4 - Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100–20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5 - Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6 - Grade 5 plus maximal visual acuity of better eye of 20/60 or less
9 - (Unknown)

❑ Record #1 in small box for presence of temporal pallor

❑ **Cerebral (or Mental) Functions**

0 - Normal
1 - Mood alteration only (does not affect EDSS score)
2 - Mild decrease in mentation
3 - Moderate decrease in mentation
4 - Marked decrease in mentation (chronic brain syndrome – moderate)
5 - Dementia or chronic brain syndrome – severe or incompetent
9 - (Unknown)

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

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

Appendix 3
SF-36 Questionnaire

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!* For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:
2. Compared to one year ago, how would you rate your health in general now?
3. The following questions are about activities you might do during a typical day.

   Does your health now limit you in these activities? If so, how much?
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups?
7. How much bodily pain have you had during the past 4 weeks?
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
11. How TRUE or FALSE is each of the following statements for you?

<u>The actual forms will be provided to the sites and should be used for assessment.</u>

Appendix 4
Visual Analogue Scale for Pain

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

Appendix 5
FACIT-Fatigue Scale

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

<u>The actual forms will be provided to the sites and should be used for assessment.</u>

Appendix 6
Modified Rankin Scale

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

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

Appendix 7
Zarit Burden Interview

INSTRUCTIONS: The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, indicate how often you feel that way; never, rarely, sometimes, quite frequently, or nearly always. There are no right or wrong answers.

1. Do you feel that your relative asks for more help than he/she needs?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

4. Do you feel embarrassed over your relative's behavior?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

5. Do you feel angry when you are around your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

6. Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

7. Are you afraid what the future holds for your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

8. Do you feel your relative is dependent upon you?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

9. Do you feel strained when you are around your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

10. Do you feel your health has suffered because of your involvement with your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

11. Do you feel that you don't have as much privacy as you would like, because of your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

12. Do you feel that your social life has suffered because you are caring for your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

13. Do you feel uncomfortable about having friends over, because of your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

14. Do you feel that your relative seems to expect you to take care of him/her, as if you were the only one he/she could depend on?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

15. Do you feel that you don't have enough money to care for your relative, in addition to the rest of your expenses?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

16. Do you feel that you will be unable to take care of your relative much longer?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

17. Do you feel you have lost control of your life since your relative's illness?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

18. Do you wish you could just leave the care of your relative to someone else?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

19. Do you feel uncertain about what to do about your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

20. Do you feel you should be doing more for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

21. Do you feel you could do a better job in caring for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

22. Overall, how burdened do you feel in caring for your relative?

0. Not at all 1. A little 2. Moderately 3. Quite a bit 4. Extremely

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

Appendix 8
EuroQol-5D (EQ-5D)

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	❑

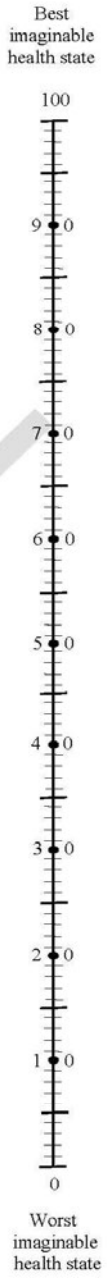
Anxiety/Depression

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



3

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

Appendix 9
CCSR Subject Withdrawal Form

- Blood Sample for DNA Analysis -

Site/Investigator name	***[monitor to complete for site]***
Protocol number	BN40900 (**SA-309JG**)
Subject number	

To be completed and signed by the investigator and faxed to: [monitor name/ fax number]

I confirm that the above mentioned subject has withdrawn his/her consent from the Chugai Clinical Sample Repository (CCSR) project.

Withdrawal is **Blood sample for DNA analysis**

Date subject withdrew from the CCSR ____/____/____ (dd/mm/yy)

Has the subject sample been shipped?

□ **Yes** **If Yes,** **date the sample was shipped** ____/____/____ (dd/mm/yy)

□ **No** **If No,**

□ **The sample was destroyed. Date destroyed** ____/____/____ (dd/mm/yy)

Or

□ **No sample was taken.**

Investigator signature _____ **Date** ____/____/____ (dd/mm/yy)

To be completed and signed by the biomarker operation at the sponsor

Date form received by the biomarker operation at the sponsor: ____/____/____ (dd/mm/yy)

☐ **I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR before sampling.**

Or

☐ **I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR to store/hold his/her sample/s. His/her sample/s has/have been destroyed at the investigator site.**

Or

☐ **I confirm that the above mentioned patient has withdrawn his/her consent for the CCSR to store/hold his/her sample/s. His/her sample/s was/were destroyed at the sponsor at :** / / (dd/mm/yy)

Biomarker operation name _____

Biomarker operation signature _____ **Date** ____/____/____ (dd/mm/yy)

- Serum and Plasma Samples -

Site/Investigator name	***[monitor to complete for site]***
Protocol number	BN40900 (**SA-309JG**)
Subject number	

To be completed and signed by the investigator and faxed to: [monitor name/ fax number]

I confirm that the above mentioned subject has withdrawn his/her consent from the Chugai Clinical Sample Repository (CCSR) project.

Withdrawal is □ **Taking serum and plasma samples hereafter**
or
□ **Testing of serum and plasma samples already collected and taking serum and plasma samples hereafter**

Date subject withdrew from the CCSR ____/____/____ (dd/mm/yy)

Have any samples of the subject been taken?

□ **Yes** **If Yes, does the patient wish to destroy the samples already collected?**
□ **Yes** **Latest shipment date if some of the samples been shipped**
And/or ____/____/____ (dd/mm/yy)
Date Destroyed samples if some of them still remain
____/____/____ (dd/mm/yy)
□ **No**
□ **No**

Investigator signature _____ **Date** ____/____/____ (dd/mm/yy)

To be completed and signed by the biomarker operation at the sponsor

Date form received by the biomarker operation at the sponsor: ____/____/____ (dd/mm/yy)

☐ **I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR before the first sampling.**

Or

☐ **I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR to take more his/her sample/s.**

Or

☐ **I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR to store/hold his/her sample/s. His/her sample/s has/have been destroyed at the investigator site.**

Or / And

☐ **I confirm that the above mentioned patient has withdrawn his/her consent for the CCSR to store/hold his/her sample/s. His/her sample/s was/were destroyed at the sponsor at :** ____/____/____ (dd/mm/yy)

Biomarker operation name _____
Biomarker operation signature _____ **Date** ____/____/____ (dd/mm/yy)

Appendix 10
C-SSRS at Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

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@childpsych.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.

Lifetime: Time He/She Felt Most Suicidal

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.
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 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 ☐

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). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: ____ *Type # (1-5)* _____ *Description of Ideation*

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)*	**Lifetime**
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:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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 ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First 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* _____	*Enter Code* _____	*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* _____	*Enter Code* _____	*Enter Code* _____

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

Appendix 11
C-SSRS since Last Visit

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?
Yes ☐ No ☐
If yes, describe:

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?
Yes ☐ No ☐
If yes, describe:

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?
Yes ☐ No ☐
If yes, describe:

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?
Yes ☐ No ☐
If yes, describe:

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?
Yes ☐ No ☐
If yes, describe:

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

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

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* _____

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

Appendix 12
Instruction for Tuberculosis (TB) Screening and Treatment

Interpretation of TB screening results

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

Definitions

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

Latent TB is said to exist when an individual is infected with *Mycobacterium tuberculosis,* as evidenced by a positive Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA - such as Quantiferon®-TB Gold) but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others. Such individuals must be treated with appropriate anti-mycobacterial therapy for at least 3 weeks prior to initiating study treatment administration in this study.

TB screening

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

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

Note:

1. The TST may be positive if the patient has had a BCG vaccination or has been infected with TB in the past; IGRA results may also be positive in some cases of past infection.
2. Positive results of the TST and IGRA test may be reduced by immune suppression.
3. Local guidance may vary depending upon the sensitivity of strains of Mycobacterium tuberculosis present locally.

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

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

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

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

TB Treatment

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

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

Management of signs/symptoms of TB during the study

If new signs/symptoms of TB infection develop during the study, perform diagnostic tests as above. If TB infection is diagnosed, interrupt study treatment and consult the Medical Monitor. Report TB infection as a "Selected Adverse Event" (see protocol Section 5.2.4).