

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

**NCT Number:** NCT02028884

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## PROTOCOL

**TITLE:** A MULTICENTER, RANDOMIZED, ADDITION TO BASELINE TREATMENT, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SATRALIZUMAB (SA237) IN PATIENTS WITH NEUROMYELITIS OPTICA (NMO) AND NMO SPECTRUM DISORDER (NMOSD)

**PROTOCOL NUMBER:** BN40898 (SA-307JG)

**VERSION NUMBER:** 11

**EUDRACT NUMBER:** 2013-003752-21

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**TEST PRODUCT:** Satralizumab (SA237) (RO5333787)

**MEDICAL MONITOR:** [REDACTED], M.D.

**CO-SPONSORS:** F. Hoffmann-La Roche Ltd  
Chugai Pharmaceutical Co. Ltd. \*

**APPROVAL DATE:** See electronic date stamp below.

## PROTOCOL AMENDMENT APPROVAL

**Date and Time (UTC)**  
10-Apr-2020 17:42:06

**Title**  
Company Signatory

**Approver's Name**  
[REDACTED]

**CONFIDENTIAL**

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\* 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.

**Satralizumab (SA237)—F. Hoffmann-La Roche Ltd**  
Protocol BN40898 (SA-307JG), Version 11

## PROTOCOL HISTORY

Protocol	
Version	Date Final
1	5 September 2013
2	29 November 2013
3	27 February 2014
4	18 December 2014
5	3 June 2015
6	19 October 2015
7	14 December 2016
8	17 April 2017
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9	14 March 2019
10 (United Kingdom)	24 December 2019

## **PROTOCOL AMENDMENT, VERSION 11: RATIONALE**

Protocol BN40898 (SA-307JG), Version 11 (global), is a merging of Version 9 (global) and Version 10 (United Kingdom). This version 11 (global) of the protocol replaces the current version 9 (global) and all United Kingdom-specific versions. Relative to Version 9 (global), the protocol has been amended to reflect a change in Sponsor for South Korea; relative to Version 9 (global) and Version 10 (United Kingdom), it has been amended to increase the duration of the open-label extension (OLE) period up to 31 December 2021. In addition, specific measures were implemented to allow continuation of treatment and ensure patient 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 OLE 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 3.1.1, 4.3.2.2, and 4.5.2.3).
- 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, 4.5.1.11, 4.5.2.2, and 5.1.1.7; Appendix 1, Table 7):
  - 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, 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 11 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, 5.1.1.7, and Appendix 1, Table 7).

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 (Section 6.7 and Appendix 1, Table 6).
- Language has been added to clarify permitted medications during the OLE period (Section 4.4.1).
- 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 4.5.1.11).
- 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).
- Patients that were enrolled as adolescents aged 18 years or older at the time they complete or discontinue from the OLE period and adolescent patients that decide to continue treatment with satralizumab outside of this study will not have to complete the Follow-Up Assessments for Adolescents (Section 4.5.2.5).
- 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, ADDITION TO  
BASELINE TREATMENT, DOUBLE-BLIND,  
PLACEBO-CONTROLLED, PHASE 3 STUDY TO  
EVALUATE THE EFFICACY AND SAFETY OF  
SATRALIZUMAB (SA237) IN PATIENTS WITH  
NEUROMYELITIS OPTICA (NMO) AND NMO  
SPECTRUM DISORDER (NMOSD)

**PROTOCOL NUMBER:** BN40898 (SA-307JG)

**VERSION NUMBER:** 11

**EUDRACT NUMBER:** 2013-003752-21

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**TEST PRODUCT:** Satralizumab (SA237) (RO5333787)

**MEDICAL MONITOR:** [REDACTED], M.D.

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

## PROTOCOL SYNOPSIS

**TITLE:** A MULTICENTER, RANDOMIZED, ADDITION TO BASELINE TREATMENT, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SATRALIZUMAB (SA237) IN PATIENTS WITH NEUROMYELITIS OPTICA (NMO) AND NMO SPECTRUM DISORDER (NMOSD)

**PROTOCOL NUMBER:** BN40898 (SA-307JG)

**VERSION NUMBER:** 11

**EUDRACT NUMBER:** 2013-003752-21

**IND NUMBER:** 118183

**TEST PRODUCT:** Satralizumab (SA237) (RO5333787)

**PHASE:** III

**INDICATION:** Neuromyelitis optica and neuromyelitis optica spectrum disorder

**CO-SPONSORS:** F. Hoffmann-La Roche Ltd  
Chugai Pharmaceutical Co. Ltd.

### Objectives

#### **Efficacy Objective**

The efficacy objective for this study is as follows:

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

#### **Safety Objective**

The safety objective for this study is as follows:

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

#### **Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To examine the pharmacokinetics, pharmacodynamics and immunogenicity of satralizumab.
- To evaluate effect on pain of satralizumab compared to placebo in patients with NMO/NMOSD, in addition to the efficacy objective of this study shown above (This is optional and will be conducted at selected sites).

### Study Design

#### **Description of Study**

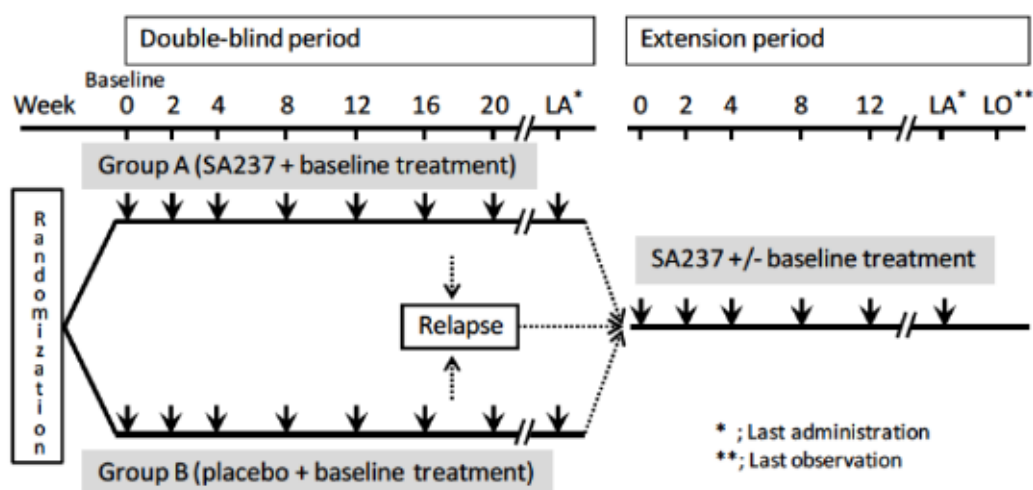
This is a multicenter, randomized, addition-to-baseline treatment, double-blind, placebo-controlled, parallel assignment study followed by an open-label extension period. Patients will be randomized to either satralizumab 120 mg (Group A) or placebo (Group B). Blinded study drug will be administered subcutaneously (SC) at Weeks 0, 2 and 4, and thereafter every 4 weeks (Q4W) in combination with one of the following baseline treatments:

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azathioprine, mycophenolate mofetil or oral corticosteroids (treatment with both oral corticosteroids and either azathioprine or mycophenolate mofetil will be accepted in patients aged 12 to 17 years at the time of informed consent). The randomization will be stratified by baseline annualized relapse rate (ARR) and geographical region. The primary efficacy endpoint is the time to first protocol-defined relapse (TFR) in the double-blind period, where the time point of relapse onset is defined as the time at which the patient experiences any new or worsening neurological NMO representing clinical symptom(s). The duration of the study will depend up on the relapse rate, since the double-blind period of the study will end when the total number of protocol-defined relapses judged by Clinical Endpoint Committee (CEC) reaches 26, while the extension period is expected to last until Last Observation Visit.

Patients who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by CEC in the double-blind period or who complete the double-blind period can enter the open-label extension period and will receive SC 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*. It is at the discretion of the Investigator to modify the baseline treatment after the double-blind period of this study. For patients who are treated with rescue therapy during the double-blind period, satralizumab can be started once disease has stabilized after rescue therapy for relapse (Day 31 or later but not more than 60 days, where Day 1 is defined as the day of onset of relapse in the double-blind period). The patients who are not treated with rescue therapy during the double-blind period can enter the extension period after 4 weeks from the last dosing in the double-blind period.



SA237 = satralizumab.

Patients who withdraw from the study in the double-blind period due to clinical relapse should be asked to continue Safety Follow-Up for a period of 24 weeks from the last dose of study drug.

For patients aged 12 to 17 years at the time of informed consent who withdraw from the study or complete the extension period, Follow-Up Assessment for Adolescents will be conducted for 1 year (48 weeks).

#### Number of Patients

Approximately 70 patients (35 per group) 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<sup>†</sup> will be capped at approximately 30% of total number of adult patients (18 to 74 years at the time of informed consent).

### **Inclusion Criteria**

Patients must meet the following criteria for study entry:

1. Patients must be diagnosed as having either:
  - a. NMO as defined by 2006 criteria\*, or
  - b. NMOSD as defined by either of the following Wingerchuk 2007 criteria with anti-aquaporin 4 antibody (AQP4Ab) 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: recurrent or simultaneous bilateral

For patients aged 12 to 17 years, a minimum of 4 patients should be positive for anti-AQP4Ab status at screening†.

† Screening result is based on either the blood sample data collected at screening visit, or the blood sample data collected before the screening visit and measured by Sponsor's designee for analysis (see Section 4.5.1.5).

2. Clinical evidence of at least 2 documented relapses (including first attack) in the last 2 years prior to screening, at least one of which has occurred in the 12 months prior to screening.
3. Expanded Disability Status Scale (EDSS) score from 0 to 6.5 inclusive at screening.
4. Age 12 to 74 years, inclusive at the time of informed consent.
5. One of the following baseline treatments must be at stable dose as a monotherapy for 8 weeks prior to baseline\*\*:
  - a. Azathioprine.
  - b. Mycophenolate mofetil.
  - c. Oral corticosteroids.

\*\* For patients aged 12 to 17 years, either of the following baseline treatments for relapse prevention can be allowed:

- d. Azathioprine + oral corticosteroids.
  - e. Mycophenolate mofetil + oral corticosteroids.
6. 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 the following three 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-immunoglobulin G seropositive status

### **Exclusion Criteria**

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

**Exclusion criteria related to previous or concomitant therapy:**

1. Any previous treatment with interleukin-6 (IL-6) inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation or bone marrow transplantation at any time.

2. Any previous treatment with anti-cluster of differentiation (CD) 20, eculizumab, belimumab, interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide or dimethyl fumarate within 6 months prior to baseline.
3. Any previous treatment with anti-CD4, cladribine or mitoxantrone within 2 years prior to baseline.
4. Treatment with any investigational agent within 3 months prior to baseline.

**Exclusions for general safety:**

5. Pregnancy or lactation.
6. 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.
7. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
8. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
9. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as:  
other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
10. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
11. Evidence of chronic active hepatitis B or C.
12. History of drug or alcohol abuse within 1 year prior to baseline.
13. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
14. Evidence of active tuberculosis (TB; excluding patients receiving chemoprophylaxis for latent TB infection).
15. Evidence of active interstitial lung disease.
16. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
17. 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).
18. History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
19. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.

**Laboratory exclusion criteria (at screening):**

20. Following laboratory abnormalities at screening\*.
  - a. White blood cells  $<3.0 \times 10^3/\mu\text{L}$
  - b. Absolute neutrophil count  $<2.0 \times 10^3/\mu\text{L}$
  - c. Absolute lymphocyte count  $<0.5 \times 10^3/\mu\text{L}$
  - d. Platelet count  $<10 \times 10^4/\mu\text{L}$
  - e. Aspartate aminotransferase or alanine aminotransferase  $>1.5$  times the upper limit of normal.

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

### **Length of Study**

#### **End of Study (Double-blind Period)**

The end of double-blind period is defined as the date of primary analysis when total number of protocol-defined relapses judged by CEC reaches 26. The duration is estimated to be approximately 30 months from first patient in (FPI).

#### **End of Study (Extension Period)**

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

### **Study Endpoints/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. The proportion of relapse-free patients
- vi. ARR
- vii. Change in modified Rankin Scale (mRS) score
- viii. Change in Zarit Burden Interview (ZBI) score
- ix. Change in EDSS score
- x. Change in visual acuity (Snellen chart)

#### **Safety Assessments**

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

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

#### **Pharmacodynamic Endpoints**

IL-6, soluble IL-6 receptor, high-sensitivity C-reactive protein, anti-AQP4 antibodies and plasmablasts.

#### **Pharmacokinetic Endpoints**

Serum satralizumab concentration.

#### **Immunogenicity Endpoints**

Incidence of anti-drug antibodies.

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

#### **Exploratory Endpoint**

Additional pain assessment.

Additional pain assessment is optional and will be conducted at selected sites (see the details in the procedure for additional pain assessment).

#### **Investigational Medicinal Products**

Throughout this protocol, 'study drug' refers to satralizumab or placebo.

#### **Test Product (Double-blind Period)**

Satralizumab 120 mg/mL

Dose and Mode of Administration: 120 mg SC at Weeks 0, 2 and 4, and Q4W thereafter.

#### **Comparator (Double-blind Period)**

Single dose of placebo SC at Weeks 0, 2 and 4, and Q4W thereafter.

### **Satralizumab (SA237)—F. Hoffmann-La Roche Ltd**

19/Protocol BN40898 (SA-307JG), Version 11

### **Test Product (Extension Period)**

Satralizumab 120 mg/mL

Dose and Mode of Administration: 120 mg SC at Weeks 0, 2 and 4, and Q4W thereafter, *with the last study drug administration on or before 31 December 2021.*

### **Non-Investigational Medicinal Products**

In the double-blind period, in addition to satralizumab or placebo, patients will receive baseline treatment with azathioprine, mycophenolate mofetil or oral corticosteroids at a stable dose not exceeding:

- Azathioprine\*: 3 mg/kg/day
- Mycophenolate mofetil\*: 3000 mg/day
- Oral corticosteroids: 15 mg/day (prednisolone equivalent).

\* Combination with oral corticosteroids (15 mg/day [prednisolone equivalent]) is permitted in patients aged 12 to 17 years at the time of informed consent.

In the double-blind period, a dose decrease is permitted only for safety reasons. Dose increase or change of baseline treatment is not permitted.

In the extension period, patients will receive satralizumab with or without baseline treatments. Change or discontinuation of baseline treatment is permitted.

### **Statistical Methods**

#### **Primary Analysis**

A stratified two-sided log-rank test using strata of baseline ARR and geographical region will be used. The Kaplan-Meier method will be used to estimate the TFR distribution for each treatment group. The median TFR is not expected to be reached in this study at the time of the primary analysis; hence relapse-free rates and their 95% confidence interval (CI) will be used every 6 months to describe TFR distribution in addition to the hazard ratio.

#### **Determination of Sample Size**

The sample size considerations are based on the following assumptions: (1) a two-sided log-rank test; (2) 80% power at the 5% significance level; (3) a 66.5% reduction in the risk of relapse, i.e., the TFR hazard ratio of satralizumab over placebo is 0.335; (4) TFR in the placebo arm following an exponential distribution, with hazard rate  $(h(t))=0.4184$ ; (5) a 2-year dropout rate of 10%.

Based on these assumptions, 26 CEC-confirmed TFR events are needed for the primary analysis. The maximum accrual rate will be approximately 8 patients per month, after the FPI plus 8 months of ramp up. The 70 patients enrolled over 1 year and followed for an additional one and a half years will provide 26 TFR events.

### **Adolescents in the Study**

#### **Study Design for Adolescents**

Adolescents (patients from 12 to 17 years old with NMO/NMOSD) will follow the above Study Design and will be randomized into the double-blind period of the study. After the total number of protocol-defined relapses judged by the CEC reaches 26, adolescents may be enrolled into the extension period if 8 adolescents are not enrolled into the double-blind period.

#### **Specific Objective for the Group of Adolescents**

The objective for adolescents who are enrolled into this study (double-blind period or extension period) is as follows:

- To evaluate the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics and immunogenicity of satralizumab in adolescents.

#### **Target Population for Adolescents**

The inclusion and exclusion criteria for adolescents who will be enrolled into the double-blind period are shown above. For adolescents who may be enrolled into the extension period

after the end of the double-blind period, the inclusion criterion 2 and the annotation “\*\*” in the exclusion criterion 20 are as follows (other criteria are same):

Inclusion Criterion 2

2. Clinical evidence of at least 2 documented relapses (including first attack) prior to screening.

The Annotation “\*\*” in the Exclusion Criterion 20

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

**Specific Outcome Measures (Endpoints) for the Group of Adolescents**

The outcome measures (endpoints) for adolescents who are enrolled into this study (double-blind period or extension period) are as follows:

Primary Outcome Measures (Endpoints)

- Safety assessments
  - Incidence and severity of AEs, AESIs, SAE and selected AEs
  - Vital signs (temperature, systolic and diastolic blood pressure and pulse rate), physical examinations, clinical laboratory tests (hematology, chemistry and urinalysis), 12 lead ECGs, suicidality (C-SSRS)
- PK, PD and immunogenicity

Secondary Outcome Measures (Endpoints)

- Time to first protocol-defined relapse (TFR)
- ARR
- Change in EDSS score
- Change in visual acuity (Snellen chart)
- Change in SF-36 score
- Change in VAS score for pain
- Change in FACIT Fatigue score
- Change in EQ-5D score
- Change in mRS score
- Change in ZBI score

**Statistical Methods:**

Summary statistics will be provided for all safety and efficacy outcome measures. Outcome measures will be reported for all adolescents who are enrolled into this study, as well as for all adolescents who are randomized into the double-blind period. Separate listings for adolescents who are enrolled into the extension period will be provided, as appropriate.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-Drug (Satralizumab) Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
APRIL	A Proliferation-inducing Ligand
AQP4	Aquaporin-4
AQP4Ab	Aquaporin-4 antibodies
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
CCSR	Chugai Clinical Sample Repository
CD	Cluster of Differentiation
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CK	Creatinine Kinase
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
CT	Computerized Tomography
C <sub>trough</sub>	Average Trough Serum Concentration
CV	Coefficient of Variance
CYP	Cytochrome P
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
DOW	Dose Outside The Visit Window
EC	<i>European Commission</i>

<b>Abbreviation</b>	<b>Definition</b>
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EU	European Union
FACIT	Functional Assessment Of Chronic Illness Therapy
<i>FDA</i>	<i>Food and Drug Administration</i>
Fc	Fragment Crystallizable
FPI	First Patient In
FSS	Functional System Score
FUAA	Follow-Up Assessment for Adolescents
GCP	Good Clinical Practice
GTP	Gamma Glutamyl Transpeptidase
Hb	Hemoglobin
HBcAb	Total Hepatitis B Core Antibody
HbsAb	Antibody To Hepatitis B Surface Antigen
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
Hct	Hematocrit
HCVAb	Hepatitis C Virus Antibody
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
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
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Injection-related Reaction



<b>Abbreviation</b>	<b>Definition</b>
ITT	Intent-To-Treat
IV	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
IxRS	Interactive Voice or Web Response System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
MMRM	Mixed-effects Model Repeated Measures
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MS	Multiple Sclerosis
NMO	Neuromyelitis Optica
NMOSD	Neuromyelitis Optica Spectrum Disorder
NSD	Needle Safety Device
<i>OLE</i>	<i>Open-Label Extension</i>
PD	Pharmacodynamic(s)
<i>PDR</i>	<i>Protocol Defined Relapse</i>
PFS	Prefilled Syringe
pJIA	Polyarticular Juvenile Idiopathic Arthritis
PK	Pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per-Protocol Set
PML	Progressive Multifocal Leukoencephalopathy
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
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SD	Standard Deviation
SF-36	Short Form Generic Health Survey
SFU	Safety Follow-Up
sIL-6R	Soluble Interleukin-6 Receptor

<b>Abbreviation</b>	<b>Definition</b>
sJIA	Systemic Juvenile Idiopathic Arthritis
TB	Tuberculosis
TBL	Total Bilirubin
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)
WD	Withdrawal
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 cerebrospinal fluid (CSF). *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).*

*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: 1) acute treatment of relapses, 2) prevention of relapses, 3) symptom management and 4) rehabilitation*

Satralizumab (also known as SA237) is expected to contribute to the prevention of relapses. 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)- $\beta$ , 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. Given the potential of a single relapse in NMO patients to cause significant disability, 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 aquaporin-4 (AQP4Ab), a major water channel protein in the central nervous system (CNS) (Lennon VA et al. 2005). Transfer of anti-AQP4Ab has been shown to exacerbate experimental autoimmune encephalomyelitis in animal models. From this observation, the role of the humoral arm of the immune system in disease pathology for NMO has been developed. Yamamura and co-workers have identified a CD19<sup>int</sup>CD27<sup>hi</sup>CD38<sup>hi</sup>CD180<sup>-</sup> (and CD20<sup>-</sup>) plasmablast B cell subset, which is associated with production of anti-AQP4Ab (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 a proliferation-inducing ligand (APRIL) or the related TNF family ligand B-cell activating factor (BAFF, known as BLyS, the target of the monoclonal antibody belimumab). IL-6, but not BAFF or APRIL, was suggested to enhance antibody production by these plasmablasts, and anti-IL-6 receptor (IL-6R) blockade selectively inhibited survival of AQP4Ab-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.

## **1.2 BACKGROUND ON SATRALIZUMAB**

Satralizumab is a fully humanized anti-human IL-6 receptor (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 (sJIA), polyarticular juvenile idiopathic arthritis (pJIA) 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 on the basis of a non-clinical study and a 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 (FcRn), and
2. Lower effector activities (e.g., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) owing to its lower binding affinity to Fcγ receptor (FcγR) 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, pharmacokinetic (PK) 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 intravenously (IV), and 24 Caucasian subjects were given satralizumab by SC injection. This study demonstrated comparable safety and PK profiles between Caucasian and Japanese volunteers. 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 was a Phase 1 open-label, randomized, parallel-group, multiple-dosing study in patients with RA. The objectives of the study were to assess safety, immunogenicity, PK/pharmacodynamics (PD) and efficacy of satralizumab as a monotherapy. All patients were given 120 mg of satralizumab at Weeks 0, 2 and 4 and then given 30 (Group C), 60 (Group B) or 120 mg (Group A) of satralizumab every 4 weeks (Q4W). Thirty-three patients were enrolled into this study and

11 patients were assigned to each group. In the primary evaluation period, 45 adverse events (AEs) were reported in 22 patients. Two serious AEs (SAEs) were reported in the primary evaluation period: one patient in Group A developed interstitial lung disease and discontinued due to this SAE. One patient in Group B developed bronchopneumonia. Following treatment in hospitalization, these events 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, 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.

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.

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

1. In addition to regular standard safety evaluations (laboratory measures, physical examinations, vital signs and electrocardiogram [ECG]), a special focus will be placed on monitoring the above risks.
2. An Independent Data Monitoring Committee (IDMC) will periodically review *AEs during the double-blind period in a unblinded manner* and, based on the review, will make recommendations on study conduct.

In summary, treatment with satralizumab is an approach for a specific therapeutic strategy in NMO with possible advantages for patients. All necessary measures will be 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 period 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) period.*

*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.*

## **2. OBJECTIVES**

### **2.1 EFFICACY OBJECTIVE**

The efficacy objective for this study is:

- To evaluate the efficacy of satralizumab 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 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. The proportion of relapse-free patients
- vi. Annualized relapse rate (ARR)
- vii. Change in modified Rankin Scale (mRS) score
- viii. Change in Zarit Burden Interview (ZBI) score
- ix. Change in EDSS score
- x. Change in visual acuity (Snellen chart)

### **2.2 SAFETY OBJECTIVE**

The safety objective for this study is:

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

Safety outcome measures:

- Incidence and severity of AEs, adverse events of special interest (AESIs), SAEs (spontaneously reported by patients and caregivers), and selected AEs.
- 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 PD 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-AQP4Ab and plasmablasts.

### **2.4 PHARMACOKINETIC OBJECTIVE**

The PK objective for this study is as follows:

- To examine the 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 Endpoints:

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

### **2.6 EXPLORATORY OBJECTIVE**

The exploratory objective for this study is as follows:

- To assess additional pain.

Additional pain assessment is optional and will be conducted at selected sites (see the details in the procedure for additional pain assessment).

Study endpoints relating to these objectives are listed in Section [3.3](#).

### **2.7 SPECIFIC OBJECTIVE FOR THE GROUP OF ADOLESCENTS**

See Section [4.8](#) for the detail of the objective for the group of adolescents.



### **3. STUDY DESIGN**

#### **3.1 DESCRIPTION OF STUDY**

##### **3.1.1 Overview**

This Phase 3 pivotal study is a multicenter, randomized, addition-to-baseline treatment, double-blind, placebo-controlled, parallel assignment study followed by an *OLE* period. The study has an add-on design (satralizumab + baseline treatment versus placebo + baseline treatment). The study aims to evaluate the efficacy, safety, PD, PK and immunogenicity of satralizumab.

Patients will be randomized to one of 2 groups and will receive either SC satralizumab at a dose of 120 mg (fixed dose) (Group A) or matching SC placebo (Group B) in a 1:1 allocation at Weeks 0, 2 and 4, and Q4W thereafter, in combination with one of the following baseline treatments: azathioprine, mycophenolate mofetil or oral corticosteroids (treatment with both oral corticosteroids and either azathioprine or mycophenolate mofetil will be accepted for patients aged 12 to 17 years at the time of informed consent). The number of patients who are negative for anti-AQP4 antibody at screening will be limited to approximately 30% of the total adult (18 to 74 years at the time of informed consent) study population. The randomization will be stratified by baseline ARR and geographical region.

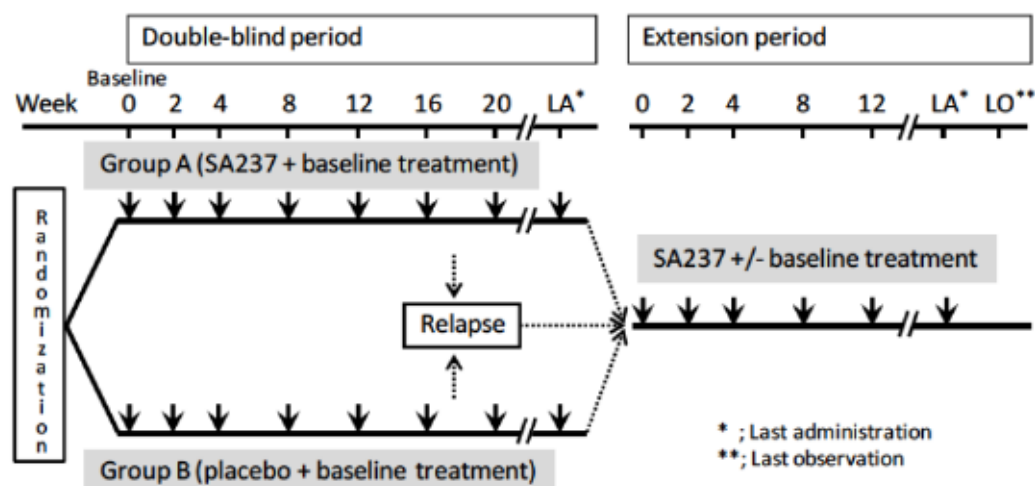
If a potential patient is selected after acute treatment for relapse, then at least 8 weeks on stable baseline treatment is required after the management of the relapse. If the potential patient is enrolled during maintenance therapy, the requirement for 8 weeks on stable medication prior to baseline will be fulfilled. Patients without any relapse-prevention maintenance therapy cannot be enrolled in this study.

Patients who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by Clinical Endpoint Committee (CEC) in the double-blind period or who complete the double-blind period can enter the *OLE* period. In the extension period, patients will 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*. It is at the discretion of the Investigator to modify the baseline treatment after the double-blind period of this study. For patients who experience a relapse in the double-blind period, appropriate rescue therapy for relapse will be initiated, and satralizumab should start once disease has stabilized 31 to 60 days from the onset of relapse in the double-blind period, where the day of onset of relapse is Day 1. If satralizumab cannot be administered by Day 60, the Investigator should consult with the Medical Monitor.

Those patients who complete the double-blind period without experiencing relapse will be instructed to return to the study site 4 weeks ( $\pm 7$  days) after the last dosing if they wish enter extension period. They can enter the extension period and undergo the Day 1 assessments for the extension period. For those patients who enter the extension period after a relapse, the Day 1 assessments of the extension phase will occur 31-60 days from the onset of relapse. The extension period is expected to last until Last Observation Visit.

Study design is summarized in [Figure 1](#).

**Figure 1: Study Design**



SA237 = satralizumab.

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

For patients aged 12 to 17 years at the time of informed consent who withdraw from the study or complete the extension period, Follow-Up Assessment for Adolescents will be conducted for 1 year (48 weeks).

See [Section 4.8](#) for adolescents who may be enrolled after the end of the double-blind period.

### 3.1.2 Investigational Subjects and Sites

It is planned to recruit approximately 70 patients (35 patients per treatment group) from sites across Europe, Asia, North America and other countries in the double-blind

period. After the total number of protocol-defined relapses judged by CEC reaches 26, the recruitment period for the patients aged 12 to 17 years may be continued in the extension period until a minimum of 8 patients aged 12 to 17 years are enrolled into the study.

### **3.1.3 Independent Data Monitoring Committee**

An IDMC will be used *during the double-blind period* to perform periodic unblinded 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*.

*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)**

During the double-blind period, a CEC will review all cases of potential relapse and adjudicate each in a blind fashion 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 CEC will be comprised of physicians with expertise in NMO and NMOSD.

Details regarding the CEC responsibilities and the process of adjudication of relapses are described in detail 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 70 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 tocilizumab suggesting an improvement in relapse rate with satralizumab.

The study uses an 'add-on' design in which patients will receive treatment with either satralizumab + baseline treatment or placebo + baseline treatment, i.e., satralizumab will be added on to baseline immunosuppressant therapy according to accepted

clinical practice. A placebo control is added to the baseline control arm in order to control the potential for Investigator or patient bias.

This study allows for enrollment of patients who are negative for anti-AQP4 antibody. In order to avoid a big difference between the study population and the clinical population, the percentage of the patients who are anti-AQP4 antibody negative 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's last visit occurs; this is expected to be 12 weeks after the last dosing in the extension period.

### **3.2.2 Rationale for Choice of Baseline Treatment**

The comparator/combination treatment regimen of azathioprine, mycophenolate mofetil and/or oral corticosteroid was chosen on the basis of being the most common treatment choice in the US, EU and Japan. Use of rituximab during the study is prohibited since its mechanism of action overlaps that of satralizumab in terms of the reduction of plasmablasts.

### **3.2.3 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, time to first relapse (TFR) was selected as the primary efficacy measure in this study. TFR is used as an alternative to ARR, which has been used as the primary endpoint in MS clinical trials. ARR is a statistical measure of the frequency of relapse. TFR 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. In addition, it allows patients the option to stop double-blind treatment after relapse and to continue in the *OLE* with satralizumab plus baseline therapy. This mitigates the ethical concern of keeping patients with NMO/NMOSD on a potentially ineffective study drug 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.

### **3.2.4 Rationale for Test Product Dosage**

Based on PK and PD assessments in Phase 1 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.

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 RA showed that satralizumab 120 mg Q4W inhibited IL-6 signaling completely, whereas lower doses (30, 60 mg Q4W) did not. Therefore, satralizumab 120 mg Q4W is expected to inhibit IL-6 signaling completely in patients with NMO and NMOSD.
- 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.
- Intravenous 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.

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

### **3.2.5 Rationale for Patient Population**

The limited literature on the topic of paediatric NMO suggests that the disease is diagnosed from around the age of 2 years upwards with a median age of onset of 14 years and a 3 or 4:1 female:male ratio. The spectrum of disease in children appears from the literature to be similar to that in adults with the possible exception of brain lesions and a relatively rapid progression of optic neuritis but the incidence is much lower at around 0.02/100,000 but varying by race (Jacob et al. 2012, Collongues et al. 2010, Lotze et al. 2008, Ketelslegers et al. 2012, Langer-Gould et al. 2011, Tillema 2012).

Recent population anthropometric data from the US, for example, show that the mean body weight for female aged 12 is 52.3 kg (5th to 95th percentile 30.6–75.7 kg) (Centers for Disease Control and Prevention). In the Japanese phase 1b RA study (SA-105JP), 4 of 11 patients treated with 120 mg satralizumab had a body weight under 45 kg. No difference in serum concentration of satralizumab between two groups by body weight (<45 kg and >45 kg) suggesting that it would be acceptable from a PK point of view to dose adolescents with the same 120 mg dose as adults.

The mean weight in older children and in boys is expected to be higher and therefore more similar to that in adults.

Animal toxicology studies with higher doses of satralizumab by body weight than are proposed here have shown no obviously drug-related toxicity. Adolescents aged 12 and upwards are expected to be developmentally mature in most ways.

There is precedent for the use of an anti-IL-6R monoclonal antibody (tocilizumab) to treat children, with and without concomitant immunosuppressant therapies (tocilizumab is licensed for the treatment of sJIA and pJIA internationally and also Castleman's disease in Japan). The safety profile in clinical trials and post-marketing has been generally similar to that in adults. Although these two antibodies are structurally different, the safety profile of tocilizumab can at least be taken to indicate the effect of IL-6R inhibition in the pediatric population.

### **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 in SF-36 score
- iv. Change in EQ-5D score
- v. The proportion of relapse-free patients
- vi. ARR
- vii. Change in mRS score
- viii. Change in ZBI score
- ix. Change in EDSS score
- x. Change in visual acuity (Snellen chart)

#### **3.3.2 Safety Outcome Measures**

- i. Incidence and severity of AEs, SAEs, AESIs, and selected AEs.
- 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 Pharmacodynamic Outcome Measures**

- i. IL-6
- ii. Soluble IL-6R (sIL-6R)
- iii. hsCRP
- iv. Anti-AQP4Ab
- v. Plasmablasts.

### **3.3.4 Pharmacokinetic Outcome Measures**

- i. Serum satralizumab concentration.

### **3.3.5 Immunogenicity Outcome Measures**

- i. Incidence of ADAs.

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

### **3.3.6 Exploratory Outcome Measures**

- i. Additional pain assessment
- ii. Additional pain assessment is optional and will be conducted at selected sites (see the details in the procedure for additional pain assessment).

### **3.3.7 Specific Outcome Measures for the Group of Adolescents**

See Section 4.8 for the detail of the outcome measures for the group of adolescents.

## **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<sup>‡</sup> will be capped at approximately 30% of total number of adult patients (18 to 74 years at the time of informed consent).

#### **4.1.1 Inclusion Criteria**

Patients must meet the following criteria for study entry:

1. Patients must be diagnosed as having either:
  - a. NMO as defined by 2006 criteria\*, or
  - b. NMOSD as defined by either of the following Wingerchuk 2007 criteria with anti-AQP4Ab seropositive status at screening<sup>‡</sup>.
    - i. Idiopathic single or recurrent events of longitudinally extensive myelitis (≥3 vertebral segment spinal cord MRI lesion)
    - ii. Optic neuritis: recurrent or simultaneous bilateral

For patients aged 12 to 17 years, a minimum of 4 patients should be positive for anti-AQP4Ab status at screening‡.

‡ Screening result is based on either the blood sample data collected at screening visit, or the blood sample data collected before the screening visit and measured by Sponsor's designee for analysis (see Section 4.5.1.5).

2. Clinical evidence of at least 2 documented relapses (including first attack) in the last 2 years prior to screening, at least one of which has occurred in the 12 months prior to screening.
3. EDSS score from 0 to 6.5 inclusive at screening.
4. Age 12 to 74 years, inclusive at the time of informed consent.
5. One of the following baseline treatments must be at stable dose as a monotherapy for 8 weeks prior to baseline\*\*.
  - a. Azathioprine.
  - b. Mycophenolate mofetil.
  - c. Oral corticosteroids.

\*\* For patients aged 12 to 17 years, either of the following baseline treatments for relapse prevention can be allowed:

- d. Azathioprine + oral corticosteroids.
  - e. Mycophenolate mofetil + oral corticosteroids.
6. 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 the following three criteria:

- I. Optic neuritis
- II. Acute myelitis
- III. At least two of three supportive criteria:
  - Contiguous spinal cord lesion identified on a magnetic resonance imaging (MRI) scan extending over 3 vertebral segments
  - Brain MRI not meeting diagnostic criteria for MS
  - NMO-IgG seropositive status



See Section 4.8 for the study criteria for adolescents who may be enrolled after the end of the double-blind period.

#### **4.1.2 Exclusion Criteria**

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

##### **Exclusion criteria related to previous or concomitant therapy:**

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

##### **Exclusions for general safety:**

5. Pregnancy or lactation.
6. 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.
7. Any surgical procedure (except for minor surgeries) within 4 weeks prior to baseline.
8. Evidence of other demyelinating disease or progressive multifocal leukoencephalopathy (PML).
9. Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as:  
other nervous system disease, cardiovascular disease,  
hematologic/hematopoiesis disease, respiratory disease, muscular disease,  
endocrine disease, renal/urologic disease, digestive system disease, congenital or acquired severe immunodeficiency.
10. Known active infection (excluding fungal infections of nail beds or caries dentium) within 4 weeks prior to baseline.
11. Evidence of chronic active hepatitis B or C.
12. History of drug or alcohol abuse within 1 year prior to baseline.

13. History of diverticulitis that, in the Investigator's opinion, may lead to increased risk of complications such as lower gastrointestinal perforation.
14. Evidence of active tuberculosis (TB; excluding patients receiving chemoprophylaxis for latent TB infection).
15. Evidence of active interstitial lung disease.
16. Receipt of any live or live attenuated vaccine within 6 weeks prior to baseline.
17. 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).
18. History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions).
19. Active suicidal ideation within 6 months prior to screening, or history of suicide attempt within 3 years prior to screening.

**Laboratory exclusion criteria (at screening):**

20. Following laboratory abnormalities at screening\*.
  - a. White blood cells (WBC)  $<3.0 \times 10^3/\mu\text{L}$
  - b. Absolute neutrophil count (ANC)  $<2.0 \times 10^3/\mu\text{L}$
  - c. Absolute lymphocyte count  $<0.5 \times 10^3/\mu\text{L}$
  - d. Platelet count  $<10 \times 10^4/\mu\text{L}$
  - 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.

See Section 4.8 for the study criteria for adolescents who may be enrolled after the end of the double-blind period.

## **4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING**

Randomization will be stratified by baseline ARR and geographical region. Patients will be randomized in a 1:1 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 will be performed in a double-blind manner. Study drugs (satralizumab and placebo) will be supplied in identical vials and will be similar in color and appearance, thereby enabling double-blind conditions.

Patients and all study site personnel will be blinded to treatment assignment until all patients have either completed the double-blind period or discontinued early from the study or as described above regarding unblinding.

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 unblinding, 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 assessor at each site to maintain the blindness of efficacy assessment – the treating Investigator responsible for the patient care and the examining assessor responsible for the administration of the EDSS/functional system score (FSS). The examining assessor must be appropriately Neurostatus 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 assessor will have access via the paper form only to the EDSS/FSS data (including the 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, other than those related to EDSS/FSS assessment, with the examining assessor in order to avoid potential unblinding of the examining assessor; the examining assessor should remind the patient of this 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 assessor will complete and sign a form which includes the kind of assessment form examining assessor 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 drug received would affect the treatment of the emergency), regulatory requirement (e.g., for SAE reporting), IDMC/IDCC or sample management at laboratory for PK and immunogenicity objectives.

The blind for each patient should 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 unblinding. All calls resulting in an unblinding event will be recorded and reported by the IxRS to the Medical Monitor. If an Investigator, site personnel performing assessments, or patient, is unblinded, 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 *OLE* period.

Serious unexpected suspected adverse reactions, which are subject to expedited reporting, should be unblinded 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 deoxyribonucleic acid (DNA) technology.
Manufacturer:	<u>Drug product in vial:</u>  Chugai Pharma Manufacturing Co., Ltd. 5-1, Ukima, 5-Chome, Kita-ku Tokyo, 115-8543, Japan  <u>Drug product in plastic prefilled syringe (PFS) with needle safety device (NSD):</u>  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 will be identical in appearance and packaging to satralizumab.

Kit identification (ID) number, 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 except Japan where Chugai, and not the contract research organization (CRO), will perform the packaging. 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 drug to a patient. 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 drug 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. 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 treatment immediately if anaphylaxis occurs. In the extension period, SC injections of satralizumab may be administered by patient or her/his caregiver at the site in Japan.

If study drug cannot be administered within the scheduled visit window and is subsequently administered outside the visit window, the next dose of study drug should be administered on schedule (minimum dosing interval should be 14 days). 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 relapse or the total number of protocol-defined relapses judged by the CEC reaches 26.

#### **4.3.2.2 Satralizumab: Extension Period**

Patients who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by CEC or who complete the double-blind period can enter the *OLE* period. In the *OLE* period, the patient will receive an SC injection of satralizumab at Weeks 0, 2 and 4, and Q4W thereafter, *with the last study drug administration on or before 31 December 2021.*

The patients who are treated with rescue therapy during the double-blind period can start administration of satralizumab once disease has stabilized after the rescue therapy for the relapse, between Day 31 to Day 60, defining the day of onset of relapse in the double-blind period as Day 1. If satralizumab cannot be administered by Day 60, the Investigator should consult with the Medical Monitor. The patients who are not treated with rescue therapy during the double-blind period can enter the extension period after 4 weeks ( $\pm$  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 11 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 the site, dispensed from the 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 electronic case report form (eCRF) as follows:

		Prior to and throughout the study	
		More than 4 weeks prior to baseline	Within 4 weeks prior to baseline until the end of study
NMO/ NMOSD treatments	Relapse prevention <sup>1)</sup>	indication, drug name <sup>2)</sup> , dose, frequency, route, first administration (date), last administration (date)/continuing at the end of the study	
	Rescue therapy <sup>1)</sup>	indication, drug name <sup>2)</sup> , route, first administration (date), last administration (date)/continuing at the end of the study	
		-	dose, frequency
	Pain	-	indication, drug name <sup>2)</sup> , route, dose, frequency, first administration (date), last administration (date)/continuing at the end of the study
Other treatments		-	indication, drug name <sup>2)</sup> , route, first administration (date), last administration (date)/continuing at the end of the study

1) For concomitant medication used more than 2 years prior to baseline, the following information is mandatory: indication, drug name, first administration (date) and last administration (date)/continuing at the end of the study. For concomitant medication used less than 2 years prior to baseline, the information listed is mandatory.

2) Trade name is preferred.

##### 4.4.1 Major Permitted Therapies for NMO

##### **Permitted Medication/Therapy During the Double-Blind Period**

###### 1. Baseline treatment

One of the drugs listed below is required as monotherapy for baseline treatment at baseline. A dose must not exceed the dose defined below and a stable dose must be maintained. Dose decrease is permitted only for safety reasons. Dose increase or change of baseline treatment is not permitted.

- Azathioprine\*: 3 mg/kg/day
- Mycophenolate mofetil\*: 3000 mg/day
- Oral corticosteroids: 15 mg/day (prednisolone equivalent)

\* Combination with oral corticosteroids (15 mg/day [prednisolone equivalent]) is permitted in patients aged 12 to 17 years at the time of informed consent.

2. Rescue therapy for clinical relapse (leads to end of the double-blind period); pulse IV corticosteroids, intravenous immunoglobulin (IVIG), and/or apheresis (including plasma exchange and plasmapheresis).

Rescue therapy should proceed at the discretion of the treating Investigator after the examining assessor has completed EDSS/FSS assessment at extra visit at relapsing (except in case of emergency when urgent treatment is required before the patient can undergo this assessment).

3. Pain medications (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).

Starting of pain medications is permitted, however the dose should be stable during the 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 (Including After Relapse in the Double-Blind Period)**

1. Baseline treatment (for patients with no relapse in the double-blind period or extension period).

One of the drugs listed below is permitted as monotherapy for baseline treatment. The dose must not exceed the dose defined below. Change or termination of baseline treatment is permitted.

- Azathioprine\*: 3 mg/kg/day
- Mycophenolate mofetil\*: 3000 mg/day
- Oral corticosteroids: 15 mg/day (prednisolone equivalent)

\* Combination with oral corticosteroids (15 mg/day [prednisolone equivalent]) is permitted in patients aged 12 to 17 years at the time of informed consent.

2. Baseline treatment (for patients who have experienced relapse in the double-blind period or extension period).

One of the following maintenance treatments is permitted. The dose must not exceed the dose defined below. Change of baseline treatment is permitted.

- Azathioprine (3 mg/kg/day) ± oral corticosteroids (1 mg/kg/day; prednisolone equivalent).

Oral corticosteroid may be tapered off according to the standard local tapering regimen at the site.

- Mycophenolate mofetil (3000 mg/day) ± oral corticosteroids (1 mg/kg/day; prednisolone equivalent).  
Oral corticosteroid may be tapered off according to the standard local tapering regimen at the site.
  - Oral corticosteroids: 1 mg/kg/day (prednisolone equivalent).  
Oral corticosteroids may be tapered to 15 mg/day or less according to the standard local tapering regimen at the site.
3. Rescue therapy for clinical relapse; pulse IV corticosteroids, IVIG, and/or apheresis (including plasma exchange and plasmapheresis).  
Rescue therapy should proceed at the discretion of the treating Investigator after the examining assessor has completed EDSS/FSS assessment at extra visit at relapsing (except in case of emergency when urgent treatment is required before the patient can undergo this assessment). Satralizumab treatment can be continued as scheduled, concurrently with rescue therapy, unless the Investigator considers it necessary to withdraw the patient.
4. Pain medication (including but not limited to pregabalin, gabapentin, carbamazepine, clonazepam, duloxetine, tramadol/acetaminophen).
5. *During the OLE period: Treatment with corticosteroids (e.g., oral, nasal) for AEs (i.e., indications other than baseline therapy or rescue therapy) is permitted; the treatment duration should be kept as short as possible.*

The rationale for the permitted baseline treatment is provided in Section 3.2.2.

#### **4.4.2 Prohibited Therapies**

1. Anti-CD20 treatment (e.g., rituximab, ocrelizumab, ofatumumab) within 6 months prior to baseline until the end of the study.
2. IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation, bone marrow transplantation prior to and throughout the study.
3. Eculizumab within 6 months prior to baseline until the end of the study.
4. Anti-B-lymphocyte stimulator (BLyS) monoclonal antibody (e.g., belimumab) within 6 months prior to baseline until the end of the study.
5. Immunosuppressants are prohibited from 8 weeks prior to baseline until the end of the study, except for azathioprine and mycophenolate mofetil.
6. Any other treatment for prevention of MS relapse (e.g., IFN, glatiramer acetate, fingolimod, natalizumab, teriflunomide, dimethyl fumarate) within 6 months prior to baseline until the end of study.

7. Anti-CD4, cladribine, mitoxantrone within 2 years prior to baseline until the end of the study.
8. Immunization with live or live attenuated vaccine within 6 weeks prior to baseline until the end of the study.
9. Treatment with any investigational agent (other than satralizumab) within 3 months prior to baseline until the end of the study.

## **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 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. The Investigator will record in the eCRF details of the patient's first documented attack of NMO/NMOSD, *including the date of NMO or NMOSD diagnosis*, and any subsequent relapse(s). 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 hepatitis B surface antigen (HBsAb) is clearly associated with vaccination against hepatitis B virus 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 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. If hepatitis B viral DNA is detectable, the patient must be excluded.

#### **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 the site according to the instruction for TB screening (see [Appendix 14](#)). The results of the screening tests will be reported on the eCRF. If the patient is positive for latent TB, then appropriate anti-mycobacterial therapy must start for the patient at least 3 weeks before initiating study drug administration in this study.

For further details on screening for TB, see [Appendix 14](#).

#### **4.5.1.5 Anti-AQP4 Antibody at Screening**

An anti-AQP4 antibody screening assessment will be conducted at screening. If the result of anti-AQP4 antibody at screening is negative in patients who must be positive for anti-AQP4 antibody at screening (see inclusion criteria 1), a blood sample collected before the screening visit can be used for the screening assessment for anti-AQP4 antibody. In that case, the blood sample should be sent to Sponsor's designee for analysis and measured.

#### **4.5.1.6 Magnetic Resonance Imaging at Screening**

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.

See the relevant manual for further details.

#### **4.5.1.7 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 drug administration. Measurement of pulse rate, temperature, SBP and DBP should take place immediately before and then at 15 ( $\pm 5$ ) and 60 ( $\pm 5$ ) minutes after study drug administration.

#### **4.5.1.8 Physical Examination**

A complete physical examination should include an evaluation of the head, neck, eyes, ears, nose and throat, and the cardiovascular, dermatological, musculoskeletal, 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.

#### **4.5.1.9 Efficacy Assessments Relapse Assessment**

Relapse assessment is detailed in Section [4.5.3](#).

#### **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.

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

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 an 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 scale 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 20-foot wall chart. The test will be performed monocularly and patients may use their habitual distance glasses or contact lenses.

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

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

### **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, Reever & Bach-Peterson, 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 member or relative) (when there is one), if the Investigator considers the caregiver to be reliable in reporting 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 the 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 patient health state looking at five specific dimensions such as mobility, self-care, usual activity, pain/discomfort and anxiety/depression and score their general health state.

A reference to the EQ-5D questionnaire is included in [Appendix 8](#).

#### **4.5.1.10 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" will be collected at baseline and the "C-SSRS since last visit" will be collected at subsequent visits.

If a patient has already received study drug before C-SSRS becomes available for this study, the patient should be assessed by the "C-SSRS already enrolled subjects" at the first visit after C-SSRS becomes available for this study, 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), [Appendix 11](#) (C-SSRS since last visit) and [Appendix 12](#) (C-SSRS already enrolled subjects).



#### 4.5.1.11 Laboratory Assessments

Samples for the following laboratory tests (except urinalysis and pregnancy tests) will be sent to the Central Laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. *If a patient cannot visit the study site in 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, 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 drug (except Week 2 of double-blind and extension period). For patients aged 12 to 17 at the time of informed consent, urine  $\beta$ -hCG will be recommended during the study except screening in order to reduce the blood volume taken (see [Appendix 13](#)). 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 postmenopausal status) will not require further pregnancy testing.* In order to qualify for and to remain in the study, the patient must have a negative pregnancy test, evidence of surgical sterility or evidence of post-menopausal status. Postmenopausal status is defined as any of the following: natural menopause with menses >1 year ago; radiation-induced with last menses >1 year ago, or *bilateral oophorectomy*.

- Complement tests (C3, C4 and CH50)
- Plasmablasts (blood sample will be collected in United Kingdom, France, Germany, Japan and Taiwan), hsCRP

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

- Pharmacokinetic / Pharmacodynamic assessments
  - Serum satralizumab concentration, IL-6, sIL-6R, anti-AQP4 antibody
- *Immunogenicity* assessments
  - ADA
- 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) <sup>[1]</sup>
Screening	28
<i>Double-blind period</i>	
Week 0	46
Week 2	34.5
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	24.5 <sup>[2]</sup>
Week 36	27.5
At extra visit on relapse	44
Follow-up assessment for adolescents	5.0
<i>Extension period</i>	
Weeks 0, 24, 48	32.5
Week 2	16
Weeks 4, 8, 16, 20, 28, 32, 40, 44	24.5
Every 12 weeks after Week 48	19
Weeks 12, 36 & Every 24 weeks after Week 48	27.5
Dose outside the visit window	3.5
At extra visit on relapse	29.5
Last observation visit and withdrawal visit	27.5
Follow-up assessment for adolescents	5.0

[1] The sample for CCSR project is included. The local laboratory samples (blood TB test and serum pregnancy test) are not included.

[2] 27.5 mL every 12 weeks after Week 48

Assessment of hsCRP, PK, IL-6, sIL-6R, ADA, anti-AQP4Ab (except screening), plasmablasts and complement (C3, C4, and CH50) will be performed in a blinded manner and results will not be available to site, PAREXEL and Sponsor until database lock for analysis of the double-blind period.

For patients aged 12 to 17 at the time of informed consent, please refer to [Appendix 13](#) for blood sample collecting (European Union, 2008).

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

#### **4.5.1.12 Electrocardiograms**

Electrocardiograms should be performed prior to any blood draws. To minimize variability, it is important that patients be in a resting position for  $\geq 10$  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 patients who consent to additional PK testing (see [Appendix 1](#)), triplicate digital ECG recordings will be obtained with approximately 2 to 5 minutes interval 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 QTc).

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 (see [Appendix 1](#)), 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.

#### **4.5.1.13 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 Day 1, unless otherwise specified. All screening evaluations must be completed and reviewed to confirm that patient meets all eligibility criteria before randomization (For

adolescents who may be enrolled after the end of the double-blind period, see Section 4.8). 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 (i.e., retest).

If a patient has not met all inclusion/exclusion criteria within 28 days of the original screening visit, rescreening (which refers to repeating the 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-AQP4Ab 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 re-screened 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 drug administration should be performed prior to administration of study drug, unless otherwise noted in the schedule of assessments.

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

If a patient misses a scheduled visit without notice, the Investigator and/or site staff should try to contact the patient via telephone or another way in order to confirm if there has been an AE or relapse.

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

*Following the implementation of Protocol Version 11, 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 (WD) Visit is for patients who withdraw from the study. Every effort should be made to conduct the visit at 12 weeks ( $\pm 7$  days) after the last dosing. Patients aged 12 to 17 years at the time of informed consent who withdraw from the study will attend the WD visit at 12 weeks ( $\pm 7$  days) after last dosing for follow-up assessments for adolescents (see Section 4.5.2.5). At the WD Visit of double-blind period, a complete set of the assessments performed every 24 weeks after Week 48 of double-blind period are to be performed (plus a chest X-ray). At the WD Visit of extension period, a complete set of the assessments performed every 24 weeks from Week 0 to Week 48 of extension period are to be performed (including a chest X-ray) with the exception of the anti-AQP4Ab assay.

Patients who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by CEC or who complete the double-blind period can enter the OLE period. Patients completing the OLE 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 OLE period. At this visit, a complete set of the assessments performed at Week 0 of extension period are to be performed (including a chest X-ray) with the exception of the anti-AQP4Ab 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 WD 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 Safety 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 for 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 safety follow-up assessments.

#### **4.5.2.5 Follow-Up Assessments for Adolescents**

Follow-Up Assessment for Adolescents is for patients aged 12 to 17 years at the time of informed consent who withdraw from the study or complete the OLE period, and will be conducted at 12 (WD visit for patient withdrawn), 24 and 48 weeks ( $\pm 7$  days) after the last dose of study drug. *Patients aged 18 years or older at the time they complete or discontinue from the OLE period and patients that complete the OLE with the last study drug administration on or before 31 December 2021 or patients that decide to continue treatment with satralizumab outside of this study will not have to complete the Follow-Up Assessments for Adolescents.*

If the patients withdraw from the study in the double-blind period due to a clinical relapse, both Safety Follow-Up and Follow-Up Assessments for Adolescents will be conducted.

Please see [Appendix 1](#) for the schedule of follow-up assessments for adolescents.

#### **4.5.2.6 Assessments at Extra Visits due to Relapse**

If patients develop new or worsening neurological symptoms during the double-blind period and extension period, they will attend for an extra visit within the reasonable shortest timeframe to have a relapse assessment at the investigational site (see Section 4.5.3). Please see [Appendix 1](#) for assessments that are required to be performed in case of such extra visits.

#### **4.5.2.7 Unscheduled Visits**

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

### **4.5.3 Relapse Assessment**

Patients should report all new or worsening neurological events compatible with NMO representing a clinical relapse immediately to the sites and a visit for relapse assessment should be scheduled as soon as possible. Patients who attend the study center for a protocol-specified study visit that includes an EDSS/FSS assessment (see [Appendix 1](#)) should be assessed to determine whether a clinical relapse has occurred or not. A clinical relapse should be confirmed whether it meets the criteria for protocol-defined relapse (Please see Section [4.5.3.4](#)). An EDSS/FSS assessment should be performed by the examining assessor in every case of potential relapse. The Relapse Assessment Form and EDSS/FSS scoring sheets and necessary data (if any) for all potential relapses during the double-blind period should be sent immediately to PAREXEL for submission to the CEC for adjudication.

#### **4.5.3.1 Relapse Assessment Structure**

There will be a treating Investigator and an examining assessor at each site to keep the blindness of the relapse assessment – the treating Investigator is responsible for the patient care and the examining assessor is responsible for the administration of the EDSS/FSS. The examining assessor must be appropriately Neurostatus 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 assessor will have access via the paper form only to the EDSS/FSS data (including the 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/FSS assessment should always be performed by the same assessor 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 assessor must perform the EDSS/FSS assessment within seven days after the patient reports the symptoms of potential relapse 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 related to the EDSS/FSS assessment, with the examining assessor; the examining assessor should remind the patient of this at the start of the examination.

#### **4.5.3.2 Procedure for Detection of Potential Relapse**

During the screening period, patients will be trained on the possible symptoms and signs of a potential relapse of NMO/NMOSD. Patients will be instructed to remember accurately the time and nature of every symptom of a possible relapse and to contact



the study site immediately if they have such symptoms. The site staff will also be trained on signs and symptoms that may be indicative of a potential relapse.

During the double-blind period, the site staff should remind the patient of the possible symptoms of potential relapse at every visit, and contact the patient by phone calls between the scheduled site visits (recommended 2 weeks after previous scheduled visit), not to miss potential relapse. The record of the phone call should be recorded on the source document.

All patients with new neurological symptoms suggestive of a relapse should have the EDSS/FSS performed. The results should be recorded on a Relapse Assessment Form as well as on an EDSS/FSS scoring sheet (to be entered into the eCRF). The Relapse Assessment Form will include the date and time of symptom onset, the nature of symptoms and the treating Investigator's judgment as to whether a protocol defined relapse has occurred or not. These records should be completed regardless of the time from the report of symptom. These records and necessary data (if any) will be sent to PAREXEL for CEC review.

Potential relapses will be detected by the following cases:

**1. Potential relapse reported by the patient**

If a patient becomes aware of signs or symptoms which might indicate a relapse, the patient will contact the site immediately and return to the site for an extra visit as soon as possible with a target date set for no more than 3 days after reporting the symptoms to the site. The examining assessor must perform the 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.

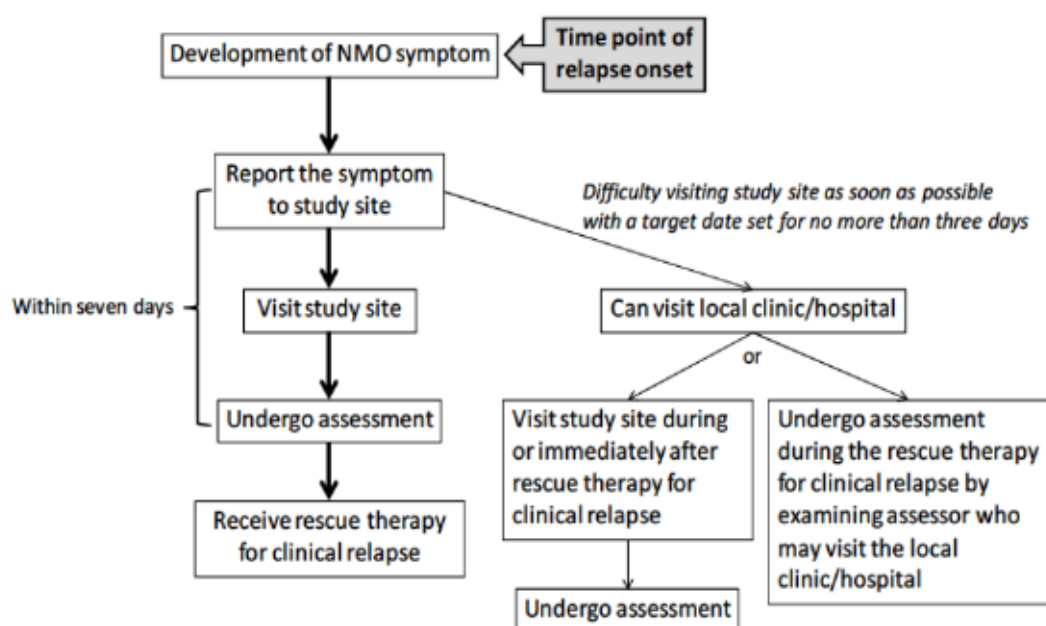
If a patient has difficulty visiting the study site within three days due to severity of the relapse, the patient can visit a local clinic/hospital for immediate management of a relapse, and then visit the study site as soon as possible (which may be during or immediately after rescue therapy for clinical relapse). Alternatively, the examining assessor may visit the local clinic/hospital to conduct the EDSS/FSS assessment during rescue therapy for a clinical relapse. Even in this case, the examining assessor must perform the EDSS/FSS assessment within seven days after the patient reports the symptoms to the site.

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.

The assessment of a relapse is summarized in [Figure 2](#).

**Figure 2 Assessment of a Relapse**



The sequence of procedures of the extra visit at relapsing should be as follows:

- a. The assessment at the extra visit at relapsing, which is listed in [Appendix 1](#), is performed, where the EDSS/FSS is assessed by examining assessor.
  - i. If the symptom is of a clinical relapse as judged by Investigator, study drug should not be administered until the patient enters extension period.
- b. The symptom is confirmed whether it meets the criteria for a protocol-defined relapse.
- c. The Relapse Assessment Form will be completed and sent to the CEC (Please see [Section 4.5.3.3](#)).
- d. Rescue therapy should proceed at the discretion of the treating Investigator (the sequence may be different in case of an emergency).

## **2. Potential relapse comes from the EDSS/FSS assessment**

If there is an EDSS/FSS change shown in Section 4.5.3.4 at an EDSS/FSS assessment visit (e.g., Week 24), the Relapse Assessment Form will be completed and sent to the CEC (please see Section 4.5.3.3).

### **4.5.3.3 Reporting a Potential Relapse to the CEC**

The Relapse Assessment Form will be sent (e.g., by fax, e-mail) immediately, together with the EDSS/FSS scoring sheets for the current visit, the most recent EDSS/FSS assessment visit, and necessary data (if any) to PAREXEL. This should be done regardless of the assessment of the site staff about whether the potential relapse meets protocol-defined relapse and regardless of the time when the EDSS/FSS assessment was performed.

During the double-blind period, the form and the data will be reviewed by the CEC. The CEC will review according to the CEC charter, and will be able to request additional information to assist in the determination of a relapse if necessary.

If the CEC considers that the protocol-defined relapse has been met, the patient should be withdrawn from the double-blind period and can enter the extension period even if Investigator considers that no protocol-defined relapse has occurred.

Details regarding the CEC responsibilities and the process of adjudication are described in the Section 3.1.4 and CEC charter.

### **4.5.3.4 Protocol-defined 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 either of following:

1. 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)
2. An increase of at least 2.0 points on one of the appropriate FSS
3. An increase of at least 1.0 point on two or more of the appropriate FSS if the baseline score was one or more

4. 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 at 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.

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 used for primary analysis. Any potential relapses not evaluated within the seven days will be censored from the primary analysis (see Section 6.5.1).

#### **4.6 CHUGAI CLINICAL SAMPLE REPOSITORY**

The collection of samples for the CCSR is an optional component of this Study BN40898 (also known as SA-307JG).

The patients will be given the option to participate in CCSR project.

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 the purpose of retrospective CCSR research analysis to understand inter-individual variability in satralizumab efficacy, safety and PK as will be explained in the ICF. The ICF for the 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 the optional specimen; if the participant declines, he/she will check a "no" box in the appropriate section and will not provide 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 ICF. 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 for 30 to 60 minutes after blood collection and then be centrifuged for 10 minutes 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 minutes 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, a "Biomarker Research Analysis Protocol" will also be prepared before the research will be performed.

The samples and results of anti-AQP4Ab 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 ID number at the study 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 study 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 drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason.

Reasons for discontinuation of study drug 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.

#### **4.7.1.1 Discontinuation from Study Drug**

In addition to the criteria listed above, reasons for withdrawal of the study drug 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 *OLE* period with a more severe intensity compared with the last relapse prior to baseline.

The 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 drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug 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 discontinue a site at any time. Reasons for discontinuing 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.

#### **4.8 ADOLESCENTS**

Adolescents (i.e., patients from 12 to 17 years old with NMO/NMOSD) will be randomized into the double-blind period of the study as well as adults. Recruitment of adolescents into the double-blind period of the study will be according to Section 3.1.2. After the total number of protocol-defined relapses judged by the CEC reaches 26, the recruitment period for the adolescents may be continued in the extension period until a minimum of 8 adolescents are enrolled into the study.

The overall study objectives remain the same and include adolescents enrolled into the double-blind period of the study. The objective and endpoints for adolescents are as follows:

##### **Specific Objective for the Group of Adolescents**

The objective for adolescents who are enrolled into this study (double-blind period or extension period) is as follows:

- To evaluate the safety, tolerability, efficacy, PK, PD and immunogenicity of satralizumab in adolescents.

## **Specific Outcome Measures (Endpoints) for the Group of Adolescents**

### **Primary Outcome Measures (Endpoints)**

- Safety assessments
  - Incidence and severity of AEs, AESIs, SAE and selected AEs
  - Vital signs (temperature, systolic and diastolic blood pressure and pulse rate), physical examinations, clinical laboratory tests (hematology, chemistry and urinalysis), 12 lead ECGs, suicidality (C-SSRS)
- PK, PD and immunogenicity

### **Secondary Outcome Measures (Endpoints)**

- TFR
- ARR
- Change in EDSS score
- Change in visual acuity (Snellen chart)
- Change in SF-36 score
- Change in VAS score for pain
- Change in FACIT Fatigue score
- Change in EQ-5D score
- Change in mRS score
- Change in ZBI score

The inclusion criteria and exclusion criteria for adolescents who will be enrolled into the double-blind period are shown in Section 4.1. For adolescents who may be enrolled after the end of the double-blind period, the inclusion criterion 2 and the annotation “\*” in the exclusion criterion 20 are as follows (other criteria are same). Baseline of the extension period will occur after the screening period. 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 the first study drug administration.

### **Inclusion Criterion 2**

Clinical evidence of at least 2 documented relapses (including first attack) prior to screening.

## **The annotation “\*” in the exclusion criterion 20**

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

## **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 identified and 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 ECG), a special focus will be placed on the above risks.

- An IDMC will periodically evaluate the safety of patients every six months *during the double-blind period of the study*.
- Dear Doctor Letters should be provided to the patient about the study and the investigational drug. Patients should be instructed to inform about this study and the investigational drug to healthcare professionals in case they 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 1 multiple dose study of satralizumab in patients with RA (SA-105JP), one case of serious infection, bronchopneumonia (1 of 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 *severe*.

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 infection) 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.

For patients with NMO participating in this protocol, therapies used to treat NMO (corticosteroids, azathioprine, mycophenolate mofetil) have been shown to be associated with infections, particularly serious infections.

#### **5.1.1.2 Neutropenia and Potential Risk of Infection**

Reversible neutropenia was reported in 1 of 33 patients with RA in Phase 1 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.*

Neutropenia has been observed during administration of tocilizumab. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

Patients with a low neutrophil count  $<2 \times 10^3/\mu\text{L}$  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 (/μL)	Action
>1,000	Maintain dose
500 – 1,000	<ul style="list-style-type: none"> <li>• If neutropenia persists, satralizumab should be interrupted until ANC is above 1,000/μL.</li> <li>• If ANC was under 1,000/μL at the previous laboratory test, ANC must be checked before treatment with the satralizumab (e.g., ANC test at site).</li> </ul>
<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 was observed in Phase 1 multiple-dose study with RA (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  $10 \times 10^4/\mu\text{L}$  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 platelet counts are shown in [Table 3](#).

**Table 3: Thrombocytopenia Risk Mitigation**

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

#### 5.1.1.4 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 interruptions based on transaminases are shown in [Table 4](#).

**Table 4: Hepatic Enzyme Risk Mitigation**

AST or ALT values	Action
$>1$ to $3x$ ULN*	<ul style="list-style-type: none"><li>Reduction (if necessary, interruption) of hepatotoxic drugs could be considered.</li><li>For persistent increases in this range, satralizumab could be interrupted until AST and ALT is below ULN*.</li></ul>
$>3$ 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: <ul style="list-style-type: none"><li>Total bilirubin <math>&gt;2x</math> ULN and/or</li><li>INR <math>&gt;1.5x</math> ULN and/or</li><li>Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia</li></ul>

AST or ALT values	Action
>5x ULN	<p>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.</p> <p>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.</p>

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

Slight increases in lipid levels (3 AEs of hyperlipidaemia [mild]) were observed in 3 out of 33 patients in Phase 1 multiple dose study (SA-105JP), *while 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 or other 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 patients who received satralizumab. Most of ADAs were characterized as neutralizing antibody. In a Phase 1 multiple dose study of satralizumab (SA-105JP) in patients with RA, 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 are not limited to, blood pressure decrease, dyspnea, loss of consciousness, dizziness, queasiness, vomiting, itchiness, flushing, etc. A decision to continue/discontinue treatment with satralizumab should be made taking into account the risks and benefits if any of these events are observed.

- *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 drug 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 RA 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 *that* 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**

Gastrointestinal perforations have not been reported in clinical trials with satralizumab treatment.

*To date*, 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*, a history of active diverticulitis may preclude patient from participation.

- Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated (X-ray, computerized tomography [CT] scan, etc.) promptly for early identification of gastrointestinal perforation and appropriate measures taken.
- Patients should be made aware of the symptomatology potentially indicative of complicated diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise.
- In patients who receive corticosteroids and/or non-steroidal anti-inflammatory drugs, prophylactic treatment with proton pump inhibitors or H2 blocker should be considered.

#### **5.1.1.10 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 MS 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.

#### **5.1.1.12 Concomitant Medications**

Patients should also be informed of the risks associated with taking corticosteroids, azathioprine or mycophenolate mofetil. Below are listed specific major risks that patients need to be aware of:

- Corticosteroids can cause immunosuppression, hypertension, diabetes mellitus, cataracts, glaucoma, bruising, thinning of the skin, weight gain, psychological changes, osteoporosis, accelerated atherosclerosis, increased risk of gastrointestinal bleeding, aseptic necrosis of bone and adrenal insufficiency. Although rare, steroid-induced hypersensitivity reactions do occur. They range from minor rashes to the more serious cardiovascular collapse. For additional safety data, refer to the local prescribing information.
- No evidence available at the time of approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigator's Brochure.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs, AESIs and selected AEs; 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 drug or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study drug (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 drug
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The exception to this definition of an SAE is in the rare event that a patient is hospitalized following an NMO relapse, as long as the reason for hospitalization is to receive standard treatment with rescue therapy for clinical relapse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe] criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

### **5.2.3 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 AEs of Special Interest 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 drug.

### **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, or 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 drug injection except where the event is not considered an allergic reaction)<sup>†</sup>

\* Selected AEs will be reviewed by Sponsor and Medical Monitor to identify infections requiring IV treatment and opportunistic infections that require treatments. AE listings will also be searched to identify any infections requiring IV treatment/opportunistic infections which have not been reported as Selected AEs.

† Each IRR will be reviewed by the Medical Monitor to assess the risk of anaphylaxis.

### **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 drug, 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 and not on the Adverse Event eCRF.

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported on the eCRF until the Withdrawal Visit or Last Observation (12 weeks after the last dose of study drug). 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 drug (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 at all patient evaluation time points. Examples of non-directive questions include the following:

“How have you felt since your last clinic visit?”

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

### 5.3.3 Assessment of Severity of Adverse Events

Table 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 drug, indicating "yes" or "no" accordingly on the AE page of the eCRF. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

### **5.3.5 Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event 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 drug injection. An IRR should be recorded on the IRR page of the eCRF as "injection-related reaction", and individual signs and symptoms should also be captured on the IRR page of the eCRF.

But exceptive conditions are as follows:

- Anaphylaxis or anaphylactic shock:  
If the event is judged as anaphylaxis or anaphylactic shock by Investigator's discretion, it will be recorded on the Adverse Event page of the eCRF.
- Obviously not allergic reaction (e.g., infection):  
If the event is judged as not allergic reaction, it will be recorded on the Adverse Event page of the eCRF.

##### *Other Adverse Events*

For AEs other than IRRs, 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 time points 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 drug (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- 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 drug (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 drug-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 drug, 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 drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
- The patient has not suffered an AE.

#### **5.3.5.11 Overdoses**

Study drug 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 drug is not an AE unless it results in untoward medical effects.

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

All AEs associated with an overdose or incorrect administration of study drug 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 drug:

- SAEs
- 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 phone 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 PAREXEL International Pharmacovigilance 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 drug. A paper pregnancy report form should be completed within 24 hours and submitted via fax to PAREXEL International Pharmacovigilance, 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 drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. *Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the Investigator will 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 International Pharmacovigilance 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 drug. A paper pregnancy report form should be completed within 24 hours of learning of the pregnancy and submitted via fax to PAREXEL International Pharmacovigilance, 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 PAREXEL International Pharmacovigilance 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 drug. The pregnant partner will need to sign an 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 patient or female partner of a male patient exposed to study drug 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.

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 drug 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 drug 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 Visit if the event is believed to be related to prior study drug 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 SAE form.

## **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 double-blind

period in the study. Patients will be analyzed as randomized for analysis purposes in the ITT.

The Per-Protocol Set (PPS) will include all patients in the ITT population who received at least 3 doses of study drug, 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 drug 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 drug. 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 (ADA) will include all patients in the SAF with at least 1 valid post-dose concentration result with a dosing record and sampling time. Pharmacodynamics variables (IL-6, sIL-6R, hsCRP, anti-AQP4Ab, plasmablast) will be analyzed using the SAF population.

### **6.1.5 Analysis population for adolescents**

The adolescent population will be defined as all adolescent patients who have received at least one dose of study drug.

## **6.2 DETERMINATION OF SAMPLE SIZE**

Approximately 70 patients need to be recruited and randomized in a 1:1 ratio to the two treatment groups (satralizumab and placebo). The sample size considerations are based on the following assumptions:

1. A two-sided log-rank test
2. 80% power at the 5% significance level
3. A 66.5% reduction in the risk of relapse, i.e., the TFR hazard ratio of satralizumab over placebo is 0.335
4. TFR in the placebo arm following an exponential distribution, with hazard rate  $h(t)=0.4184$
5. A 2-year dropout rate of 10%

Based on these assumptions, 26 TFR events are needed for the primary analysis. TFR events are defined as protocol-defined relapses confirmed by the CEC with EDSS/FSS assessment performed by the examining assessor within 7 days after relapse symptoms were reported to site by the patient. The maximum accrual rate is estimated to be approximately 8 patients per month, after the first patient in (FPI) plus 8 months of ramp up. The 70 patients enrolled over one year and followed for an additional one and a half years will provide 26 TFR events. The primary analysis will be performed once 26 TFR events have been observed. 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  $\sqrt{2}$ . 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 0.753 (Cossburn et al. 2012) and patients entering this study have an ARR  $\geq 1$  owing to inclusion criterion 2, we calculate the zero-truncated mean of the Gamma-Poisson distribution with the mean of 0.75 and the mean and variance ratio of  $\sqrt{2}$ , then the baseline ARR is estimated at 1.6. The two Phase 3 MS trials above reported that pre- and post-baseline ARR in the placebo group were 1.4 and 0.4, so the post-baseline ARR in placebo group in this trial is estimated at 0.5.

Using the proportion of zero under supposed ARR distribution, we estimate the relapse-free rate at a year in placebo group at 65.8%. The relapse-free rate is assumed to follow the exponential distribution with a constant hazard, and then we set the hazard ratio of 0.4184 in placebo group.

According to tocilizumab case reports 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. Moreover, the azathioprine's data showed the pre- and post- baseline mean ARR ratio was 0.33 ( $=0.77/2.32$ , the mean ARR were estimated from the median ARR and the distribution supposition above) and the rituximab data showed the pre- and post-baseline mean ARR ratio was 0.125 ( $=0.3/2.4$ ), then we estimate the rituximab mean ARR ratio compared with azathioprine at 0.38 ( $=0.125/0.33$ ).

Under the assumption of ARR and relapse-free rate distribution above, the mean ARR ratio is coincided with the hazard ratio. Tocilizumab hazard ratio data (0.25) could have a possibility of overestimation because of the case report with only three patients and the hazard ratio between rituximab and azathioprine (0.38) is the comparison with an active control, then we consider the satralizumab hazard ratio compared to placebo should exist between 0.25 and 0.38. So we have set the satralizumab hazard ratio compared with placebo at 0.335.

### **6.3 SUMMARIES 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 SUMMARIES OF TREATMENT GROUP COMPARABILITY**

Demographics (age, sex and race/ethnicity) and baseline characteristics (hepatitis status, baseline ARR and number of previous episodes within 2 years before enrollment) of patents will be collected at screening or baseline visit before administration of first dose of study drug.

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 protocol-defined relapses confirmed by the CEC with EDSS/FSS assessment performed by the examining assessor within 7 days after relapse symptoms were reported to site by the patient. TFR is defined as the time from the date of the randomization until the first occurrence of relapse throughout the double-blind period. The time point of relapse onset is defined as the time at which the patient experiences any new or worsening neurological NMO representing clinical relapse(s). Events which are judged by the CEC to meet the protocol-defined relapse will be included in the primary analysis of the primary endpoint if EDSS/FSS is assessed by the examining assessor within seven days after

the patient reports the symptoms to the site. For patients who have not relapsed, not switched baseline treatment or not increased baseline treatment at the time of analysis, the TFR will be censored on the date when total number of protocol-defined relapses judged by CEC reaches 26. For patients who have switched baseline treatment or increased baseline treatment, the TFR will be censored on the date of switching or increasing the baseline treatment. For patients who have received rescue therapy without experiencing a protocol-defined relapse for which the EDSS/FSS assessment was not performed within seven days after the patient reports the symptoms to the site, the TFR will be censored on the date of receiving rescue therapy.

The primary analysis of the study is to test the equality of the TFR distribution in the satralizumab (SA237) +baseline treatment (satralizumab [SA237]) and Placebo +baseline treatment (placebo) arms:

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

A stratified two-sided log-rank test using strata of baseline ARR (one vs. more than one) and geographical region will be used.

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

## **6.5.2 Secondary Efficacy Endpoints**

### **Key Secondary Efficacy Endpoints**

The key secondary efficacy endpoints are change in VAS for pain and change in the 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, baseline ARR and geographical region, as well as the continuous covariates of baseline VAS for pain score.

### **Change in FACIT Fatigue Score**

FACIT fatigue scale includes 13 statements, which measures 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, baseline ARR and geographical region, 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<sup>5</sup>) distinct health states. These states may then be converted into a single index value by using the time trade-off (TTO) based tariff methods. The best possible answer would be (1,1,1,1,1) and the worst possible answer would be (3,3,3,3,3). A shift table will be used to evaluate the number and percentage of patients having a different post-baseline status when compared to their baseline status. The mean change in EQ-5D score 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 should be 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**

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 *the two* treatment arms, negative binomial regression model will be used with ARR as response variable *and* treatment group, baseline ARR and geographical region 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 symptoms 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, baseline ARR and geographical region 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.

### **Analysis of Secondary Endpoints**

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, mRS, ZBI and EQ-5D scores, as well as visual function testing. 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, generalized estimating equation or generalized linear mixed-effect model analysis will be used. The assessment will be performed prior to unblinding 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, baseline ARR and geographical region 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 the following populations will be analyzed for TFR:

- Patients with clinical relapse
- Patients with treated clinical relapse
- Patients with treated clinical relapse: Optic Neuritis
- Patients with protocol-defined relapse based on CEC adjudication (regardless of assessment limit of seven days)
- Patients with protocol-defined relapse based on EDSS/FSS increase relative to baseline

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 for TFR will be presented by AQP4Ab status at screening (positive/negative) in NMO and NMO/NMOSD. In case that satralizumab does not show the effectiveness in NMO patients with AQP4Ab negative at all, companion diagnostics co-development will be considered by using this data. The subgroup analysis for adolescent will also be conducted.

Further details will be described in the SAP.

### Adolescents:

Summary statistics will be provided for efficacy outcome measures. Outcome measures will be reported for all adolescents who are enrolled into this study, as well as for all adolescents who are randomized into the double-blind period. Separate listings for adolescents who are enrolled into the extension period will be provided, as appropriate.

## **6.6 SAFETY ANALYSES**

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

Summary tables for number and percentage of patients with adverse drug reactions (i.e., AEs related to study drug) will be tabulated.

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

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

Laboratory values (including hematology, blood chemistry, and urinalysis), frequencies of laboratory abnormalities, vital signs (temperature, 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.

### Adolescents:

Safety outcome measures will be summarized. Summaries will be reported for all adolescents who are enrolled into this study, as well as for all adolescents who are randomized into the double-blind period. Separate listings for adolescents who are enrolled into the extension period will be provided, as appropriate.

## **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-AQP4Ab 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 PD (CRP, IL-6, sIL-6R, plasmablasts and anti-AQP4Ab) 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 and SA-105JP 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 ( $C_{\text{trough}}$ )] will be computed.

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

### Adolescents:

PK/PD outcome measures will be summarized. Summaries will be reported for all adolescents who are enrolled into this study, as well as for all adolescents who are randomized into the double-blind period. Separate listings for adolescents who are enrolled into the extension period will be provided, as appropriate.

## **6.8 IMMUNOGENICITY**

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

### Adolescents:

Immunogenicity outcome measures will be summarized. Summaries will be reported for all adolescents who are enrolled into this study, as well as for all adolescents who are randomized into the double-blind period. Separate listings for adolescents who are enrolled into the extension period will be provided, as appropriate.

## **6.9 HANDLING MISSING DATA**

For TFR, patients who have not relapsed, not switched baseline treatment or not increased baseline treatment dose at the time of analysis, the TFR will be censored on the date when total number of protocol-defined relapses judged by CEC reaches 26. For patients who have switched baseline treatment or increased baseline treatment dose, the TFR will be censored on the date of switching the baseline treatment or increasing the baseline treatment dose. For patients who have received rescue therapy without experiencing a protocol-defined relapse for which the EDSS/FSS assessment was not performed within seven days after the patient reports the symptoms to the site, the TFR will be censored on the date of receiving rescue therapy.

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 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 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 Good Clinical Practice 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, informed assent form for minors and consent form for the patient's legally authorized representative, ICF 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 in 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 US, each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act 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 INDEPENDENT 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/IEC. Investigators are also responsible for promptly informing the IRB/IEC 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 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 Food and Drug Administration 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 regulatory 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 drug inventory, management and to randomize patients to study drug. 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).

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## Appendix 1 Schedule of Assessments

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

	Screening	Double-blind period															
Week	-4 to -1	0 (BL)	2	4	5 <sup>d)</sup>	6 <sup>d)</sup>	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 drug injection (SC)		X	X	X			X	X	X	X	X	X	X	X	X	X	X
Informed consent	X <sup>u)</sup>																
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 <sup>i)</sup>	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X
ECG <sup>n)</sup>	X	X <sup>l)</sup>			X <sup>l)</sup>	X <sup>l)</sup>					X <sup>l)</sup>						X <sup>l)</sup>
TB screening <sup>k)</sup>	X																
Chest X-ray	X																
Pregnancy test <sup>g)</sup>	X	X		X			X	X	X	X	X	X	X	X	X	X	X
Laboratory test <sup>a)</sup>	X <sup>i)</sup>	X	X	X			X	X	X	X	X	X	X	X	X	X	X
Hepatitis test <sup>b)</sup>	X																
Hepatitis B viral DNA	X <sup>q)</sup>							X <sup>r)</sup>			X <sup>r)</sup>			X <sup>r)</sup>			X <sup>r)</sup>
C-SSRS		X	X	X			X	X	X	X	X	X	X	X	X	X	X
Phone call		Between the scheduled visits (recommended 2 weeks after previous scheduled visit)															
<b>Safety</b>																	
Adverse events		Monitor and record throughout the study															
Concomitant medications		Monitor and record throughout the study															
<b>Efficacy</b>																	

Appendix 1: Schedule of Activities (cont.)

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

	Screening	Double-blind period															
Week	-4 to -1	0 (BL)	2	4	5 <sup>d)</sup>	6 <sup>d)</sup>	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
Relapse assessment		Monitor and record throughout the study															
EDSS/FSS, visual function testing <sup>m)</sup> , SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D	X <sup>e)</sup>	X									X						X
ZBI <sup>p)</sup>		X									X <sup>o)</sup>						X <sup>o)</sup>
MRI	X <sup>h)</sup>																
<b>PK-PD</b>																	
PK sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD sample <sup>c)</sup>		X	X	X			X	X	X	X	X	X	X	X	X	X	X
Plasmablasts <sup>f, t)</sup>		X	X	X			X	X			X						X
Anti-AQP4 antibody <sup>s)</sup>	X	X <sup>t)</sup>	X <sup>t)</sup>	X <sup>t)</sup>			X <sup>t)</sup>	X <sup>t)</sup>			X <sup>t)</sup>						X <sup>t)</sup>
<b>Immunogenicity</b>																	
Anti-drug antibody		X		X			X	X	X	X	X	X	X	X	X	X	X
<b>CCSR<sup>d, t)</sup></b>																	
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.

## Appendix 1: Schedule of Activities (cont.)

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

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- e) Only EDSS is conducted.
- f) Blood sample for plasmablasts will be collected in United Kingdom, France, Germany, Japan and Taiwan.
- g) For females of child-bearing potential. Serum  $\beta$ -hCG must be performed at screening. During the study, serum or urine [sensitivity of at least 25 mIU/mL]  $\beta$ -hCG will be performed. For patients aged 12 to 17 at the time of informed consent, urine  $\beta$ -hCG will be recommended (see [Appendix 13](#)).
- h) Patients who are classified as PML or MS must be excluded. If PML cannot be ruled out, JC virus in the cerebrospinal fluid (CSF) will be measured.
- i) WBC, ANC, ALC, PLT, AST, ALT.
- j) Body temperature, systolic and diastolic blood pressure and pulse rate are measured just before dosing and 15 min ( $\pm 5$  min) and 60 min ( $\pm 5$  min) after dosing in case of study drug injection visit.
- k) TB test (e.g., tuberculin test and/or Quantiferon<sup>®</sup> test) should be conducted according as local guidance.
- l) The copies of ECG chart should be collected for only patients who obtained informed consent to additional PK sampling.
- m) Visual function testing is not required if it is implemented with FSS assessment.
- n) ECG should be performed prior to blood draws.
- o) Window in days is within  $\pm 28$  days.
- p) ZBI is optional and will be performed 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) For patients aged 12 to 17 at the time of informed consent, the guidance provided in [Appendix 13](#) should be considered.
- u) 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). If first screening assessment is not performed within 3 months from the day informed consent is obtained, re-consent is needed prior to all screening assessment.



Appendix 1: Schedule of Activities (cont.)

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

Week	Double-blind period				WD <sup>g)</sup>	SFU <sup>f)</sup>	FUAA <sup>r)</sup>
	After Week 48		Extra visit at relapsing	DOW <sup>q)</sup>			
	Every 4 weeks	Every 24 weeks					
Window in days	±7	±7	-	-	-	-	±7
Study drug injection (SC)	X	X		X			
Body weight		X			X		
Physical examination	X	X	X	X	X		
Vital signs <sup>m)</sup>	X	X	X	X	X		
ECG <sup>l)</sup>		X			X		
Chest X-ray					X		
Pregnancy test <sup>e)</sup>	X	X			X		
Laboratory test <sup>a)</sup>	X	X	X		X		
Hepatitis B viral DNA <sup>n)</sup>	X <sup>o)</sup>	X			X		
C-SSRS	X	X		X	X		
Phone call	Between the scheduled visits (recommended 2 weeks after previous scheduled visit)					X	
<b>Safety</b>							
Adverse events	Monitor and record throughout the study		X	X	X		X
Concomitant medications	Monitor and record throughout the study		X	X	X	X <sup>k)</sup>	
<b>Efficacy</b>							
Relapse assessment	Monitor and record throughout the study		X	X	X	X	
EDSS/FSS		X	X		X		
Visual function testing <sup>i)</sup> , SF-36, VAS for pain, FACIT-fatigue, mRS, EQ-5D		X			X		
ZBI <sup>h, l)</sup>		X			X		
<b>PK-PD</b>							
PK sample	X	X	X	X	X		
PD sample <sup>b)</sup>	X	X	X		X		
Plasmablast <sup>d, p)</sup>		X	X		X		
Anti-AQP4 antibody <sup>p)</sup>		X	X		X		

**Appendix 1: Schedule of Activities (cont.)**

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

Week	Double-blind period				WD <sup>g)</sup>	SFU <sup>h)</sup>	FUAA <sup>i)</sup>
	After Week 48		Extra visit at relapsing	DOW <sup>q)</sup>			
	Every 4 weeks	Every 24 weeks					
Window in days	±7	±7	-	-	-	-	±7
<b>Immunogenicity</b>							
Anti-drug antibody	X	X			X		X <sup>j)</sup>
<b>CCSR <sup>c, p)</sup></b>							
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,  $\gamma$ -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.
- d) Blood sample for plasmablasts will be collected in United Kingdom, France, Germany, Japan and Taiwan.
- e) For females of child-bearing potential. Serum or urine  $\beta$ -hCG [sensitivity of at least 25 mIU/mL] will be performed. For patients aged 12 to 17 at the time of informed consent, urine  $\beta$ -hCG will be recommended (see [Appendix 13](#)).
- 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. Patients aged 12 to 17 years at the time of informed consent who withdraw from the study will attend WD visit at 12 weeks ( $\pm 7$  days) after last dosing for FUAA.
- h) Window in days is within  $\pm 28$  days.
- i) Visual function testing is not required if it is implemented with FSS assessment.
- j) 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 for caregiver who signed informed consent to caregiver burden assessment.
- m) Body temperature, SBP, DBP and pulse rate are measured just before dosing and 15 min ( $\pm 5$  min) and 60 min ( $\pm 5$  min) after dosing in case of study drug injection visit.

**Appendix 1: Schedule of Activities (cont.)**

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

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- 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) For patients aged 12 to 17 at the time of informed consent, the guidance provided in [Appendix 13](#) should be considered.
- 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.
- r) For patients aged 12 to 17 years at the time of informed consent who withdraw from the study, Follow-Up Assessment for Adolescents (FUAA) will be conducted at 12 (WD visit), 24 and 48 weeks after the last dose of study drug.

Appendix 1: Schedule of Activities (cont.)

Table 7: Observation and Test Schedule in the Extension Period

Week	Extension period										WD <sup>e)</sup>	FUAA <sup>p)</sup>
	0 (BL) <sup>i)</sup>	2	From Week 0 to Week 48		After Week 48 <sup>w)</sup>			Extra visit at relapsing	DOW <sup>o)</sup>	Last observation <sup>d)</sup>		
			Every 4 weeks	Every 24 weeks	Every 4 weeks <sup>v)</sup>	Every 12 weeks	Every 24 weeks					
Window in days	-	±3	±7	±7	±7	±7	±7	-	-	±7	-	±7
Satralizumab injection (SC)	X	X	X	X	X <sup>v)</sup>	X <sup>v)</sup>	X <sup>v)</sup>		X			
Inclusion/exclusion criteria	X <sup>s)</sup>											
Body height	X <sup>s)</sup>											
Body weight	X			X			X			X	X	
Physical examination	X	X	X	X		X	X	X	X	X	X	
Vital signs <sup>k)</sup>	X	X	X	X		X	X	X	X	X	X	
ECG <sup>h)</sup>	X			X			X			X	X	
Chest X-ray										X	X	
Pregnancy test <sup>c)</sup>	X		X	X		X	X			X	X	
Laboratory test <sup>a)</sup>	X	X	X	X		X	X	X		X	X	
Hepatitis B viral DNA <sup>l)</sup>	X <sup>l)</sup>		X <sup>m)</sup>	X		X	X			X	X	
C-SSRS	X	X	X	X		X	X		X	X	X	
<b>Safety</b>												
Adverse events	Monitor and record throughout the study							X	X	X	X	X
Concomitant medications	Monitor and record throughout the study							X	X	X	X	

Appendix 1: Schedule of Activities (cont.)

Table 7: Observation and Test Schedule in the Extension Period (cont.)

Week	Extension period										WD <sup>e)</sup>	FUAA <sup>p)</sup>
	0 (BL) <sup>i)</sup>	2	From Week 0 to Week 48		After Week 48 <sup>w)</sup>			Extra visit at relapsing	DOW <sup>o)</sup>	Last observation <sup>d)</sup>		
			Every 4 weeks	Every 24 weeks	Every 4 weeks <sup>x)</sup>	Every 12 weeks	Every 24 weeks					
Window in days	-	±3	±7	±7	±7	±7	±7	-	-	±7	-	±7
<b>Efficacy</b>												
Relapse assessment	Monitor and record throughout the study							X	X	X	X	
EDSS/FSS	X			X			X	X		X	X	
Visual function testing <sup>g)</sup> , SF-36, VAS for pain, FACIT-fatigue, mRS, EQ- 5D	X			X			X			X	X	
ZBI <sup>j)</sup>	X <sup>u)</sup>			X <sup>f)</sup>			X <sup>f)</sup>			X <sup>f)</sup>	X <sup>f)</sup>	
<b>PK-PD</b>												
PK sample	X		X	X			X	X	X	X	X	
PD sample <sup>b)</sup>	X		X	X				X <sup>q)</sup>		X	X	
Anti-AQP4 antibody <sup>n)</sup>	X			X				X				
<b>Immunogenicity</b>												
Anti-drug antibody	X		X	X			X	X <sup>r)</sup>		X	X	X

a) RBC, Hb, Ht, WBC, WBC differentiation, PLT, INR, fibrinogen, total protein, albumin, total bilirubin, ALP, AST, ALT,  $\gamma$ -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. *After Week 48, 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]  $\beta$ -hCG will be performed. For patients aged 12 to 17 at the time of informed consent, urine  $\beta$ -hCG will be recommended (see Appendix 13).

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

## Appendix 1: Schedule of Activities (cont.)

**Table 7: Observation and Test Schedule in the Extension Period (cont.)**

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- 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. Patients aged 12 to 17 years at the time of informed consent who withdraw from the study will attend WD visit at 12 weeks ( $\pm 7$  days) after last dose of satralizumab for FUAA.
- f) Window in days is within  $\pm 28$  days.
- g) Visual function testing is not required if it is implemented with FSS assessment.
- h) ECG should be performed prior to blood draws.
- i) For the patients who will enter the extension period (see Section 4.3.2.2), the patients who are treated rescue therapy in the double-blind period can enter the extension period after rescue therapy for relapse, between Day 31 to Day 60, defining the day of onset of relapse in the double-blind period as Day 1. The patients who are not treated with rescue therapy during the double-blind period can enter the extension period after 4 weeks ( $\pm 7$  days) from the last dosing in the double-blind period. For adolescents who are enrolled into the extension period after the end of the double-blind period, this visit is baseline.
- j) ZBI is optional and will be performed 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 ( $\pm 5$  min) and 60 min ( $\pm 5$  min) after dosing in case of study drug 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) For patients aged 12 to 17 at the time of informed consent, the guidance provided in Appendix 13 should be considered.
- 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) For patients aged 12 to 17 years at the time of informed consent who withdraw from the study or complete extension period, FUAA will be conducted at 12 (WD visit for patient withdrawn), 24 and 48 weeks after the last dose of satralizumab.
- q) Until week 48.
- r) After week 48.
- s) Only for adolescents who are enrolled into the extension period after the end of the double-blind period.
- t) Only for patients who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by CEC in the double-blind period or who complete the double-blind period.
- u) Window in days is within  $\pm 28$  days for patients who experience a relapse, which is treated with rescue therapy, and/or a protocol-defined relapse, which is adjudicated by CEC in the double-blind period or who complete the double-blind period.
- v) *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]*

## Appendix 1: Schedule of Activities (cont.)

**Table 7: Observation and Test Schedule in the Extension Period (cont.)**

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*general physician, or home administration by a mobile nurse) will be allowed in emergency situations such as the SARS-CoV-2 (COVID-19) pandemic.*

- w) 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.*
- x) Following the implementation of Protocol Version 11 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.*

### **Abbreviations:**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AQP4 = Aquaporin-4; AST = Aspartate aminotransferase; BL = Baseline; BUN = blood urea nitrogen; CK = creatine kinase; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = diastolic blood pressure; DNA = deoxyribonucleic acid; DOW = dose outside the visit window; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; FACIT = Functional Assessment of Chronic Illness Therapy; FSS = functional status scale; FUAA = Follow-Up Assessment for Adolescents;  $\gamma$ -GTP = gamma glutamyl transpeptidase; Hb = hemoglobin; hCG = Human chorionic gonadotropin; HCT = hematocrit; HBsAg = Hepatitis B surface antigen; HBcAb = Total hepatitis B core antibody; HBsAb = Antibody to hepatitis B surface antigen; HBV = hepatitis B virus; HCVAb = Hepatitis C antibody; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IL-6 = Interleukin-6; INR = international normalized ratio; IU = International Units; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; PK = pharmacokinetics; PLT = platelet; sIL-6R = soluble IL-6 receptor; SBP = systolic blood pressure; SC = subcutaneous; SF-36 = Short Form generic health survey; SFU = Safety follow-up; TB = tuberculosis; VAS = visual analogue scale; WBC = White blood cell; WD = Withdrawal; ZBI = Zarit Burden Interview.

## Appendix 2 EDSS/FSS Assessment Form

### Kurtzke Expanded Disability Status Scale (EDSS)

- 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 0 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 MS.
- 

\*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*. 1963 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 spheres)
- 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**

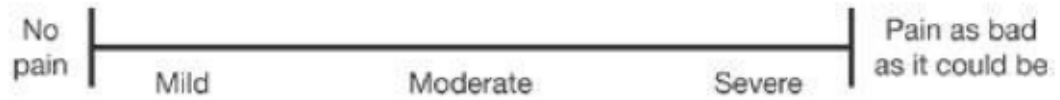
This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

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, neighbours 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?

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

## 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 past 7 days.

		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

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

## 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

Please circle the response the best describes how you feel.

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always	Score
1. Do you feel that your relative asks for more help than he/she needs?	0	1	2	3	4	
2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0	1	2	3	4	
3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0	1	2	3	4	
4. Do you feel embarrassed over your relative's behaviour?	0	1	2	3	4	
5. Do you feel angry when you are around your relative?	0	1	2	3	4	
6. Do you feel that your relative currently affects our relationships with other family members or friends in a negative way?	0	1	2	3	4	
7. Are you afraid what the future holds for your relative?	0	1	2	3	4	
8. Do you feel your relative is dependent on you?	0	1	2	3	4	
9. Do you feel strained when you are around your relative?	0	1	2	3	4	
10. Do you feel your health has suffered because of your involvement with your relative?	0	1	2	3	4	
11. Do you feel that you don't have as much privacy as you would like because of your relative?	0	1	2	3	4	
12. Do you feel that your social life has suffered because you are caring for your relative?	0	1	2	3	4	
13. Do you feel uncomfortable about having friends over because of your relative?	0	1	2	3	4	

**Appendix 7: Zarit Burden Interview (cont.)**

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	1	2	3	4	
15. Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	0	1	2	3	4	
16. Do you feel that you will be unable to take care of your relative much longer?	0	1	2	3	4	
17. Do you feel you have lost control of your life since your relative's illness?	0	1	2	3	4	
18. Do you wish you could leave the care of your relative to someone else?	0	1	2	3	4	
19. Do you feel uncertain about what to do about your relative?	0	1	2	3	4	
20. Do you feel you should be doing more for your relative?	0	1	2	3	4	
21. Do you feel you could do a better job in caring for your relative?	0	1	2	3	4	
22. Overall, how burdened do you feel in caring for your relative?	0	1	2	3	4	
<b>Total Score (out of 88)</b>						

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Interpretation of Score:	
0 – 21	little or no burden
21 – 40	mild to moderate burden
41 – 60	moderate to severe burden
61 – 88	severe burden

Score values and interpretation are guidelines only, as discussed in: Hebert R, Bravo G, and Preville M (2000). *Canadian J Aging* 19: 494-507.

**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)***

UK (English) © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group.

## Appendix 8: EuroQol-5D (EQ-5D) (cont.)

---

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

## Appendix 8: EuroQol-5D (EQ-5D) (cont.)

---

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

Best  
imaginable  
health state

100

90

80

70

60

50

40

30

20

10

0

Worst  
imaginable  
health state

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	BN40898 (SA-307JG)
Subject number	

<i>To be completed and signed by the investigator and faxed to: [ monitor name/ fax number]</i>	
I confirm that the above mentioned subject has withdrawn his/her consent from the Chugai Clinical Sample Repository (CCSR) project.	
Withdrawal is	<b><u>Blood sample for DNA analysis</u></b>
Date subject withdrew from the CCSR	____/____/____ dd mm yy
Has the subject sample been shipped?	
<input type="checkbox"/> Yes	If Yes, date the sample was shipped ____/____/____ dd mm yy
<input type="checkbox"/> No	If No,
<input type="checkbox"/>	The sample was destroyed. Date destroyed ____/____/____ dd mm yy
Or	
<input type="checkbox"/>	No sample was taken.
Investigator signature _____	Date ____/____/____ dd mm yy
<i>To be completed and signed by the biomarker operation at the sponsor</i>	
Date form received by the biomarker operation at the sponsor: ____/____/____ dd mm yy	
<input type="checkbox"/>	I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR before sampling.
Or	
<input type="checkbox"/>	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	
<input type="checkbox"/>	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 9: CCSR Subject Withdrawal Form (cont.)

- Serum and Plasma Samples -

Site/Investigator name	[ monitor to complete for site]
Protocol number	BN40898 (SA-307JG)
Subject number	

<i>To be completed and signed by the investigator and faxed to: [ monitor name/ fax number]</i>	
I confirm that the above mentioned subject has withdrawn his/her consent from the Chugai Clinical Sample Repository (CCSR) project.	
Withdrawal is <input type="checkbox"/> Taking serum and plasma samples hereafter or <input type="checkbox"/> 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?	
<input type="checkbox"/> Yes If Yes, does the patient wish to destroy the samples already collected?	
<input type="checkbox"/> Yes Latest shipment date if some of the samples been shipped ___/___/___ dd mm yy	
And/or Date Destroyed samples if some of them still remain ___/___/___ dd mm yy	
<input type="checkbox"/> No	
<input type="checkbox"/> No	
Investigator signature _____	Date ___/___/___ dd mm yy
<i>To be completed and signed by the biomarker operation at the sponsor</i>	
Date form received by the biomarker operation at the sponsor: ___/___/___ dd mm yy	
<input type="checkbox"/> I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR before the first sampling.	
Or	
<input type="checkbox"/> I confirm that the above mentioned subject has withdrawn his/her consent for the CCSR to take more his/her sample/s.	
Or	
<input type="checkbox"/> 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	
<input type="checkbox"/> 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](mailto:posnerk@childpsych.columbia.edu)  
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**Appendix 10: C-SSRS at Baseline (cont.)**

<b>SUICIDAL IDEATION</b>		Lifetime: Time He/She Felt Most Suicidal
<i>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.</i>		
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>2. Non-Specific Active Suicidal Thoughts</b> 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. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> 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." <i>Have you been thinking about how you might do this?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thought of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>INTENSITY OF IDEATION</b>		Most Severe
<i>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.</i>  <b>Most Severe Ideation:</b> _____ <div style="display: flex; justify-content: space-around;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>		
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-3 times in week (4) Daily or almost daily (5) Many times each day		_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 9 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____
<b>Deterrents</b> <i>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?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____
<b>Reasons for Ideation</b> <i>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?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (6) Does not apply		_____

Version 1/14/09

**Appendix 10: C-SSRS at Baseline (cont.)**

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>		<b>Lifetime</b>		
<b>Actual Attempt:</b> 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 <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i> , 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. <b>Inferred Intent:</b> 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. <b>Have you made a suicide attempt?</b> <b>Have you done anything to harm yourself?</b> <b>Have you done anything dangerous where you could have died?</b> <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> <b>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)?</b> (Self-Injurious Behavior without suicidal intent) If yes, describe:		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____  <b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>		
<b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b>		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>		
<b>Interrupted Attempt:</b> When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act ( <i>if not for that, actual attempt would have occurred</i> ). 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. <b>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?</b> If yes, describe:		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____		
<b>Aborted Attempt:</b> 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. <b>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?</b> If yes, describe:		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____		
<b>Preparatory Acts or Behavior:</b> 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). <b>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)?</b> If yes, describe:		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>		
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?		<b>Yes</b> <b>No</b> <input type="checkbox"/> <input type="checkbox"/>		
<b>Answer for Actual Attempts Only</b>		<b>Most Recent Attempt Date:</b>	<b>Most Lethal Attempt Date:</b>	<b>Initial/First Attempt Date:</b>
<b>Actual Lethality/Medical Damage:</b> 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 _____
<b>Potential Lethality: Only Answer if Actual Lethality=0</b> 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 failed 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](mailto:posnerk@nyspi.columbia.edu)  
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## Appendix 11: C-SSRS since Last Visit (cont.)

<b>SUICIDAL IDEATION</b>		Since Last Visit
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.		
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>2. Non-Specific Active Suicidal Thoughts</b> 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. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> 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." <i>Have you been thinking about how you might do this?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> 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." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>INTENSITY OF IDEATION</b>		Most Severe
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).		
<b>Most Severe Ideation:</b> _____ <div style="display: flex; justify-content: space-around;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>		
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (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		_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____
<b>Deterrents</b> <i>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?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____
<b>Reasons for Ideation</b> <i>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?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply		_____

Version 1/14/09

**Appendix 11: C-SSRS since Last Visit (cont.)**

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Since Last Visit
<p><b>Actual Attempt:</b> 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 <i>any</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <b>There does not have to be any injury or harm</b>, 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. <b>Have you made a suicide attempt?</b> <b>Have you done anything to harm yourself?</b> <b>Have you done anything dangerous where you could have died?</b> <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> <i>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)</i> If yes, describe.</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b></p> <p><b>Interrupted Attempt:</b> 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. <b>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?</b> If yes, describe.</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>
<p><b>Aborted Attempt:</b> 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. <b>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?</b> If yes, describe.</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>
<p><b>Preparatory Acts or Behavior:</b> 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). <b>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)?</b> If yes, describe.</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Suicide:</b></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>Answer for Actual Attempts Only</b></p>	<p>Most Lethal Attempt Date:</p>
<p><b>Actual Lethality/Medical Damage:</b> 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</p>	<p>Enter Code _____</p>
<p><b>Potential Lethality: Only Answer if Actual Lethality=0</b> 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</p>	<p>Enter Code _____</p>

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

## Appendix 12 C-SSRS Already Enrolled Subjects

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Already Enrolled Subjects

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](mailto:posnerk@childpsych.columbia.edu)  
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## Appendix 12: C-SSRS Already Enrolled Subjects (cont.)

<b>SUICIDAL IDEATION</b>		
<p><i>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.</i></p>	<p>Prior to Study Entry: Time He/She Felt Most Suicidal</p>	<p>Since Study Start:</p>
<p><b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>2. Non-Specific Active Suicidal Thoughts</b> 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/as committed methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> 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." <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <i>some intent to act on such thoughts</i>, as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p><b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<b>INTENSITY OF IDEATION</b>		
<p><i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-3 from above, with 1 being the least severe and 3 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal.</i></p> <p>Prior to Study Entry - Most Severe Ideation: _____ Type # (1-3) Description of Ideation</p> <p>Since Study Start - Most Severe Ideation: _____ Type # (1-3) Description of Ideation</p>	<p>Most Severe</p>	<p>Most Severe</p>
<p><b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-3 times in week (4) Daily or almost daily (5) Many times each day</p>	<p>—</p>	<p>—</p>
<p><b>Duration</b> <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time</p>	<p>—</p>	<p>—</p>
<p><b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts</p>	<p>—</p>	<p>—</p>
<p><b>Deterrents</b> <i>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?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply</p>	<p>—</p>	<p>—</p>
<p><b>Reasons for Ideation</b> <i>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?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply</p>	<p>—</p>	<p>—</p>

Version 1/14/09

**Appendix 12: C-SSRS Already Enrolled Subjects (cont.)**

<b>SUICIDAL BEHAVIOR</b> <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>		<b>Prior to Study Entry</b>	<b>Since Study Start</b>
<b>Actual Attempt:</b> 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 <i>ANY</i> intent/desire to die associated with the act, then it can be considered an actual suicide attempt. <i>There does not have to be any injury or harm</i> , 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 <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____  Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of Attempts _____  Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</b> <b>Interrupted Attempt:</b> 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 <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of interrupted _____
<b>Aborted Attempt:</b> 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 <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____	Yes No <input type="checkbox"/> <input type="checkbox"/>  Total # of aborted _____
<b>Preparatory Acts or Behavior:</b> 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 <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Suicidal Behavior:</b> Suicidal behavior was present during the assessment period?		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Completed Suicide:</b>		Yes No <input type="checkbox"/> <input type="checkbox"/>	Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>Answer for Actual Attempts Only</b>		<b>Most Recent Attempt Date:</b>	<b>Most Lethal Attempt Date:</b>
<b>Actual Lethality/Medical Damage:</b> 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
<b>Potential Lethality: Only Answer if Actual Lethality=0</b> 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; lying 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

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



## **Appendix 13**

### **The Guidance for Blood Sampling**

**For patients aged 12 to 17 at the time of informed consent, blood sampling should be performed in accordance with the following EMA guidelines - Ethical considerations for Clinical Trials on Medicinal products conducted with the Paediatric population, 2008.**

As per the above guideline, the total blood loss per individual at any single time should not exceed 1% of the total blood volume, where total blood volume is estimated at 80 to 90 mL/kg body weight. In addition, total blood volume withdrawn over a period of four weeks should not exceed 3% of total blood volume, which estimates to 2.4 mL blood per kg of body weight.

#### **Blood sampling at each single visit**

Total blood volume taken at each single visit is recommended to be satisfied with the following criterion.

**Total blood volume at each single visit (mL)  $\leq$  Body weight (kg)  $\times$  0.8 (mL/kg)**

For example, if the body weight is 40 kg, the total amount of blood withdrawal at any single visit should not exceed 32 mL.

#### **Blood sampling for 4 weeks**

Total blood volume taken for 4 weeks is recommended to be satisfied with the following criterion.

**Total blood volume for 4 weeks (mL)  $\leq$  Body weight (kg)  $\times$  2.4 (mL/kg)**

For example, if the body weight is 40 kg, the total amount of blood withdrawal for 4 weeks should not exceed 96 mL.

If the total amount of blood withdrawal required is more than the permissible volume shown above, then the blood sample collection should be adjusted as per the following recommended order of priority accordingly in an ascending order of the number (i.e., "i" should be considered first).

## Appendix 13: The Guidance for Blood Sampling (cont.)

Maximum blood volume taken at any single visit is shown in Section 4.5.1.11 (the blood volumes for Hepatitis B viral DNA after baseline and CCSR project are included in the maximum blood volume summarized in Table 1).

### a. Screening

- i. Blood samples for local laboratory measurements (TB test and/or pregnancy test) should be collected on a different day to other blood samples at screening, and/or TB skin test is performed as per the local guidance.

### b. From baseline

- Recommended order of priority for sampling
- High  
↓  
Low
- i. If the patient participates in CCSR project, blood and/or serum/plasma samples for CCSR are not collected.
  - ii. For pregnancy test, urine  $\beta$ -hCG will be performed instead of serum test.
  - iii. Blood samples for anti-AQP4Ab and/or plasmablasts are not collected.

### Required Blood Volume for Sampling

Sample	mL	
Hepatitis B viral DNA	3.0	
TB test with using blood sample	X	
Serum pregnancy test	X	
Anti-AQP4 Ab	Asia	3.0
	Europe	5.0
Plasmablasts	5.0	
CCSR (blood)	2.0	
CCSR (serum/plasma)	9.5	

X; the value is depending on the study site.

## **Appendix 14**

### **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. Appropriate anti-mycobacterial therapy must start for such individuals at least 3 weeks before initiating study drug administration in this study, because the effect of anti-mycobacterial therapy may not appear immediately after initiating.

#### **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.

## Appendix 14: Instruction for Tuberculosis (TB) Screening and Treatment (cont.)

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 drug administration and if committed to completing this course of treatment, because the effect of anti-mycobacterial therapy may not appear immediately after initiating.

**Appendix 14: Instruction for Tuberculosis (TB) Screening and Treatment (cont.)**

	TST or IGRA result	Chest X-ray		Interpretation/Action
		Evidence of current, active TB	Evidence of old TB	
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.
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 entry 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 appropriate anti-mycobacterial therapy must start for the patient at least 3 weeks before initiating study drug administration in this study, because the effect of anti-mycobacterial therapy may not appear immediately after initiating. Treatment regimens should be followed by the local

#### **Appendix 14: Instruction for Tuberculosis (TB) Screening and Treatment (cont.)**

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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 drug and consult the Medical Monitor. Report TB infection as a "Selected Adverse Event" (see protocol Section 5.2.4).