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)

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PAREXEL®

Chugai Pharmaceutical Co. Ltd.

SA-307JG

A multicenter, randomized, addition to baseline treatment, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of SA237 in patients with neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD)

Statistical Analysis Plan

PAREXEL Project Number: 211853

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Approved by: [redacted] 20 APR 2018
Date

[redacted]
Chugai Pharmaceutical co. Ltd.

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LIST OF ABBREVIATIONS

ADA	Anti-SA237 antibody
AE(s)	Adverse event(s)
ALQ	Above the upper limit of quantification
ANCOVA	Analysis of covariance
AQP4	Aquaporin-4
ARR	Annualized relapse rate
ATC	Anatomical Therapeutic and Chemical
BLQ	below the limit of quantification
BOCF	baseline observation carried forward
CEC	Clinical Endpoint Committee
CI	Confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic Case Report form
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EU	European Union
FACIT	Functional Assessment Of Chronic Illness Therapy
FPI	First patient in
GEE	Generalized Estimating Equation
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-treat
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measures
mRS	Modified Rankin Scale
N.C.	Not calculated
NMO	Neuromyelitis optica
NMOSD	NMO spectrum disorder
PD	Pharmacodynamics
PK	Pharmacokinetics
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set

PT	Preferred term
Q4W	Every 4 Weeks
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SC	Subcutaneously
SD	Standard deviation
SF-36	Short Form Generic Health Survey
SF-MPQ	Short Form McGill Pain Questionnaire
SFU	Safety Follow-Up
SOC	System organ class
SAF	Safety Set
TFR	Time to first relapse
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary
ZBI	Zarit Burden Interview

1 AMENDMENTS FROM PREVIOUS VERSION

The following changes were made in this SAP from the previous version of SAP due to the amendment to the protocol.

- Adolescents population was added based on the protocol amendment (Protocol version 8.0)
- Only treatment-emergent adverse events are collected in this study. Previously the SAP contained summaries of adverse events and treatment-emergent adverse events, the latter were removed to avoid redundancy.
- Detailed description on the identification of the following adverse event were added: serious infections, opportunistic infections, anaphylaxis, injection related reactions and injection site reactions.
- Detailed description of the following efficacy evaluation were added: EQ-5D Scoring and Visual acuity function.
- Detailed description of the immunogenicity and immunogenicity analyses were added.
- The analysis of relapse-free subjects using logistic regression will not be conducted because of a lot of early events.
- Clarify the definition of baseline ARR.
- Resolve inconsistencies mainly for scope of analysis in SAP.

2 INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the results of the study. It should be read in conjunction with following documents:

- Study Protocol, Version 8.0, 17th April 2017
- Electronic Case Report Form (eCRF), Version 10.0, 30th June, 2017

3 STUDY OBJECTIVES

The objective of this study is to evaluate the efficacy and safety of SA237 in subjects with neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD).

4 INVESTIGATIONAL PLAN

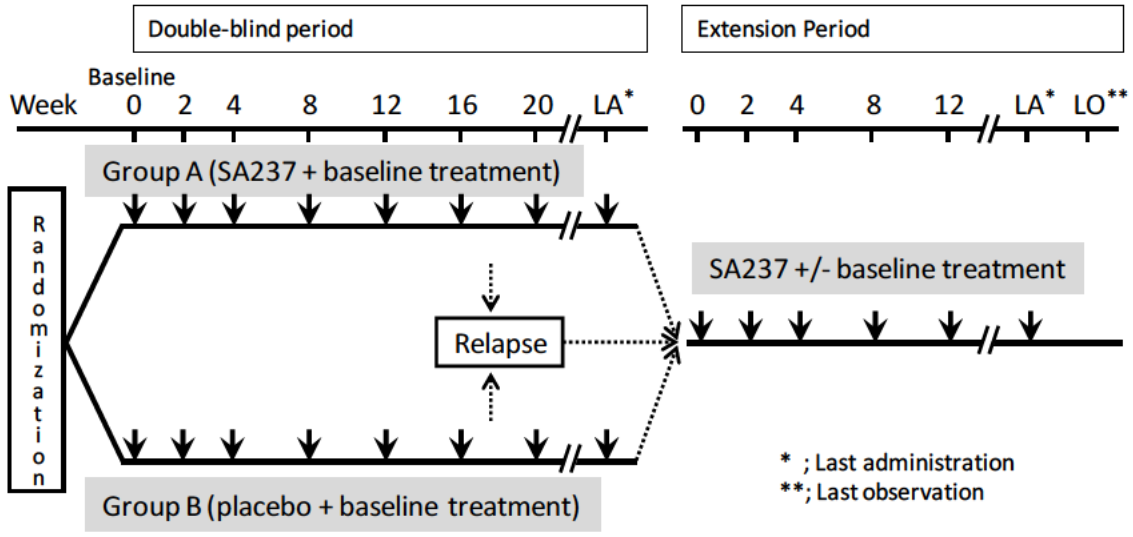
4.1 Overall Study Design and Plan

This is a multicenter, randomized, addition-to-baseline treatment, double-blind, placebo-controlled, parallel assignment study followed by an open-label extension period. Subjects will be randomized to either SA237 120 mg or placebo. 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 maintenance treatments: azathioprine, mycophenolate mofetil or oral corticosteroids (treatment with both oral

corticosteroids and either azathioprine or mycophenolate mofetil will be accepted in subjects aged 12 to 17 years at the time of informed consent). The randomization will be stratified by baseline annual relapse rate (ARR) and geographic region (Asia and European (EU)/Other). The primary efficacy endpoint is the time to first relapse (TFR) based on protocol-defined relapse, where the time point of relapse onset is defined as the time at which the subject experiences any new or worsening neurological NMO representing clinical symptom(s). The duration of the study will depend 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.

Subjects 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. In the extension period, subjects can receive open-label treatment with 120 mg SA237 SC at Weeks 0, 2 and 4 and Q4W thereafter, until commercial availability of SA237 or Sponsor's decision of discontinuation of the development program in combination with a baseline treatment or as a monotherapy. This is the discretion of the Investigator to modify the baseline treatment after the double-blind period of this study. For subjects who are treated with rescue therapy during the double-blind period, SA237 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 subjects 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.

Figure 1: Study Design



Subjects 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.

4.2 Efficacy and Safety Variables

4.2.1 Efficacy Variables

The primary efficacy variable is the TFR based on protocol-defined relapses with CEC evaluations. TFR is defined as the time from the date of the randomization until the first occurrence of relapse throughout the double-blind period.

The secondary efficacy variables include change in Visual Analogue Scale (VAS) for pain score, change in Functional Assessment Of Chronic Illness Therapy (FACIT) fatigue scale score, change in Short Form generic health survey (SF-36) PCS and MCS scores, change in EQ-5D score , annualized relapse rate (ARR), the proportion of relapse-free subjects, change in modified Rankin Scale (mRS) score, change in Zarit Burden Interview (ZBI) score, change in Expanded Disability Status Scale (EDSS) score and change in visual acuity (Snellen chart) score.

4.2.2 Safety Variables

The safety variables are incidence and severity of adverse reactions, adverse events (AEs), adverse events of special interest (AESIs), serious AEs (SAEs), selected AEs (including infusion/injection related reactions), injection site reactions (ISRs), subject withdrawals due to AEs, vital signs (temperature, systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate), physical examination, clinical laboratory tests (hematology, chemistry, and urinalysis), 12-lead ECG, and suicidality (Columbia-Suicide Severity Rating Scale [C-SSRS]).

5 STATISTICAL METHODS

5.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

5.2 General Presentation Considerations

Unless otherwise specified, Week 0 (Day 1) visit, which in most cases should correspond to the date of first dose, will be the baseline in the double-blind period, in which the baseline measurements will be collected at Day 1 prior to the first injection.

The date of first SA237 dose will be the baseline in the All-Subjects-Treated (All SA237) population analyses, in which the baseline measurements will be collected on the day of the first dose, prior to the study drug injection.

The definition of each duration for analysis is as follows:

- Double blind period for efficacy analysis
  - Double-blind period starts on the day of the randomization. The double-blind period ends on the earliest day of 1) clinical cutoff date (CCOD), 2) the day before the first

treatment in the extension period, 3) the end of the study, or 4) last contact for patients lost to follow up.

- Double blind period for safety analysis
  - Double blind period starts on the day of first dose of study drug. The double-blind period ends on the same day as efficacy analysis..

- SA237 exposure duration for safety analysis (for All SA237 analysis)
  - SA237 exposure duration starts on the day of first dose of SA237. SA237 exposure duration ends on the earliest day of 1) CCOD, 2) the end of the study, or 3) last contact for patients lost to follow up.

The definition of summaries by visit is as follows:

- Summaries by visit for double blind period
  - Baseline is defined as the latest data before the date of first administration for all data. Summarized visits except for baseline are defined as follows. Irregular visits such as unscheduled visit between week X, dose outside the visit window (DOW), extra visit at relapsing, and the end of the study are out of scope. Week X visits are directly used for categories of time. In other words, time window is not applied. If there are the same visits data, one representative assessment nearest to the scheduled visit day will be summarized.

- Summaries by visit for All SA237 analysis
  - Baseline is defined as the latest data before the date of first administration of SA237 for all data. Summarized visits except for baseline are defined as follows. Irregular visits such as unscheduled visit between week X, dose outside the visit window (DOW), extra visit at relapsing, and the end of the study are out of scope. Time window is applied as if visit schedules continue in the double blind period. Middle of each specified day of visit will be used for the range of time window of each visit. One representative assessment nearest to the specified day of visit in time window of each visit will be summarized.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median and SD will be reported to one more decimal place than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics. If the data contains inequality signs, use the number on the end (i.e. treat "<= 0.02" as "0.02") in analysis for calculation of representative value to be presented in the summaries.

For categorical parameters, the number and percentages of subjects in each category will be presented at the relevant time point. The denominator for percentage will be based on

the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, percentages will be presented to one decimal place. Percentages will not be presented for zero counts and 100% will be presented as an integer. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise noted. Missing category will only be displayed when there are missing data.

For pharmacokinetic endpoint, concentrations will be analyzed using all reported decimal places, and displayed to the same number of decimal places as they are recorded in the database. If any samples are collected outside of the protocol defined time window (Appendix 1 in the protocol), the relevant values will be excluded for the calculation of descriptive statistics. Furthermore, if the samples are collected more than 6 weeks after the last administration, the relevant values will be excluded for the calculation of descriptive statistics considering the half-life of IgG. Descriptive statistics will include number of the subjects, geometric mean, geometric CV and the 95% confidence interval for the geometric mean for the concentrations, as well as arithmetic mean, SD, median, minimum, and maximum of SA237 concentrations will be calculated by visit and per defined time window post-dose for the Pharmacokinetics Per-Protocol Set (PK-PPS). The CV will be presented with 1 decimal place. For the calculation of descriptive statistics, a serum concentration below limit of quantification will be substituted by half of lower limit of quantification (i.e. LLOQ/2) If more than half of the measured values are BLQ at any blood sampling time point, the statistics will not be tabulated for that time point and will be shown as “N.C.”.

For immunogenicity, below rules will be applied to neutralizing antibody.

- Neutralinzing antibody will be only assessed if anti- SA237 antibody is positive.
- If SA237 concentration is over 1 ug/mL, the data of the neutralizing antibody will be excluded for the calculation of descriptive statistics. This is because neutralizing antibody analysis may be false negative or false positive affected by SA237.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a p-value is only presented to four decimal places (by SAS) it will not be rounded again, but will be presented to four decimal places. P-values less than 0.001 will be presented as “<0.001”.

Confidence intervals (CIs) will be presented to one more decimal place than the raw data.

The confidence interval for hazard ratio will be calculated based on the Wald type and the relapse rate confidence interval will be provided using Kaplan Meier method with a LOGLOG transformation.

All report outputs will be produced using SAS® version 9.2 or a later version in a secure and validated environment.

5.3 Handling of Missing data

Medications with a missing start date and whose stop date is either unknown or after the date of the first dose of study drug, will be considered concomitant. Medications with a missing start date and whose stop date is prior to the date of the first dose of study drug, will be considered as prior medications.

Where the adverse events start dates of year part are missing then the value will not be imputed. For the partial missing situation (month or day missing), the value will be imputed for the analysis purpose.

Missing pattern	Start Date / Pre-Dosing	End Date / Post-Dosing
completely missing	leave missing	
missing year	leave missing	
missing month	set to 'JAN'	set to 'DEC'
missing day	set to '01'	set to last day of the month
missing month and day	set to '01JAN'	set to '31DEC'
missing time (concomitant medication)	set to '00:00:00' missing hours: 0 missing minutes: 0 missing seconds: 0	set to '23:59:59' missing hours: 23 missing minutes: 59 missing seconds: 59
missing time (adverse event)	set to '23:59:59' missing hours: 23 missing minutes: 59 missing seconds: 59	

These rules apply to AE and concomitant medication. For AE, beginning/end date of AE, first date of study treatment and date of death are considered to avoid inconsistency.

For Visit data other than efficacy, only missing time rules apply. For efficacy visit data, no imputation is made. For birth date, set missing month to '06' and/or set missing day to '15'.

5.4 Study Subjects

5.4.1 Disposition of Subjects

Summary tables of subject disposition will be provided as follows:

- A summary table of the number of subjects who were randomized to study treatment, number of subjects receiving at least one dose of study drug, number of subjects ending the double-blind period, number of withdrawal from the double-blind period, reason for withdrawal in the double-blind period, number of subjects entering the safety follow-up after double-blind period, number of subjects finishing the safety follow-up after double-blind period, number of subjects entering the open-label extension period, number of withdrawal from the extension period, reason for withdrawal in the extension period, number of subjects conducting last observation visit or withdrawal visit will be provided by treatment group and overall for both the blinded period and the open label extension.
- A by-subject listing of disposition status, including the date of informed consent, date of treatment with study drug and study completing/withdrawal, and reason for withdrawal from treatment and from study.

5.4.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. The impact of major protocol deviations on the efficacy results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 5.5), both including and excluding data potentially affected by major protocol deviations.

A summary table and listing of protocol deviations will be provided as follows:

- The number and percentage of subjects without any deviation, without any major deviation, with at least 1 major deviation, type of major deviations will be summarized by randomized treatment group, overall and by site.
- A by-subject listing of protocol deviations will be presented.

5.5 Analysis Populations

The intent-to-treat (ITT) population will serve as the primary population for the analysis of efficacy, which consists of all randomized subjects. Subjects will be analyzed as randomized for analysis purposes. In case even a subject is incorrectly stratified at time of randomization, the analysis will be performed using the stratification for randomization.

The Per-Protocol Set population (PPS) will include all subjects 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. Subjects will be analyzed as treated for analysis purposes in the PPS.

The Safety Set (SAF) population will include all randomized subjects who have received at least one dose of active study drug or placebo. Subject will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the SAF population, i.e. patients who received at least one dose of SA237 will be assigned to the SA237 treatment arm, irrespective of randomized arm. .

The All-Subjects-Treated (All SA237) population will be defined as all enrolled subjects who took at least one dose of active study drug at any time. Date of the first active study drug administration will be defined as Day 1 for All SA237 analysis (i.e. Day 1 of subjects allocated in placebo group is redefined on the day of first dose of SA237 when entering extension period.

The Pharmacokinetics Per-Protocol Set (PK-PPS) and immunogenicity (anti-SA237 antibody; ADA) will include all subjects in the SAF with at least 1 valid post-dose concentration result with a dosing record and sampling time. Pharmacodynamics variables will be analyzed using the SAF population.

The Adolescents population will be defined as all enrolled subjects from 12 to 17 years old (< 18 years) at the first informed consent. 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 following summary and listing will be provided:

- A summary of analysis populations, including the number and percentage of subjects in the defined analysis sets by treatment group and overall.
- A by-subject listing of analysis population (ITT, PPS, SAF, All SA237, PK-PPS, Adolescents Population, and PK-Adolescents Population) information will be provided.

This listing should include: subject number, inclusion/exclusion flag for each population and reason for exclusion from each population.

Subgroup analysis will be conducted based on the following variables:

- Age category (<18, ≥18 years)
- NMO/NMOSD and AQP4 Status at screening (5 categories: NMO, NMOSD, NMO and AQP4 positive, NMO and AQP4 negative, and NMO/NMOSD and AQP4 positive)
- Baseline treatment (azathioprine, mycophenolate mofetil, oral corticosteroids, azathioprine + oral corticosteroids, mycophenolate mofetil + oral corticosteroids)
- Baseline ARR (1, >1) based on the last two years before screening
- Geographic region (Asia, Europe/other)
- Japanese, Non-Japanese subjects
- ADA status (ADA negative subjects, ADA unaffected subjects, Treatment-boosted ADA subjects, Treatment-induced ADA subjects) (see Section 5.13)

For safety analyses, baseline weight (<median, ≥median) will be included in addition.

5.6 Demographic and Other Baseline Characteristics

Summary tables and listing will be provided as follows for ITT, PK-PPS and SAF:

- Demographics will be summarized as collected at screening or baseline visit before administration of first dose of study drug and will include gender, race (American Indian/Alaska Native, Asian [Japanese], Asian [Non-Japanese], Black/African American, Native Hawaiian/other Pacific Islander, White and Other), Geographic region (Asia, Europe/other), age (years), age category (<18, ≥18), ethnicity, racial subgroup, height, body weight (the first and the third quartiles of body weight will be presented), body mass index (BMI, kg/m2), BMI category (<18.5, ≥18.5 to <25, ≥25 to <30, and ≥30 kg/m2), Baseline ARR (1, >1) , AQP4 status at screening (positive, negative), Diagnosis (NMO, NMOSD) and Baseline treatment (azathioprine, mycophenolate mofetil, oral corticosteroids, azathioprine + oral corticosteroids, mycophenolate mofetil + oral corticosteroids) by treatment group and overall.
- A by-subject listing of demographic data.

  Age will be calculated as the number of complete years between a subject's birth date and the date of the first informed consent.

The subgroup summary tables will be presented for ITT and SAF by the defined variables with the exception of ADA status (See section 5.5).

5.7 Medical History

Medical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Medical conditions are categorized as past or concomitant as follows:

- Past diseases: Medical conditions which are specified as start date is before Day 1 Visit date with no ongoing status or the stop date is prior to Day 1 Visit date
- Baseline diseases: Medical conditions which are specified as start date is before Day 1 Visit date with ongoing status or the stop date is on or after Day 1 Visit date.

The following summaries will be provided by treatment group and overall, based on the SAF.

- A summary table of past diseases will be presented by system organ class (SOC) and preferred term (PT).
- A summary table of concomitant diseases will be presented by SOC and PT, by treatment group and overall.
- A by-subject listing of medical history data will be provided.

5.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Medication start and stop dates will be compared to the date of the first dose of randomized study drug and thus the medications will be classified as Prior or Concomitant.

Medications that start and stop prior to the date of first dose of study drug will be classified as Prior medications. Medications taken on or after (including ongoing) the first dose of study drug will be classified as Concomitant medication. If a medication starts before the date of first dose of study drug and stops on or after the date of first dose of study drug then the medication will be classified as both Prior and Concomitant medication. NMO/NMOSD pain drugs will be reported as collected on the CRF.

The following summaries will be provided by treatment group and overall, based on the Safety population.

- A summary table of Prior Medications (other treatments than NMO/NMOSD) will be provided by anatomical therapeutic chemical (ATC) and PT.
- A summary table of Concomitant Medications (other treatments than NMO/NMOSD) will be provided by ATC and PT.
- A summary table of Prior NMO/NMOSD drugs for relapse prevention will be provided by ATC and PT.
- A summary table of Concomitant NMO/NMOSD drugs for relapse prevention will be provided by ATC and PT.
- A summary table of Prior NMO/NMOSD drugs for relapse/rescue therapy will be provided by ATC and PT.

- A summary table of Concomitant NMO/NMOSD drugs for relapse/rescue therapy will be provided by ATC and PT.
- A summary table of Prior NMO/NMOSD pain drugs will be provided by ATC and PT.
- A summary table of Concomitant NMO/NMOSD pain drugs will be provided by ATC and PT.
- A summary table of Prior other NMO/NMOSD drugs will be provided by ATC and PT.
- A summary table of Concomitant other NMO/NMOSD drugs will be provided by ATC and PT.
- A by-subject listing of Prior medication data will be provided for NMO/NMOSD pain drugs and others separately.
- A by-subject listing of concomitant medication data will be provided.

5.9 Treatment Compliance

Compliance will be computed by determining the number of SC injections relative to the number of SC injections that should have been administered. The compliance will be evaluated during the double-blind period. If a subject who experience a relapse which is treated with rescue therapy and/or a protocol-defined relapse which is adjudicated by CEC or early discontinued from study treatment, the number of planned and actual SC will be counted based on the visits before the discontinuation. Treatment compliance will be summarized in terms of compliance based on the Safety population. Administration using prefilled syringe will be flagged in the listing of administration.

Compliance will be calculated using the following formula:

$$\text{Compliance (\%)} = \frac{\text{Number of SC injections during the double-blind period}}{\text{Number of planned SC injections during the double-blind period}} \times 100$$

The following summaries and listings will be provided:

- A summary table of compliance will be presented by treatment group, and overall. The number and percentage of treatment compliance will also be presented by categorized compliance as: <80%, 80%-100%, >100%,
- A by-subject listing of study drug administration as well as overall compliance during the double blind and whole period.

5.10 Efficacy Evaluation

For the definition of the double-blind period for efficacy evaluations see section 5.2. See Appendix 7.7 how to descrive models with SAS code.

5.10.1 Analysis and Data Conventions

This study is designed to assess the efficacy of SA237 over placebo on the treatment of NMO/NMO-SD. The null hypothesis for primary endpoint will be that there is no difference on the TFR between SA237 and placebo during double-blinded period. The alternative hypothesis will be that there is a difference in TFR during double-blinded period.

A two-sided stratified log-rank test at 5% level will be used to test this hypothesis.

5.10.1.1 Multi-center Studies

For the purpose of the summaries and analyses, the term 'Center' will be used to define each site.

All centers will be pooled by country for the purpose of analysis.

Descriptive summaries will not be presented by individual center. Subject data listing will be provided by individual center.

5.10.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

- Baseline ARR: one or more than one based on the last two years before screening
- Geographic region: Asia and EU/Other.

In addition, for each covariate, a statistical test for the presence of a treatment-by-covariate interaction will be performed, by including the interaction term in the secondary analysis model. Subgroup analyses will be performed to explore the treatment-by-covariate interactions. If any of the treatment-by-covariate are found to be statistically significant, conclusions based on the secondary analysis (no interaction) will be interpreted with caution.

In addition, a Mixed-effect model repeated measures (MMRM) for secondary endpoints will be adjusted for Baseline ARR and Geographical region (stratification factors).

5.10.1.3 Handling of Missing Data

For details on censoring rule for the primary endpoint, see section 5.10.2.

For secondary continuous endpoints, a Mixed-effects model repeated measures (MMRM) analysis incorporating all data in double blind period will be used to utilize all the 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 subjects with incomplete data from some scheduled time points.

For 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.

5.10.1.4 Multiple Comparisons/Multiplicity

The serial gatekeeping methodology will be employed to control the rate of false positive for the primary endpoint (TFR based on protocol-defined relapses) and key secondary endpoints (change in VAS for pain at week 24 and change in the FACIT fatigue scale at week 24). The 3 efficacy endpoints will be analyzed in hierarchical order, beginning with the TFR based on protocol-defined relapses, followed by the VAS for pain, and ending with FACIT fatigue. A fixed-sequence approach will be applied to control the overall significance level at 0.05. An initial null hypothesis will be tested for the first hierarchical primary efficacy endpoint, the TFR based on protocol-defined relapses. If this is significant, then a repeat of the aforementioned testing procedure for the second hierarchical key secondary end point, the VAS for pain will be done. This will be repeated a third time for the FACIT fatigue if the VAS for pain showed a significant difference.

5.10.1.5 Examination of Subgroups

Descriptive statistics by subgroup for the demographic data, primary efficacy and key secondary variables will be presented by the defined variables in Section 5.5.

Additionally, main safety data will be presented by Japanese/Non-Japanese subgroup.

5.10.1.6 EQ-5D Scoring Algorithm

The EQ-5D 3 level version (EQ-5D 3L) descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problem, some problems, and extreme problems. The scoring algorithm (US) as described in appendix 7.3 will be used but other norms may be explored for sensitivity analysis.

The EQ-5D index score will be missing in case any answer to one of the five EQ-5D dimensions is missing.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale ranging from 0 to 100 where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

5.10.1.7 SF-36 Scoring Algorithm

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 physical and mental health component summary measures (PCS and MCS).

The SF36 will be scored using the Quality Metric proprietary scoring system (version 4.5). Component and domain scores are transformed to a 0-100 scale based on the 2009 US Normative population. Higher scores are indicative of better health related quality of life and a score of 50 is average for the US population.

For the SF-36, missing data rules will be applied according to the proprietary scoring software provided by the license holder (Maruish et al. 2011 p57 and p60).

5.10.1.8 FACIT-Fatigue Scale Scoring Algorithm

The FACIT Fatigue scale is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the past 7 days. As each of the 13 items of the scale ranges from 0-4, the range of possible scores is 0-52, which 0 being the worst possible score and 52 the best. Items are scored as follows: 0 = Not at all; 1= A little bit; 2= Somewhat; 3= Quite a bit; 4= Very much. All items are reverse scored except item An5 (*I have energy*) and An7 (*I am able to do my usual activities*). See Table 5-1 for further guidance.

When there are missing data, a total score is prorated from the score of the answered items, as long as more than 50% of the items are answered (i.e. a minimum of 7 of 13 items). The prorated score is calculated as the average of the non-missing scores multiplied by 13.

Table 5-1: FACIT scoring

Item code	Reverse item		Item response	Item score
HI7	4	-	=	
HI12	4	-	=	
An1	4	-	=	
An2	4	-	=	
An3	4	-	=	
An4	4	-	=	
An5	0	+	=	
An7	0	+	=	
An8	4	-	=	
An12	4	-	=	
An14	4	-	=	
An15	4	-	=	
An16	4	-	=	
			Sum individual item scores: Multiply by 13: Divide by number of items answered:_____=FACIT score	

5.10.1.9 EDSS Scoring

The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurological exam) to 10 (death due to NMO) in 0.5 unit increments that represent higher levels of disability. The EDSS scoring will be based on the score recorded on CRF.

5.10.1.10 mRS Scoring

The mRS is a 7-point disability scale that assesses the degree of disability in subjects with neurological impairment. Possible scores range from 0 (no symptom at all) up to 6 (death). The higher scores reflect increased disability. The mRS scoring will be based on the score recorded on CRF.

5.10.1.11 ZBI Scoring

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. The ZBI scoring will be based on the score recorded on CRF. For summary tables, only questionnaire with responses to 17 or more out of 22 questions (>= 75% valid response) are used.

The ZBI can be scored if 17 or more items are completed. Interpretation approach can be used if at least 75% of the items have been completed:

1. Sum the items that were answered.
2. Divide the sum by the number of items that were answered to yield the mean response per item.
3. Multiply the mean response per item by 22 (the total items in the scale).

5.10.1.12 Visual acuity function (Snellen chart)

Visual acuity will be measured by a Snellen 20-foot wall chart. The test will be performed monocularly and subjects may use their habitual distance glasses or contact lenses. If visual acuity is less than 20/200, these data will be recorded on CRF as below:

- If the subject can count fingers, this is recorded as “20/300” (CF).
- If the subject can see finger movements, this is recorded as “20/400” (HM).
- If the subject can perceive the flashlight, this is recorded as “20/500” (LP).
- If the subject cannot perceive the flashlight, this is recorded as “20/600” (NLP).
-

In order to calculate change from baseline, visual acuity scores will be converted to logMAR visual acuity scoring. Transformation of scores will be conducted based on the following table. If the record of visual acuity score (Snellen chart) is worse than 20/200 (i.e. CF, HM, LP or NLP in this study), the score will be converted to logMAR 1.85, logMAR 2.00, logMAR 2.70 and logMAR 3.00, respectively. If score which is not in the table is recorded, it would adjust to the following lower one (e.g. 20/27 will be converted to 20/30).

Table 5-2: logMAR visual acuity scoring

Snellen chart	LogMAR
20/10	-0.30
20/12.5	-0.20
20/15	-0.12
20/16	-0.10
20/20	0.00
20/25	0.10
20/30	0.18
20/32	0.20
20/40	0.30
20/50	0.40
20/60	0.48
20/63	0.50
20/70	0.54
20/80	0.60
20/100	0.70
20/114	0.76
20/125	0.80
20/150	0.88
20/160	0.90
20/200	1.00
CF	1.85
HM	2.00
LP	2.70
NLP	3.00

5.10.2 Primary Efficacy Variable

The primary efficacy analyses will be based on the ITT population. Supportive evaluations will be performed using the PPS population.

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 subject. TFR is defined as the time from the date of the randomization until the first occurrence of relapse throughout the study. Time point of relapse onset is defined as time at which the subject experiences any new or worsening neurological NMO representing clinical relapse(s) which is later confirmed by the CEC as protocol-defined.

Censor is defined as the earliest day of 1) the end of double blind period for efficacy analysis, 2) switching or increasing the baseline treatment (for details on the identification of the switch and increase in baseline therapy see appendix 7.4), or 3) receiving rescue therapy for clinical relapse.

The primary analysis of the study is to test the equality of the TFR distribution based on protocol-defined relapse in the SA237 + baseline treatment (SA237) and Placebo + baseline treatment (placebo) arms:

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

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

The Kaplan-Meier method will be used to estimate the TFR based on protocol-defined relapses 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% CIs using a stratified (baseline ARR and geographical region) Cox proportional-hazards model (Exact method will be used for tie data). Treatment by covariate interactions will be assessed by including the pairwise interaction terms in the Cox proportional-hazards model.

The following summary tables, figures and analysis will be provided for the ITT and PPS:

- A summary table of Kaplan-Meier estimate of TFR (protocol-defined relapse) will be presented by treatment group.
- A figure of Kaplan-Meier estimate of TFR (protocol-defined relapse) will be presented by treatment group.
- Analysis of TFR (protocol-defined relapse) will be performed using the stratified log-rank test.
- Analysis of TFR (protocol-defined relapse) will be performed using the stratified Cox regression.

The subgroup forest plot of HR of TFR (protocol-defined relapse) will be presented by the defined variables in Section 5.5.

Additionally, summary tables of sensitivity analysis of TFR (clinical relapse), TFR (treated clinical relapse), TFR (treated clinical relapse: optic neuritis) , protocol-defined relapse

based on CEC adjudication (regardless of assessment limit of 7 days) and protocol-defined relapse based on EDSS/FSS increase relative to baseline will be conducted for ITT as follows. All relapses reported by investigators will be handled as events for TFR (clinical relapse). Relapses treated with rescue therapy will be handled as events in addition to protocol-defined relapses for TFR (treated clinical relapse). Relapses treated with rescue therapy and judged optic neuritis by investigator will be handled as events in addition to protocol-defined relapses for TFR (treated clinical relapse: optic neuritis). Optic neuritis will be identified via relapse assessment form before data base lock (for details see appendix 7.4).. The same censoring rules as for the primary endpoint will be applied, except for the specific event of interest.

- A summary table of Kaplan-Meier estimate of TFR (clinical relapse) will be presented by treatment arm.
- A summary table of Kaplan-Meier estimate of TFR (treated clinical relapse) will be presented by treatment arm.
- A summary table of Kaplan-Meier estimate of TFR (treated clinical relapse: optic neuritis) will be presented by treatment arm.
- A summary table of Kaplan-Meier estimate of TFR (protocol-defined relapse based on CEC adjudication (regardless of assessment limit of 7 days)) will be presented by treatment arm.
- A summary table of Kaplan-Meier estimate of TFR (protocol-defined relapse based on EDSS/FSS increase relative to baseline) will be presented by treatment arm.
- A figure of Kaplan-Meier estimate of TFR (clinical relapse) will be presented by treatment group.
- A figure of Kaplan-Meier estimate of TFR (treated clinical relapse) will be presented by treatment group.
- A figure of Kaplan-Meier estimate of TFR (treated clinical relapse: optic neuritis) will be presented by treatment group.
- Analysis of TFR (clinical relapse) will be performed using the stratified log-rank test.
- Analysis of TFR (treated clinical relapse) will be performed using the stratified log-rank test.
- Analysis of TFR (treated clinical relapse: optic neuritis) will be performed using the stratified log-rank test.
- Analysis of TFR (clinical relapse) will be performed using the stratified Cox regression.
- Analysis of TFR (treated clinical relapse) will be performed using the stratified Cox regression.
- Analysis of TFR (treated clinical relapse: optic neuritis) will be performed using the stratified Cox regression.

- Analysis of TFR (protocol-defined relapse based on CEC adjudication (regardless of assessment limit of 7 days)) will be performed using the stratified Cox regression.
- Analysis of TFR (protocol-defined relapse based on EDSS/FSS increase relative to baseline) will be performed using the stratified Cox regression.
- TFR (clinical relapse) is defined if the relapse will be reported in eCRF. TFR (treated clinical relapse) is defined if the subject received rescue therapy for clinical relapse.
- A by-subject listing of TFR, which also includes clinical relapse, treated clinical relapse, treated clinical relapse: optic neuritis, will be provided.

5.10.3 Secondary Efficacy Variables

The key secondary efficacy endpoints are change from baseline in VAS for pain score and the FACIT fatigue scale score at week 24. All efficacy analyses will be based on the ITT population in double-blind period.

5.10.3.1 Key Secondary Endpoints

- Analysis of change in VAS for pain score from baseline at week 24 using ANCOVA.
- Analysis of change in FACIT fatigue scale score from baseline at week 24 using ANCOVA.

The ANCOVA will include treatment group as fixed effect; the baseline measurements and stratification factors as covariates.

The missing data will be imputed by baseline observation carried forward (BOCF) method.

For sensitivity analysis, random hot deck multiple imputation method using a regression based approach will be conducted. In this imputation method, missing values will be replaced with values from a similar responding unit. Uncertainty with this imputation will be considered via Multiple Imputations (MI) combining rules (Rubin, 1987; Little, 1988).

- Analysis of change in VAS for pain score from baseline at week 24 using ANCOVA by hot deck multiple imputation method.
- Analysis of change in FACIT fatigue scale score from baseline at week 24 using ANCOVA by hot deck multiple imputation method.

The imputation for FACIT fatigue questionnaire written in Section 5.10.1.8 will be applied before conducting multiple imputations.

The following summary tables and analyses will also be provided:

- A summary table of change in VAS for pain score from baseline to every 24 weeks.
- A summary table of change in FACIT fatigue scale score from baseline to every 24 weeks.
- Analysis of change in VAS for pain score from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in FACIT fatigue scale score from baseline to every 24 weeks using MMRM analysis.

The MMRM will include treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements and stratification factors as a covariate; and visit as a repeated measure. The unstructured covariance matrix 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, the full model will be kept.

If the normality assumption for the key secondary variable does not hold, GEE or Generalized Linear Mixed-effect model analysis will be used. The assessment will be performed prior to unblinding.

5.10.3.2 Other Secondary Endpoints

The following summary tables, figures and analysis will be provided for the ITT:

- A summary table of change in SF-36 domain scores from baseline to every 24 weeks.
- A summary table of change in SF-36 summary score (physical and mental) from baseline to every 24 weeks.
- A summary table of change in EQ-5D scores from baseline to every 24 weeks.
- A summary table of the proportion of relapse-free subjects.
- A summary table of ARR (protocol-defined relapse).

  The ARR is calculated as the total number of relapses experienced divided by the person-years at risk. The 95% CI will be presented based on the Poisson distribution. ARR based on the person-years at risk on the total study period will also be provided. In order to account for different study treatment exposure durations among subjects, log-transformed exposure time will be included in the model as an “offset” variable for appropriate computation of ARR.
- A summary table of ARR (clinical relapse).
- A summary table of ARR (treated clinical relapse).
- Analysis of ARR will be performed using negative binomial regression model (protocol-defined relapse).

  For comparing the difference between 2 treatment arms, relapse number will be the response variable; treatment group, baseline ARR and geographic region as covariates Log-transformed exposure time will be included in the model as an “offset” variable.
- summary table of change in mRS scores from baseline to every 24 weeks.
- A summary table of change in ZBI scores from baseline to every 24 weeks.
- A summary table of change in EDSS scores from baseline to every 24 weeks.
- A summary table of change in visual acuity (Snellen chart) scores from baseline to every 24 weeks.

- Analysis of change in SF-36 domain scores from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in SF-36 components (physical and mental) from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in EQ-5D scores from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in mRS scores from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in ZBI scores from baseline to every 24 weeks using MMRM analysis.
- Analysis of change in EDSS scores from baseline to every 24 weeks using MMRM analysis.

The MMRM will include treatment group, protocol-specified visit, treatment-by-visit interaction as fixed effects; the baseline measurements and stratification factors as covariates; and visit as a repeated measure. The unstructured covariance matrix will be assumed in the model.

If the unstructured covariance matrix does not converge, compound symmetric structure will be used. If treatment-by-visit interaction is not statistically significant, the full model will be kept.

If the normality assumption for other secondary variables does not hold, GEE or Generalized Linear Mixed-effect model analysis will be used. The assessment will be performed prior to unblinding.

5.10.3.3 Examination of Adolescents

The following endpoints will be presented for the adolescent population in listings:

- TFR (protocol-defined relapse).
- EDSS scores.
- Visual acuity (Snellen chart) scores.
- SF-36 domain scores.
- SF-36 summary score (physical and mental).
- VAS for pain score.
- FACIT fatigue scale score.
- EQ-5D scores.
- mRS scores.
- ZBI scores.

5.11 Safety Evaluation

Unless otherwise specified, all safety analyses will be based upon the SAF for double blind period and All SA237 for overall period as defined in Section 5.5.

Subgroup population was defined in Section 5.5.

If we have low numbers of AEs only listings may be provided.

5.11.1 Extent of Exposure

Duration of exposure to study drug (days) is defined as date of last dose - date of first dose + 1, and will be summarized.

Number of doses and total cumulative dose of study drug will be summarized. Descriptive statistics will be presented by treatment group.

5.11.2 Adverse Events

Adverse events will be coded using most recent version of MedDRA. All summaries will be sorted alphabetically by System Organ Class (SOC) and preferred term (PT), starting with the most frequent event. All adverse events reported in whole study will be reported in listings. For AEs, if the AE intensity is missing, the worst case (severe) will be assumed. If the drug relationship is missing, the worst case (drug related) will be assumed. In summaries, multiple occurrences of the same PT event in one individual counted only once.

The following summary tables of AEs will be provided:

- An overall summary of AEs will be presented. It will include the number and percentage of subjects with at least 1 AE, serious AE, AE leading to early discontinuation of treatment, and severe AE and number of death.
- A summary of AEs by SOC and PT.
- A summary of AEs by Intensity, SOC and PT.
- A summary of AEs leading to discontinuations of treatment.
- A summary of AEs leading to drug interruption.
- A summary of adverse drug reactions (ADRs) by SOC and PT.
- A by-subject listing of all AEs.
- A by-subject listing of all AEs leading to treatment discontinuation.
- A by-subject listing of all AEs leading to drug interruption.
- A by-subject listing of all ADRs.

5.11.3 Serious Adverse Events and Death

SAE will be provided by treatment group. SAE will be provided by subgroups defined in Section 5.5. As for C-SSRS, scores reported in Baseline and Prior to study page of CRF will be handled as baseline score. Scores reported in Since Last Visit and Since Study Start

page of CRF will be summarized by visit when the data is recorded. The following summary tables of SAEs will be provided:

- A summary of incidence of serious AEs (SAEs) by SOC and PT.
- A summary of incidence of SAEs leading to discontinuation by SOC and PT.
- A by-subject listing for all deaths.
- A summary of C-SSRS.
- A by-subject listing of C-SSRS.

5.11.4 AESI: ALT/AST, Infection Agent Transmission and Selected AEs

AESI are defined in the protocol as follows and collected in the eCRF using a specific question. The following summary tables and listings will be provided:

- A summary of AESI by SOC and PT.
- Suspected transmission of an infectious agent by the study drug.
- A by-subject listing of all AESI.
- A by-subject listing for infection (SOC: Infections and infestations) medicated by IV treatment.
- A by-subject listing for opportunistic infection (defined by MedDRA basket in Appendix) medicated by PO treatment.

AST and ALT will be categorized into four group (>3-5 xULN, 6-10 xULN, 11-20 xULN and 21- xULN) based on maximum post-baseline levels within baseline and post-baseline respectively for each test by maximum post-baseline levels for total bilirubin and alkaline phosphatase (total bilirubin <= 2xULN, total bilirubin > 2xULN, total bilirubin > 2xULN and alkaline phosphatase < 2xULN, total bilirubin > 2xULN and alkaline phosphatase <= 5xULN). The denominator is the number of subjects with any valid assessment at baseline and post-baseline respectively. Subjects with AST or ALT results fulfilling criteria for more than one category are counted only once, in the category indicating the highest elevation level within baseline and post-baseline.

- Summary of AST and ALT Results.

5.11.5 Infections, Serious Infection, Opportunistic Infection

- Serious adverse event in “SOC: Infections and infestations” will be summarized. Opportunistic infections are defined by MedDRA basket in Appendix.. Serious infection will be provided per 100 subject-year by treatment group during the double blind period. The patient-years will be based on the double blind period for safety analysis (see section 5.2). The rate per 100 subject-years by treatment group (along with the 95% CI) will be calculated for serious infections.

The number of serious infections per 100 subject-years is calculated as:

Total number of serious infections / Total number of subject-years ×100

The 95% CI for the number of serious infections per 100 subject-years is calculated as follows:

Exact lower 95% confidence limit = chisq (p = 0.025, df = 2 Y) / (2T)

Exact upper 95% confidence limit = chisq [p = 0.975, df = 2(Y + 1)] / (2T)

where Y is the total number of serious infections, T is total number of subject-years at risk and chisq (p,df) is the quantile of the upper tail probability of the X2 distribution on df degrees of freedom. This approach has the advantage of providing an estimate for the upper 95% confidence limit even when the total number of serious infections is zero.

The following summary tables will be provided.

- A summary of serious infection by SOC and PT.
- Rates of serious infections by 100 patient-years.
- A by-subject listing of Infections.
- A by-subject listing of Opportunistic Infections.

5.11.6 Anaphylaxis

Anaphylaxis is defined by MedDRA SMQ “Anaphylactic reaction - Narrow” and will be listed.

- A by-subject listing of Anaphylaxis.

5.11.7 IRR and ISR

IRR in CRF selected AE (IRR) page will be summarized. ISR flagged as “Injection site reaction” in CRF selected AE (IRR) or general AE page will be summarized. The following summary tables will be provided:

- A summary of IRRs.
- A summary of ISRs by SOC and PT.
- A by-subject listing of all IRRs.
- A by-subject listing of all ISRs.

5.11.8 Safety evalutions for the Adolescent population

The following analyses will be provided for the Adolescent population:

- A by-subject listing of all AESI.
- A by-subject listing of all SAE.
- A by-subject listing of all IRRs.
- A by-subject listing of all Infections.
- A by-subject listing of C-SSRS.

5.11.9 Clinical Laboratory Evaluation

For continuous laboratory measurements including hematology, clinical chemistry, and urinalysis, summary using descriptive statistics of the actual values and their change from baseline will be presented by treatment group at each visit. The laboratory tests to be performed are presented in Table 4-4.

When analyzing categorical data, the number and percentage of subjects in each category will be presented. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-baseline status when compared to their baseline status.

A subject data listing will be provided for all laboratory data. Values outside the normal range will be flagged within the listing. A subject data listing will also be provided for all treatment emergent marked laboratory abnormalities (see Section 7.1).

The following summaries, listings and figures will be provided:

- A summary of each laboratory parameter in Table 4-4 and change from baseline will be provided by visit.
- A shift table based on the normal range for each laboratory parameter will be presented by double-blind period endpoint value relative to baseline by treatment group.
- A by-subject listing of laboratory parameters.

The summaries above will be provided by treatment group.

Table 4-4 Laboratory measurements

Hematology	Clinical chemistry	Urinalysis	Complement
Hematocrit Hemoglobin International normalized ratio Platelet count Red blood cell (RBC) count WBC count Absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells)	Calcium Phosphorus Serum electrolytes (sodium, potassium, chloride) Ferritin Albumin Total serum protein Blood urea nitrogen (BUN) Creatinine Uric acid Alkaline phosphatase AST ALT GGT Total bilirubin Fibrinogen	Glucose Protein Urinary occult blood Urobilinogen	Complement tests (C3, C4 and CH50)

	Lactate dehydrogenase (LDH) Total cholesterol Low density lipoprotein (LDL) cholesterol High density lipoprotein (HDL) cholesterol Triglycerides Creatine kinase (CK)		

5.11.10 Electrocardiograms

For quantitative ECG measurements (heart rate, PR interval, QRS duration, QT interval, and corrected QT intervals using Bazett and Fridericia correction methods), values during the double-blind period will be presented by treatment group for all visits.

The Bazett corrected QT (QTcB) will be calculated as

$QTcB=QT/RR^{0.5}$, where RR = 60/HR.

The Fridericia corrected QT (QTcF) will be calculated as

$QTcF=QT/RR^{0.33}$, where RR = 60/HR.

The following summaries and listings will be provided:

- A summary of 12-lead by treatment group at each specified visit.
- The number and percentage of subjects with a QTc (using Bazett and Fridericia corrected) of ≤450ms, >450 to ≤480ms, >480 to ≤500ms, and >500ms will be summarized by treatment group at each specified visit.
- The number and percentage of subjects with a QTc (using Bazett and Fridericia corrected) of an increase from baseline of >0 to ≤30ms, >30 to ≤60ms, and >60ms will be summarized by treatment group at each specified visit.
- The number and percentage of subjects with PR interval values ≤120ms, >120 to ≤220ms, and >220ms, and the number and percentage of subjects with QRS interval values ≤60ms, >60 to ≤120ms, and >120ms will be presented by treatment group at each specified visit.
- The number and percentage of subjects with abnormal ECG findings at Visit 1, and the number and percentage of subjects in the SAF with an abnormal ECG after the start of dose of study medication drug will be summarized by visit and treatment group in separate tables. Subjects with a clinically relevant abnormal ECG as determined by the investigator will be listed.

- A summary of incidence of treatment-emergent abnormality 12-lead ECG findings after start of study drug by treatment group.
- A by-subject listing of abnormal 12-lead ECG data will be provided.

5.11.11 Vital Signs, Physical Findings and Other Observations Related to Safety

Noninvasive pulse rate, temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured at visits with the subject in a sitting position after at least 10 minutes at rest, according to the tabular schedule of study procedures in the protocol. Summary statistics of the actual measurement and their changes from baseline will be presented by treatment group at each specified visit.

In addition, summary statistics for the actual value and change from baseline will be presented by treatment group for all visits during the double-blind period.

Abnormal vital signs will be summarized by treatment group for double-blind and extension period.

Abnormal vital sign criteria as follows:

- diastolic blood pressure [DBP]: <50, >90, >100 mmHg
- systolic blood pressure [SBP]: <90, >140, >160 mmHg
- pulse rate [PR]: <60, >100 bpm
- Temperature: <36.0, >38.0

The following summaries and listings will be provided:

- A summary of pulse rates, temperature, blood pressure and change from baseline by treatment group and visit.
- The number and percentage of subjects with abnormal vital signs during double-blind period and extension period by treatment group.
- A by-subject listing of vital signs.

5.12 Pharmacokinetics and Pharmacodynamics

The serum SA237 concentrations will be reported using the PK-PPS. The PD variables (IL-6, sIL-6R, hsCRP, anti-AQP4Ab, plasmablast) will be reported using the SAF population.

To determine the concentrations of SA237, serum samples will be drawn at various time points throughout the study. At Week 0, blood specimens for PK and PD samples will be collected prior to first dose administration of study drug (blank value). At other visits, PK and PD samples will be collected along with hematology samples at any time prior to study drug administration according to the Schedule of Study assessments.

To support the Japanese BLA, the following reports will be produced. Concentration for SA237 and PD variables in serum will be listed and summarized using descriptive statistics (including geometric mean and CV%, arithmetic mean and SD, median, observed maximums and minimums, and sample size). Arithmetic mean ± SD serum concentration-

time profile and combined all subjects serum concentration-time profiles (spaghetti plot) will be plotted using linear and semi-log scale. In addition, individual serum concentration-time profile will be plotted for each subjects using linear and semi-log scale.

Concentration for SA237 and PD variables (absolute values as well as change from baseline) in serum will be summarized using descriptive statistics and arithmetic mean ± SD serum concentration-time profile will be plotted by following subgroup using linear scale.

Samples that were excluded from the summary statistics will be marked in the listing.

Summary tables, figures, and listings of SA237 concentration and PD variables will be provided as follows:

- Summaries of concentrations of SA237 by visit will be presented by age category, Japanese/non-Japanese, relapse/no-relapse, ADA status, and overall.
- Summary of concentration of IL-6, sIL-6R, and hsCRP by visit will be presented by age category, Japanese/non-Japanese, relapse/no-relapse and overall in each of treatment group.
- Summary of titer for anti AQP4 antibody status, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), and Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%) and CD19+ (cells/uL)) by visit will be presented by NMO/NMOSD and AQP4 Status, relapse/no-relapse and overall in each of treatment group.

  *Plasmablast and CD19+ cells will be calculated by following equation

  - Plasmablasts (cells/uL) = CD45+Abs * Plasmablasts/CD45+ (%)
  - CD19+ (cells/uL) = CD45+Abs * CD19+/CD45+ (%)
- A by-subject listing of concentration for SA237 in serum.
- A by-subject listing of IL-6, sIL-6R, and hsCRP
- A by-subject listing of anti-AQP4 antibody (positive/negative and titer)
- Plasmablast (Plasmablasts/CD19+(%), Plasmablasts/CD45+(%), and Plasmablast (cells/uL)), and CD19+ cells (CD19+/CD45+(%) and CD 19+ (cells/uL))
- A by-subject spaghetti plot of concentration for SA237 in serum by subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) using linear scale and overall using linear and semi log scale.
- A by-subject spaghetti plot of the absolute value and the change from baseline for concentration of IL-6, sIL-6R, and hsCRP by treatment group using linear and semi log scale.

- A by-subject spaghetti plot of the absolute value for concentration of IL-6, sIL-6R, and hsCRP by subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) in each of treatment group using linear scale
- A by-subject spaghetti plot of the absolute value for concentration of IL-6, sIL-6R, and hsCRP by treatment group in each subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) using linear scale
- A by-subject spaghetti plot of the absolute value and the change from baseline for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), and Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%), and CD19+ (cells/uL)) by treatment group using linear and semi-log scale
- A by-subject spaghetti plot of the absolute value for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), and Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%), and CD19+ (cells/uL)) by subgroup (NMO/NMOSD and AQP4 Status, relapse/no-relapse) in each of treatment group using linear scale.
- A by-subject spaghetti plot of the absolute value for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), and Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%), and CD19+ (cells/uL)) by treatment group in each subgroup (NMO/NMOSD and AQP4 Status, relapse/no-relapse) using linear scale.
- An Arithmetic mean ± SD plot of concentration for SA237 in serum by subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) using linear scale and overall using linear and semi log scale.
- An Arithmetic mean ± SD plot of the absolute value and the change from baseline for concentration of IL-6, sIL-6R, and hsCRP by treatment group using linear and semi-log scale.
- An Arithmetic mean ± SD plot of the absolute value for concentration of IL-6, sIL-6R, and hsCRP by subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) in each of treatment group using linear scale.
- An Arithmetic mean ± SD plot of the absolute value for concentration of IL-6, sIL-6R, and hsCRP by treatment group in each subgroup (age category, Japanese/non-Japanese, relapse/no-relapse, ADA status) using linear scale
- An Arithmetic mean ± SD plot of the absolute value and the change from baseline for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%) and CD19+ (cells/uL)) by treatment group using linear and semi-log scale

- An Arithmetic mean ± SD plot of the absolute value for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%) and CD19+ (cells/uL)) by subgroup (NMO/NMOSD and AQP4 Status, relapse/no-relapse) in each of treatment group using linear scale
- An Arithmetic mean ± SD plot of the absolute value for titer of anti-AQP4 antibody, Plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), Plasmablasts (cells/uL)), and CD19+ cells (CD19+/CD45+ (%) and CD19+ (cells/uL)) by treatment group in each subgroup (NMO/NMOSD and AQP4 Status, relapse/no-relapse) using linear scale.
- A by-subject listing of actual doses, date and time of sampling, visit, relative day, and the accession number.
- Scatter plot of anti-AQP4 antibody titer versus plasmablast (Plasmablasts/CD19+ (%), Plasmablasts/CD45+ (%), Plasmablasts (cells/uL)) will be presented at Weeks 0, 2 and 4, 8, 12, 24, and Q24W. When the data of anti-AQP4 antibody is negative, put "1" as a titer for negative samples and replace to "BLQ".
- Scatter plots of serum SA237 concentration versus body weight at weeks 2, 4, Q4W respectively.

5.13 Immunogenicity

ADA subgroup using confirmatory sample status are defined as below.

- ADA negative subjects: subjects without positive ADA during study. If sample at baseline is missing and no sample after the the baseline is positive, the subject is defined as " ADA negative subjects".
- ADA unaffected subjects: subjects who have pre-existing ADA (POSITIVE at baseline) that was NOT boosted to a higher level after the post dose. "NOT boosted to a higher level" means that ADA titer after the baseline is <fourfold than the ADA titer at baseline.
- Treatment-boosted ADA subjects: subjects who have pre-existing ADA that was boosted to a higher level at least one time point after baseline "Boosted to a higher level" means as follow
  1) ADA titer after the baseline is greater fourfold than the ADA titer at baseline
- Treatment-induced ADA subjects: subjects who have positive ADA not at baseline but after the baseline. If sample at baseline is missing and at least one sample after the baseline is positive, the subject is defined as " Treatment-induced ADA subjects"

The immunogenicity will be analyzed using the SAF population.

- The numbers and proportions of subjects with positive ADA at baseline will be presented by treatment group and overall.
- The numbers and proportions of ADA negative subjects, ADA unaffected subjects, treatment-boosted ADA subjects, and treatment-induced ADA subjects will be

summarized. The numbers and proportions of transient ADA and persistent ADA will be summarized in the treatment-induced ADA subjects.

Transient ADA: 1) Treatment-induced ADA detected only at one sampling time point (excluding the last sampling time point) during the study or 2) treatment-induced ADA detected at two or more sampling time points during the study, where the period between first and last ADA-positive sampling time points is less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA: 1) Treatment-induced ADA detected at two or more sampling time points during the study, where the period between first and last ADA-positive sampling time points is 16 weeks or longer or 2) where the period between first and last ADA-positive sampling time points is less than 16 weeks, and the subject's last sampling time point is ADA-positive or 3) treatment-induced ADA detected only at the last sampling time point.

- The numbers and proportions of patients with positive/negativeanti-SA237 antibody and neutralizing antibody will be presented at Week 0 and Q4W in SA237 group by visit.
- A by-subject listing of anti-SA237 antibody (confirmatory judgment (positive/negative), titer, ratio of peak titer/baseline titer, and ADA subgroup), neutralizing judgment (positive/negative)), and adverse events in the subject having anti-SA237 antibody at least once at any point in time.

5.14 Determination of Sample Size

Approximately 70 subjects need to be recruited and randomized in a 1:1 ratio to the two treatment groups (SA237 and placebo). The sample size considerations are based on the following assumptions:

- A two-sided log-rank test
- 80% power at the 5% significance level
- A 66.5% reduction in the risk of relapse, i.e. the TFR hazard ratio of SA237 over placebo is 0.335
- TFR in the placebo arm following an exponential distribution, with hazard rate for one year $h(t) = 0.4184$
- A 2-year dropout rate of 10%

Based on the 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 subject. The maximum accrual rate is estimated to be approximately 8 subjects per month, after the FPI plus 8 months of ramp up. The 70 subjects enrolled over one year and followed for an additional one and a half year will provide 26 TFR events. The primary analysis will be performed once 26 TFR events have been observed. Sponsor will conduct blind review during the double-blind period and might take appropriate action based on blind review.

Since the annualized relapse rate (ARR) is the number of relapse counts observed when every subject is observed for a year and suppose that the distribution follows a Gamma-Poisson distribution and that the mean and variance ratio (variance / mean) is a constant value of √2. The ratio was estimated using MS trials' data[1, 2)] because there are no approved medications for NMO.

Because the mean ARR of NMO subjects is estimated at 0.753[3)] and eligibility criterion 2 says more than one ARR subjects are selected, we calculate the zero-truncated mean of the Gamma-Poisson distribution with the mean of 0.75 and the mean and variance ratio of √2, then the baseline ARR is estimated at 1.6. The two phase III 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 for one year of 0.4184 in placebo group.

According to tocilizumab case report in NMO subjects, 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 subjects and the hazard ratio between rituximab and azathioprine (0.38) is the comparison with an active control, then we consider the SA237 hazard ratio compared to placebo should exist between 0.25 and 0.38. So we have set the SA237 hazard ratio compared with placebo at 0.335.

6 REFERENCES

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7 APPENDIX

7.1 Laboratory Data Conversion and Transformation Rules

- Conversion to Système International (SI) Units
  Laboratory data should be stored on the database in the units in which they were originally delivered by the laboratory.
  For analysis and reporting purposes, the data will be converted to SI units to allow the comparison of data delivered in different original units.
  Results that include inequality sign will be converted into a numeric form removing inequality sign.
  Results that cannot be converted into an expected numeric form nor interpreted, such as alphabetic entries like “adequate”, will usually not be further processed, but displayed in patient listings.

- Marked Laboratory Abnormalities
  For each laboratory test, a Marked Abnormality Range has been defined. A value outside of this range is considered to be potentially clinically relevant. This Marked Abnormality Range is wider than the Reference Range.
  In addition, for each laboratory test, a percentage change, as an increase and/or decrease, has been defined which represents a clinically relevant change from baseline.
  A Marked Abnormality is therefore defined as a test result:
  which is outside of the Marked Abnormality Range,
  and
  which also represents a clinically relevant change from baseline of at least the designated amount
  during or within 30 days after end of trial treatment.
  Baseline is taken as the last valid value before starting treatment. If no baseline is available, the midpoint of the Reference Range will be substituted for processing purposes for determination of Marked Abnormalities.
  For urinalysis a missing baseline value will be replaced by 0 (zero).
  NOTE: For calculating means and mean changes over time, missing values will not be included. If no baseline is available, no change from baseline will be calculated.
  Values above and below the Reference Range are flagged on the listing by H and L, respectively. Marked Abnormalities are flagged by HH or LL.

- Reference Ranges

Laboratory Test Class	Laboratory Test	SI Unit	Reference Range [1,2]	Marked Abnormality Range	Direction of Change	Clinically Relevant Change from Baseline
Hematology	**Hematocrit**	fraction	M: 0.37 – 0.49 F : 0.36 – 0.46 [b]	0.31 – 0.56	Increase Decrease	≥ 15% ≥ 15%
	Hemoglobin	g/L	M: 130 – 180 F : 120 – 160 [b]	110 – 200	Increase Decrease	≥ 15% ≥ 15%
	Leukocytes (WBC)	10^9/L	4.5 – 11.0	3.0 – 18.0	Increase Decrease	≥ 30% ≥ 30%
	Platelets	10^9/L	150 – 350	100 – 550	Increase Decrease	≥ 50% ≥ 30%
	Mean corpuscular hemoglobin (MCH)	pg/cell	25.0 – 35.0	21.2 – 40.2	Increase Decrease	≥ 15% ≥ 15%
	Mean corpuscular hemoglobin concentration (MCHC)	g/L	310 – 370	260 – 430	Increase Decrease	≥ 15% ≥ 15%
	Mean corpuscular volume (MCV)	fL	78 – 100	66 – 115	Increase Decrease	≥ 15% ≥ 15%
	Erythrocytes (RBC)	10^{12}/L	M: 4.50 – 5.30 F : 4.10 – 5.10 [b]	3.80 – 6.10	Increase Decrease	≥ 15% ≥ 15%
Differentials	Bands	10^9/L	0 – 0.70	0 – 1.40	Increase	≥ 30%
	Bands	fraction	0 – 0.05	0 - 0.10	Increase	≥ 30%
	Basophils	10^9/L	0 – 0.20	0 – 0.40	Increase	≥ 100%
	Basophils	fraction	0 – 0.03	0 – 0.06	Increase	≥ 100%
	Lymphocytes	10^9/L	1.00 – 4.80	0.70 – 7.60	Increase Decrease	≥ 30% ≥ 30%
	Lymphocytes	fraction	0.16 – 0.46	0.10 – 0.72	Increase Decrease	≥ 30% ≥ 30%
	Monocytes	10^9/L	0 – 0.80	0 – 1.70	Increase	≥ 100%
	Monocytes	fraction	0 – 0.11	0 – 0.22	Increase	≥ 100%
	Neutrophils	10^9/L	1.80 – 7.70	1.50 – 9.25	Increase Decrease	≥ 20% ≥ 20%
	Neutrophils	fraction	0.45 – 0.75	0.37 – 0.90	Increase Decrease	≥ 20% ≥ 20%
	Eosinophils	10^9/L	0 – 0.45	0 – 0.90	Increase	≥ 100%
	Eosinophils	fraction	0 – 0.08	0 – 0.16	Increase	≥ 100%
Coagulation	Prothrombin Time, normalized ratio (PTINR)	ratio	0.70 – 1.30	≤ 2.00	Increase	≥ 30%
	Partial Thromboplastin Time, activated (PTT)	seconds	22.1 – 34.1	0 – 45	Increase	≥ 40%
	Fibrinogen	g/L	1.75 – 4.00 [a]	≥ 1.30	Decrease	≥ 30%
	Antithrombin 3	fraction	0.80 - 1.30	≥ 0.60	Decrease	≥ 20%
Heart Function	**ASAT (SGOT)**	U/L	M: 0 – 40 [c] F : 0 – 25 [b]	0 – 80	Increase	≥ 50%
	Lactic Dehydrogenase (LDH)	U/L	0 – 210 [c]	0 – 420	Increase	≥ 50%
	Creatine phosphokinase (CPK) total	U/L	M: 60 – 400 [a] F : 40 – 150 [b]	≤ 800	Increase	≥ 50%
	CPK (MB Fraction)	µg/L	0 – 5 [c]	≤ 5	Increase	0%

Laboratory Test Class	Laboratory Test	SI Unit	Reference Range [1,2]	Marked Abnormality Range	Direction of Change	Clinically Relevant Change from Baseline
Liver Function	**Alkaline Phosphatase**	U/L	M: 0 – 115 [c] F : 0 – 100 [b]	0 – 220	Increase	≥ 50%
	ALAT (SGPT)	U/L	M: 0 – 55 [c] F : 0 – 30 [b]	0 – 110	Increase	≥ 50%
	Total Bilirubin	µmol/L	0 – 17 [c]	0 – 34	Increase	≥ 75%
	Direct bilirubin	µmol/L	0 – 7 [c]	0 – 14	Increase	≥ 75%
	γ-GTP	U/L	M: 0 – 94 [c] F : 0 – 70 [b]	0 – 190	Increase	≥ 50%
Renal Function	**BUN**	mmol/L	2.9 – 8.9	0 – 14.3	Increase	≥ 50%
	Creatinine	µmol/L	0 – 133	0 – 154	Increase	≥ 50%
Thyroid Function	Triiodothyronine (T3)	nmol/L	0.92 – 2.78	0.74 - 3.30	Increase Decrease	≥ 20% ≥ 20%
	Thyroxine (T4)	nmol/L	58 – 140	30 - 164	Increase Decrease	≥ 20% ≥ 20%
	Free T4	pmol/L	10 – 36	5 – 40	Increase Decrease	≥ 20% ≥ 20%
	TSH	mU/L	0 – 5.0 [c]	0 – 10.0	Increase	≥ 30%
Protein	**Albumin**	g/L	35.0 – 55.0	≥ 30	Decrease	≥ 20%
	Total Protein	g/L	60 – 80	55 – 87	Increase Decrease	≥ 20% ≥ 20%
Lipid Chemistry	Triglycerides (fasting)	mmol/L	0.45 – 1.69	0 – 2.83	Increase	≥ 100%
	Cholesterol	mmol/L	0 – 6.18	0 – 8.30	Increase	≥ 30%
	LDL-Cholesterol	mmol/L	0 – 4.13	0 – 5.4	Increase	≥ 30%
	HDL-Cholesterol	mmol/L	≥ 0.91	≥ 0.65	Decrease	≥ 30%
Electrolytes	**Chloride**	mmol/L	100 – 108	95 – 115	Increase Decrease	≥ 7% ≥ 7%
	Potassium	mmol/L	3.4 – 4.8	2.9 – 5.8	Increase Decrease	≥ 20% ≥ 20%
	Sodium	mmol/L	135 – 145	130 – 150	Increase Decrease	≥ 7% ≥ 7%
	Bicarbonate	mmol/L	22 – 26	18 – 28	Increase Decrease	≥ 20% ≥ 20%
	Calcium	mmol/L	2.10 – 2.60	2.00 – 2.90	Increase Decrease	≥ 10% ≥ 10%
	Phosphorus inorganic	mmol/L	0.84 – 1.45	0.75 – 1.60	Increase Decrease	≥ 30% ≥ 30%
	Blood Glucose (fasting)	mmol/L	3.90 – 6.10	2.80 – 11.10	Increase Decrease	≥ 75% ≥ 75%
	Uric Acid	µmol/L	M: 214 – 506 F: 137 – 393 [b]	0 – 600	Increase	≥ 50%
Urinalysis Dipstick	**Proteinuria**	1 to 6	1 – 3	1 – 3	Increase	≥ 2 units [d]
	Glycosuria	1 to 6	1 – 3	1 – 3	Increase	≥ 2 units [d]
	Hematuria	1 to 6	1 – 3	1 – 3	Increase	≥ 2 units [d]
	Leukocyturia	1 to 6	1 – 3	1 – 3	Increase	≥ 2 units [d]
Urinalysis Microscopic [e]	Casts	/HPF	0 – 2	0 – 2	Increase	≥ 2 units
	WBCs	/HPF	0 – 2	0 – 2	Increase	≥ 2 units
	RBCs	/HPF	0 – 2	0 – 2	Increase	≥ 2 units
	Urinary spec. gravity [f]	No unit	1.001 – 1.035	not defined	not defined	not defined

a) For reporting and analyzing, the data are linearly transformed to the Reference Range according to the formula below.
b) For reporting and analyzing, the data for females are linearly transformed to the Reference Range

for males according to the formula below.

c) For reporting and analyzing, the data are linearly transformed to the Reference Range according to the formula below.
To prevent transformed values becoming negative, the investigator lower limit is replaced by zero.

d) Note that baseline values of 5 and 6 do not allow a subsequent clinically relevant change.

e) To be done if dipstick is positive and microscopic examination needed for specific quantitation/confirmation.

f) Specific gravity is a measurement of solute load in the urine. It is increased markedly by both proteinuria and glycosuria.
A value > 1.030 in the absence of proteinuria or glycosuria is most commonly caused by radiographic contrast. In volume depletion specific gravity is usually >1.020. A fixed value of 1.010 (isosthenuria) is characteristic of chronic renal impairment. A fixed value of 1.000 - 1.005 occurs in diabetes insipidus. Specific gravity has an important influence on urine microscopy because cells lyse more rapidly in dilute urine, which may lead to considerable inaccuracies in quantitation of cells. Cells swell and rupture in dilute urine and shrink in concentrate urine. Casts are rarely seen at low urine osmolality [5].
Conclusion: increase or decrease in urine specific gravity clinically relevant in context with other parameters from urinalysis.

Note: The following modification is applied to creatinine and TSH as needed.
Creatinine: The transformation of data described above as c) is applied for only Japanese patients study as needed.
TSH: The lower limit of the reference range and Marked Abnormal Range are modified and Clinically Relevant Change from Baseline for decrease is provided as needed.

- Formula for Linear Transformation

  $$R_T = S_L + [(R_U - I_L) / (I_H - I_L)]*(S_H - S_L)$$

  R_T : transformed value

  R_U : untransformed value

  I_L : I_H investigator limits, low and high

  S_L : S_H reference limits, low and high

  For female to male transformation replace I_L, I_H by the reference limits for female, and S_L, S_H by the reference limits for male.

7.2 MedDRA basket

Opportunistic infections

Meningomyelitis herpes	Capnocytophaga test positive	Eye infection toxoplasmal	Histoplasmosis disseminated	Mycobacterium ulcerans infection	Pulmonary trichosporonosis
Abscess fungal	Central nervous system fungal infection	Eye infection viral	Human anaplasmosis	Mycotic corneal ulcer	Pulmonary tuberculoma
Acid fast bacilli infection	Central nervous system viral infection	Female genital tract tuberculosis	Human bocavirus infection	Mycotic endophthalmitis	Pulmonary tuberculosis
Acinetobacter bacteraemia	Cerebral aspergillosis	Flavobacterium infection	Human ehrlichiosis	Myocarditis mycotic	Pyelonephritis fungal
Acinetobacter infection	Cerebral candidiasis	Focal epithelial hyperplasia	Human herpesvirus 8 infection	Myocarditis toxoplasmal	Q fever
Acute haemorrhagic conjunctivitis	Cerebral fungal infection	Fungaemia	Indeterminate leprosy	Nasal herpes	Raoultella ornithinolytica infection
Acute hepatitis B	Cerebral toxoplasmosis	Fungal abscess central nervous system	Infection in an immunocompromised host	Necrotising fasciitis fungal	Renal tuberculosis
Acute hepatitis C	Cervix warts	Fungal cystitis	Intestinal tuberculosis	Necrotising herpetic retinopathy	Respiratory moniliasis
Acute pulmonary histoplasmosis	Chromoblastomycosis	Fungal endocarditis	Isosporiasis	Neurocryptococcosis	Respiratory tract infection fungal
Adrenal gland tuberculosis	Chronic pulmonary histoplasmosis	Fungal labyrinthitis	JC virus granule cell neuronopathy	Neutropenic infection	Retinitis histoplasma
Aeromonas infection	Coccidioides encephalitis	Fungal oesophagitis	JC virus infection	Neutropenic sepsis	Retinitis viral
Aeromonas test positive	Coccidioidomycosis	Fungal peritonitis	JC virus test	Nocardia sepsis	Rhodococcus infection
Alcaligenes infection	Colitis herpes	Fungal pharyngitis	JC virus test positive	Nocardia test positive	Rhodococcus test positive
Allescheriosis	Conjunctivitis tuberculous	Fungal retinitis	Joint tuberculosis	Nocardiosis	Salpingitis tuberculous
Alternaria infection	Coxiella infection	Fungal sepsis	Kaposi's sarcoma	Oesophageal candidiasis	Scedosporium infection
Amoebiasis	Creutzfeldt-Jakob disease	Fungal tracheitis	Kaposi's sarcoma AIDS related	Oesophageal tuberculosis	Sepsis pasteurella
Amoebic brain abscess	Cronobacter infection	Fusarium infection	Kaposi's varicelliform eruption	Ophthalmic herpes simplex	Shewanella algae bacteraemia
Amoebic colitis	Cronobacter necrotising enterocolitis	Gastritis fungal	Keratitis fungal	Ophthalmic herpes zoster	Sinusitis aspergillus

Amoebic dysentery	Cryptococcal cutaneous infection	Gastritis herpes	Keratitis viral	Opportunistic infection	Sinusitis fungal
Amoebic lung abscess	Cryptococcal fungaemia	Gastroenteritis cryptococcal	Keratouveitis	Oral candidiasis	Sphingomonas paucimobilis infection
Amoebic skin ulcer	Cryptococcosis	Gastroenteritis cryptosporidial	Laryngitis fungal	Oral fungal infection	Spleen tuberculosis
Anal fungal infection	Cryptococcus test	Gastrointestinal candidiasis	Legionella infection	Oral hairy leukoplakia	Splenic candidiasis
Angina gangrenous	Cryptococcus test positive	Gastrointestinal fungal infection	Lepromatous leprosy	Oral herpes	Splenic infection fungal
Angiostrongylus infection	Cryptosporidiosis infection	Genital herpes	Leprosy	Oral tuberculosis	Stenotrophomonas infection
Anogenital warts	Cutaneous coccidioidomycosis	Genital herpes simplex	Leptotrichia infection	Oro-pharyngeal aspergillosis	Stenotrophomonas sepsis
Anorectal human papilloma virus infection	Cutaneous tuberculosis	Genital herpes zoster	Leuconostoc infection	Oropharyngeal candidiasis	Stomatococcal infection
Anti-JC virus antibody index	Cytomegalovirus chorioretinitis	Granulicatella bacteraemia	Listeria encephalitis	Oropharyngitis fungal	Stomatococcus test positive
Arthritis fungal	Cytomegalovirus colitis	Granulicatella infection	Listeria sepsis	Orthopox virus infection	Strongyloidiasis
Aspergilloma	Cytomegalovirus duodenitis	Hepatic candidiasis	Listeria test positive	Osteomyelitis blastomyces	Superinfection fungal
Aspergillosis oral	Cytomegalovirus enteritis	Hepatic infection fungal	Listeriosis	Osteomyelitis fungal	Superinfection mycobacterial
Aspergillus infection	Cytomegalovirus enterocolitis	Hepatitis B	Lower respiratory tract herpes infection	Otitis media fungal	Systemic candida
Aspergillus test	Cytomegalovirus gastritis	Hepatitis C	Lower respiratory tract infection fungal	Pancreatitis fungal	Systemic mycosis
Aspergillus test positive	Cytomegalovirus gastroenteritis	Hepatitis toxoplasmal	Lower respiratory tract infection viral	Pantoea agglomerans infection	Thyroid tuberculosis
Atypical mycobacterial infection	Cytomegalovirus gastrointestinal infection	Hepatosplenic candidiasis	Lupus vulgaris	Paracoccidioides infection	Tonsillitis fungal
Atypical mycobacterial lower respiratory tract infection	Cytomegalovirus gastrointestinal ulcer	Herpes oesophagitis	Lymph node tuberculosis	Parasitic encephalitis	Toxoplasmosis
Atypical mycobacterial lymphadenitis	Cytomegalovirus hepatitis	Herpes ophthalmic	Lymphadenitis fungal	Parvimonas infection	Tuberculoid leprosy
Atypical mycobacterial pneumonia	Cytomegalovirus infection	Herpes pharyngitis	Male genital tract tuberculosis	Parvimonas micra infection	Tuberculoma of central nervous system

Atypical mycobacterium pericarditis	Cytomegalovirus mucocutaneous ulcer	Herpes sepsis	Meningitis aspergillus	Peliosis hepatis	Tuberculosis
Atypical pneumonia	Cytomegalovirus myelomeningoradiculitis	Herpes simplex	Meningitis candida	Penicillium infection	Tuberculosis bladder
Babesiosis	Cytomegalovirus myocarditis	Herpes simplex cervicitis	Meningitis coccidioides	Pericarditis fungal	Tuberculosis gastrointestinal
Bacillary angiomatosis	Cytomegalovirus oesophagitis	Herpes simplex colitis	Meningitis cronobacter	Pericarditis histoplasma	Tuberculosis liver
Balamuthia infection	Cytomegalovirus pancreatitis	Herpes simplex encephalitis	Meningitis cryptococcal	Pericarditis tuberculous	Tuberculosis of central nervous system
BK virus infection	Cytomegalovirus pericarditis	Herpes simplex gastritis	Meningitis exserohilum	Peritoneal candidiasis	Tuberculosis of eye
Blastocystis infection	Cytomegalovirus syndrome	Herpes simplex hepatitis	Meningitis fungal	Peritoneal tuberculosis	Tuberculosis of genitourinary system
Blastomycosis	Cytomegalovirus test	Herpes simplex meningitis	Meningitis herpes	Phaehyphomycosis	Tuberculosis of intrathoracic lymph nodes
Bone tuberculosis	Cytomegalovirus test positive	Herpes simplex meningoencephalitis	Meningitis histoplasma	Pharyngeal abscess	Tuberculosis of peripheral lymph nodes
Borderline leprosy	Cytomegalovirus urinary tract infection	Herpes simplex meningomyelitis	Meningitis listeria	Pneumocystis jirovecii infection	Tuberculosis ureter
Botryomycosis	Cytomegalovirus viraemia	Herpes simplex necrotising retinopathy	Meningitis toxoplasmal	Pneumocystis jirovecii pneumonia	Tuberculous abscess central nervous system
Bovine tuberculosis	Dengue fever	Herpes simplex oesophagitis	Meningitis tuberculous	Pneumocystis test positive	Tuberculous endometritis
Brachyspira infection	Disseminated Bacillus Calmette-Guerin infection	Herpes simplex otitis externa	Meningoencephalitis herpes simplex neonatal	Pneumonia blastomyces	Tuberculous laryngitis
Brevibacterium infection	Disseminated cryptococcosis	Herpes simplex pharyngitis	Meningoencephalitis herpetic	Pneumonia cryptococcal	Tuberculous pleurisy
Bronchitis fungal	Disseminated cytomegaloviral infection	Herpes simplex pneumonia	Meningoencephalitis viral	Pneumonia cytomegaloviral	Tuberculous tenosynovitis
Bronchopulmonary aspergillosis	Disseminated tuberculosis	Herpes simplex sepsis	Methylobacterium infection	Pneumonia fungal	Upper respiratory fungal infection
Burkholderia cepacia complex infection	Disseminated varicella zoster vaccine virus infection	Herpes simplex visceral	Microsporidia infection	Pneumonia herpes viral	Urinary tract infection fungal

Burkholderia cepacia complex sepsis	Ear tuberculosis	Herpes virus infection	Miliary pneumonia	Pneumonia legionella	Variant Creutzfeldt-Jakob disease
Burkholderia gladioli infection	Encephalitis cytomegalovirus	Herpes zoster	Mucocutaneous candidiasis	Pneumonia toxoplasmal	Varicella
Burkholderia infection	Encephalitis fungal	Herpes zoster cutaneous disseminated	Mucormycosis	Polyomavirus-associated nephropathy	Varicella keratitis
Burkholderia mallei infection	Encephalitis post varicella	Herpes zoster disseminated	Mycetoma mycotic	Porphyromonas infection	Varicella zoster gastritis
Burkholderia pseudomallei infection	Endocarditis candida	Herpes zoster infection neurological	Mycobacterial infection	Presumed ocular histoplasmosis syndrome	Varicella zoster oesophagitis
Burkholderia test positive	Endocarditis histoplasma	Herpes zoster meningitis	Mycobacterial peritonitis	Progressive multifocal leukoencephalopathy	Varicella zoster pneumonia
Candida endophthalmitis	Endocarditis Q fever	Herpes zoster meningoencephalitis	Mycobacterium abscessus infection	Progressive vaccinia	Varicella zoster virus infection
Candida infection	Enterocolitis fungal	Herpes zoster meningomyelitis	Mycobacterium avium complex immune restoration disease	Prostatitis tuberculous	Viral keratouveitis
Candida osteomyelitis	Epididymitis blastomyces	Herpes zoster necrotising retinopathy	Mycobacterium avium complex infection	Pseudallescheria infection	Viral myelitis
Candida pneumonia	Epididymitis tuberculous	Herpes zoster oticus	Mycobacterium chelonae infection	Pseudallescheria sepsis	Viral oesophagitis
Candida retinitis	Exserohilum infection	Herpes zoster pharyngitis	Mycobacterium fortuitum infection	Pseudomonal sepsis	Viral sepsis
Candida sepsis	Extrapulmonary tuberculosis	Histoplasmosis	Mycobacterium kansasii infection	Pseudomonas aeruginosa meningitis	Viral uveitis
Capnocytophaga infection	Eye infection fungal	Histoplasmosis cutaneous	Mycobacterium marinum infection	Pulmonary mycosis	Yersinia sepsis

7.3 EQ-5D Scoring Algorithm:

This program computes the U.S. preference-weighted index score using self-reported EQ-5D data.
It is presumed that the data set includes the following 5 variables:

Dimension	Variable Name	Range
Mobility	MO	1-3
Self-care	SC	1-3
Usual activities	UA	1-3
Pain/discomfort	PD	1-3
Anxiety/depression	AD	1-3

Where a 1 indicates no problems, a 2 indicates moderate problems, and a 3 indicates severe problems.

To get U.S. EQ-5D index scores, paste data to the first 5 columns and read values from the last colomn.
The index score will not be generated when responses are missing for 1 or more of the 5 dimensions.
If there are more than 5,000 respondents, apply the algorithms for all the variables excepte the first 5 to more lines.

MO	**SC**	**UA**	**PD**	**AD**	m1	s1	u1	p1	a1	m2	s2	u2	p2	a2	d1	i2	i22	i3	i32	pred	full health	**EQ-5D index(US_D1)**
3	3	3	3	3	0	0	0	0	0	1	1	1	1	1	4	0	0	4	16	-0.1090707	-0.109	**-0.1090707**
3	3	2	3	3	0	0	1	0	0	1	1	0	1	1	4	0	0	3	9	-0.0996728	-0.100	**-0.0996728**
3	3	1	3	3	0	0	0	0	0	1	1	0	1	1	3	0	0	3	9	-0.0995382	-0.100	**-0.0995382**
3	3	3	3	2	0	0	0	0	1	1	1	1	1	0	4	0	0	3	9	-0.0402381	-0.040	**-0.0402381**
3	2	3	3	3	0	1	0	0	0	1	0	1	1	1	4	0	0	3	9	-0.0383556	-0.038	**-0.0383556**
3	3	3	3	1	0	0	0	0	0	1	1	1	1	0	3	0	0	3	9	-0.02361	-0.024	**-0.02361**
3	3	2	3	2	0	0	1	0	1	1	1	0	1	0	4	1	1	2	4	-0.0119344	-0.012	**-0.0119344**
3	2	2	3	3	0	1	1	0	0	1	0	0	1	1	4	1	1	2	4	-0.0100519	-0.010	**-0.0100519**
3	1	3	3	3	0	0	0	0	0	1	0	1	1	1	3	0	0	3	9	-0.002608	-0.003	**-0.002608**
3	3	1	3	2	0	0	0	0	1	1	1	0	1	0	3	0	0	2	4	-0.001113	-0.001	**-0.001113**
3	2	1	3	3	0	1	0	0	0	1	0	0	1	1	3	0	0	2	4	0.0007695	0.001	**0.0007695**
3	3	2	3	1	0	0	1	0	0	1	1	0	1	0	3	0	0	2	4	0.0153805	0.015	**0.0153805**
3	3	1	3	1	0	0	0	0	0	1	1	0	1	0	2	0	0	2	4	0.0155151	0.016	**0.0155151**
3	3	3	2	3	0	0	0	1	0	1	1	1	0	1	4	0	0	3	9	0.0300077	0.030	**0.0300077**

3	1	2	3	3	0	0	1	0	0	1	0	0	1	1	3	0	0	2	4	0.0363825	0.036	**0.0363825**
3	1	1	3	3	0	0	0	0	0	1	0	0	1	1	2	0	0	2	4	0.0365171	0.037	**0.0365171**
3	2	3	3	2	0	1	0	0	1	1	0	1	1	0	4	1	1	2	4	0.0493828	0.049	**0.0493828**
3	3	2	2	3	0	0	1	1	0	1	1	0	0	1	4	1	1	2	4	0.0583114	0.058	**0.0583114**
3	3	3	1	3	0	0	0	0	0	1	1	1	0	1	3	0	0	3	9	0.0633035	0.063	**0.0633035**
3	3	1	2	3	0	0	0	1	0	1	1	0	0	1	3	0	0	2	4	0.0691328	0.069	**0.0691328**
3	2	3	3	1	0	1	0	0	0	1	0	1	1	0	3	0	0	2	4	0.0766977	0.077	**0.0766977**
2	3	3	3	3	1	0	0	0	0	0	1	1	1	1	4	0	0	3	9	0.0774663	0.077	**0.0774663**
1	3	3	3	3	0	0	0	0	0	0	1	1	1	1	3	0	0	3	9	0.0838874	0.084	**0.0838874**
3	2	2	3	2	0	1	1	0	1	1	0	0	1	0	4	2	4	1	1	0.0859055	0.086	**0.0859055**
3	1	3	3	2	0	0	0	0	1	1	0	1	1	0	3	0	0	2	4	0.0958172	0.096	**0.0958172**
3	3	2	1	3	0	0	1	0	0	1	1	0	0	1	3	0	0	2	4	0.102294	0.102	**0.102294**
3	3	1	1	3	0	0	0	0	0	1	1	0	0	1	2	0	0	2	4	0.1024286	0.102	**0.1024286**
2	3	2	3	3	1	0	1	0	0	0	1	0	1	1	4	1	1	2	4	0.10577	0.106	**0.10577**
3	1	3	3	1	0	0	0	0	0	1	0	1	1	0	2	0	0	2	4	0.1124453	0.112	**0.1124453**
2	3	1	3	3	1	0	0	0	0	0	1	0	1	1	3	0	0	2	4	0.1165914	0.117	**0.1165914**
3	3	3	2	2	0	0	0	1	1	1	1	1	0	0	4	1	1	2	4	0.1177461	0.118	**0.1177461**
3	2	1	3	2	0	1	0	0	1	1	0	0	1	0	3	1	1	1	1	0.1181005	0.118	**0.1181005**
3	2	3	2	3	0	1	0	1	0	1	0	1	0	1	4	1	1	2	4	0.1196286	0.120	**0.1196286**
1	3	2	3	3	0	0	1	0	0	0	1	0	1	1	3	0	0	2	4	0.1228779	0.123	**0.1228779**
1	3	1	3	3	0	0	0	0	0	0	1	0	1	1	2	0	0	2	4	0.1230125	0.123	**0.1230125**
3	2	2	3	1	0	1	1	0	0	1	0	0	1	0	3	1	1	1	1	0.134594	0.135	**0.134594**
3	3	3	2	1	0	0	0	1	0	1	1	1	0	0	3	0	0	2	4	0.145061	0.145	**0.145061**
3	2	1	3	1	0	1	0	0	0	1	0	0	1	0	2	0	0	1	1	0.1454154	0.145	**0.1454154**
3	1	2	3	2	0	0	1	0	1	1	0	0	1	0	3	1	1	1	1	0.1537135	0.154	**0.1537135**
3	3	2	2	2	0	0	1	1	1	1	1	0	0	0	4	2	4	1	1	0.1542688	0.154	**0.1542688**
3	2	2	2	3	0	1	1	1	0	1	0	0	0	1	4	2	4	1	1	0.1561513	0.156	**0.1561513**
3	3	3	1	2	0	0	0	0	1	1	1	1	0	0	3	0	0	2	4	0.1617287	0.162	**0.1617287**
3	2	3	1	3	0	1	0	0	0	1	0	1	0	1	3	0	0	2	4	0.1636112	0.164	**0.1636112**
3	1	1	3	2	0	0	0	0	1	1	0	0	1	0	2	0	0	1	1	0.1645349	0.165	**0.1645349**
2	3	3	3	2	1	0	0	0	1	0	1	1	1	0	4	1	1	2	4	0.1652047	0.165	**0.1652047**
3	1	3	2	3	0	0	0	1	0	1	0	1	0	1	3	0	0	2	4	0.166063	0.166	**0.166063**
2	2	3	3	3	1	1	0	0	0	0	0	1	1	1	4	1	1	2	4	0.1670872	0.167	**0.1670872**

3	3	3	1	1	0	0	0	0	0	1	1	1	0	0	2	0	0	2	4	0.1783568	0.178	**0.1783568**
3	1	2	3	1	0	0	1	0	0	1	0	0	1	0	2	0	0	1	1	0.1810284	0.181	**0.1810284**
3	1	1	3	1	0	0	0	0	0	1	0	0	1	0	1	0	0	1	1	0.181163	0.181	**0.181163**
1	3	3	3	2	0	0	0	0	1	0	1	1	1	0	3	0	0	2	4	0.1823126	0.182	**0.1823126**
1	2	3	3	3	0	1	0	0	0	0	0	1	1	1	3	0	0	2	4	0.1841951	0.184	**0.1841951**
3	3	1	2	2	0	0	0	1	1	1	1	0	0	0	3	1	1	1	1	0.1864638	0.186	**0.1864638**
3	2	1	2	3	0	1	0	1	0	1	0	0	0	1	3	1	1	1	1	0.1883463	0.188	**0.1883463**
2	3	3	3	1	1	0	0	0	0	0	1	1	1	0	3	0	0	2	4	0.1925196	0.193	**0.1925196**
1	3	3	3	1	0	0	0	0	0	0	1	1	1	0	2	0	0	2	4	0.1989407	0.199	**0.1989407**
3	1	3	1	3	0	0	0	0	0	1	0	1	0	1	2	0	0	2	4	0.1993588	0.199	**0.1993588**
2	3	2	3	2	1	0	1	0	1	0	1	0	1	0	4	2	4	1	1	0.2017274	0.202	**0.2017274**
3	3	2	2	1	0	0	1	1	0	1	1	0	0	0	3	1	1	1	1	0.2029573	0.203	**0.2029573**
2	2	2	3	3	1	1	1	0	0	0	0	0	1	1	4	2	4	1	1	0.2036099	0.204	**0.2036099**
2	1	3	3	3	1	0	0	0	0	0	0	1	1	1	3	0	0	2	4	0.2135216	0.214	**0.2135216**
3	3	1	2	1	0	0	0	1	0	1	1	0	0	0	2	0	0	1	1	0.2137787	0.214	**0.2137787**
3	2	3	2	2	0	1	0	1	1	1	0	1	0	0	4	2	4	1	1	0.215586	0.216	**0.215586**
3	3	2	1	2	0	0	1	0	1	1	1	0	0	0	3	1	1	1	1	0.219625	0.220	**0.219625**
1	1	3	3	3	0	0	0	0	0	0	0	1	1	1	2	0	0	2	4	0.2199427	0.220	**0.2199427**
3	2	2	1	3	0	1	1	0	0	1	0	0	0	1	3	1	1	1	1	0.2215075	0.222	**0.2215075**
3	1	2	2	3	0	0	1	1	0	1	0	0	0	1	3	1	1	1	1	0.2239593	0.224	**0.2239593**
3	3	1	1	2	0	0	0	0	1	1	1	0	0	0	2	0	0	1	1	0.2304464	0.230	**0.2304464**
3	2	1	1	3	0	1	0	0	0	1	0	0	0	1	2	0	0	1	1	0.2323289	0.232	**0.2323289**
2	3	1	3	2	1	0	0	0	1	0	1	0	1	0	3	1	1	1	1	0.2339224	0.234	**0.2339224**
3	1	1	2	3	0	0	0	1	0	1	0	0	0	1	2	0	0	1	1	0.2347807	0.235	**0.2347807**
2	3	3	2	3	1	0	0	1	0	0	1	1	0	1	4	1	1	2	4	0.2354505	0.235	**0.2354505**
2	2	1	3	3	1	1	0	0	0	0	0	0	1	1	3	1	1	1	1	0.2358049	0.236	**0.2358049**
1	3	2	3	2	0	0	1	0	1	0	1	0	1	0	3	1	1	1	1	0.2402089	0.240	**0.2402089**
1	2	2	3	3	0	1	1	0	0	0	0	0	1	1	3	1	1	1	1	0.2420914	0.242	**0.2420914**
3	3	2	1	1	0	0	1	0	0	1	1	0	0	0	2	0	0	1	1	0.2469399	0.247	**0.2469399**
3	3	1	1	1	0	0	0	0	0	1	1	0	0	0	1	0	0	1	1	0.2470745	0.247	**0.2470745**
2	3	2	3	1	1	0	1	0	0	0	1	0	1	0	3	1	1	1	1	0.2504159	0.250	**0.2504159**
1	3	1	3	2	0	0	0	0	1	0	1	0	1	0	2	0	0	1	1	0.2510303	0.251	**0.2510303**
1	3	3	2	3	0	0	0	1	0	0	1	1	0	1	3	0	0	2	4	0.2525584	0.253	**0.2525584**

1	2	1	3	3	0	1	0	0	0	0	0	0	1	1	2	0	0	1	1	0.2529128	0.253	**0.2529128**
3	2	2	2	2	0	1	1	1	1	1	0	0	0	0	4	3	9	0	0	0.2603277	0.260	**0.2603277**
2	3	1	3	1	1	0	0	0	0	0	1	0	1	0	2	0	0	1	1	0.2612373	0.261	**0.2612373**
2	2	3	3	2	1	1	0	0	1	0	0	1	1	0	4	2	4	1	1	0.2630446	0.263	**0.2630446**
3	2	3	2	1	0	1	0	1	0	1	0	1	0	0	3	1	1	1	1	0.2642745	0.264	**0.2642745**
1	3	2	3	1	0	0	1	0	0	0	1	0	1	0	2	0	0	1	1	0.2675238	0.268	**0.2675238**
1	3	1	3	1	0	0	0	0	0	0	1	0	1	0	1	0	0	1	1	0.2676584	0.268	**0.2676584**
3	1	2	1	3	0	0	1	0	0	1	0	0	0	1	2	0	0	1	1	0.2679419	0.268	**0.2679419**
3	1	1	1	3	0	0	0	0	0	1	0	0	0	1	1	0	0	1	1	0.2680765	0.268	**0.2680765**
2	1	2	3	3	1	0	1	0	0	0	0	0	1	1	3	1	1	1	1	0.2714179	0.271	**0.2714179**
2	3	2	2	3	1	0	1	1	0	0	1	0	0	1	4	2	4	1	1	0.2719732	0.272	**0.2719732**
2	3	3	1	3	1	0	0	0	0	0	1	1	0	1	3	0	0	2	4	0.2794331	0.279	**0.2794331**
3	2	3	1	2	0	1	0	0	1	1	0	1	0	0	3	1	1	1	1	0.2809422	0.281	**0.2809422**
2	1	1	3	3	1	0	0	0	0	0	0	0	1	1	2	0	0	1	1	0.2822393	0.282	**0.2822393**
3	1	3	2	2	0	0	0	1	1	1	0	1	0	0	3	1	1	1	1	0.283394	0.283	**0.283394**
1	3	3	1	3	0	0	0	0	0	0	1	1	0	1	2	0	0	2	4	0.2858542	0.286	**0.2858542**
1	1	2	3	3	0	0	1	0	0	0	0	0	1	1	2	0	0	1	1	0.2885258	0.289	**0.2885258**
1	1	1	3	3	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	0.2886604	0.289	**0.2886604**
1	2	3	3	2	0	1	0	0	1	0	0	1	1	0	3	1	1	1	1	0.3015261	0.302	**0.3015261**
2	3	1	2	3	1	0	0	1	0	0	1	0	0	1	3	1	1	1	1	0.3041682	0.304	**0.3041682**
2	2	2	3	2	1	1	1	0	1	0	0	0	1	0	4	3	9	0	0	0.3077863	0.308	**0.3077863**
3	2	3	1	1	0	1	0	0	0	1	0	1	0	0	2	0	0	1	1	0.3082571	0.308	**0.3082571**
1	3	2	2	3	0	0	1	1	0	0	1	0	0	1	3	1	1	1	1	0.3104547	0.310	**0.3104547**
3	1	3	2	1	0	0	0	1	0	1	0	1	0	0	2	0	0	1	1	0.3107089	0.311	**0.3107089**
2	2	3	3	1	1	1	0	0	0	0	0	1	1	0	3	1	1	1	1	0.3117331	0.312	**0.3117331**
3	2	1	2	2	0	1	0	1	1	1	0	0	0	0	3	2	4	0	0	0.3138963	0.314	**0.3138963**
1	3	1	2	3	0	0	0	1	0	0	1	0	0	1	2	0	0	1	1	0.3212761	0.321	**0.3212761**
3	1	3	1	2	0	0	0	0	1	1	0	1	0	0	2	0	0	1	1	0.3273766	0.327	**0.3273766**
1	2	3	3	1	0	1	0	0	0	0	0	1	1	0	2	0	0	1	1	0.328841	0.329	**0.328841**
3	2	2	2	1	0	1	1	1	0	1	0	0	0	0	3	2	4	0	0	0.3303898	0.330	**0.3303898**
2	1	3	3	2	1	0	0	0	1	0	0	1	1	0	3	1	1	1	1	0.3308526	0.331	**0.3308526**
2	3	3	2	2	1	0	0	1	1	0	1	1	0	0	4	2	4	1	1	0.3314079	0.331	**0.3314079**
2	2	3	2	3	1	1	0	1	0	0	0	1	0	1	4	2	4	1	1	0.3332904	0.333	**0.3332904**

2	3	2	1	3	1	0	1	0	0	0	1	0	0	1	3	1	1	1	1	0.3373294	0.337	**0.3373294**
3	1	3	1	1	0	0	0	0	0	1	0	1	0	0	1	0	0	1	1	0.3440047	0.344	**0.3440047**
3	2	2	1	2	0	1	1	0	1	1	0	0	0	0	3	2	4	0	0	0.3470575	0.347	**0.3470575**
1	1	3	3	2	0	0	0	0	1	0	0	1	1	0	2	0	0	1	1	0.3479605	0.348	**0.3479605**
2	3	1	1	3	1	0	0	0	0	0	1	0	0	1	2	0	0	1	1	0.3481508	0.348	**0.3481508**
3	1	2	2	2	0	0	1	1	1	1	0	0	0	0	3	2	4	0	0	0.3495093	0.350	**0.3495093**
1	3	2	1	3	0	0	1	0	0	0	1	0	0	1	2	0	0	1	1	0.3544373	0.354	**0.3544373**
1	3	1	1	3	0	0	0	0	0	0	1	0	0	1	1	0	0	1	1	0.3545719	0.355	**0.3545719**
2	1	3	3	1	1	0	0	0	0	0	0	1	1	0	2	0	0	1	1	0.3581675	0.358	**0.3581675**
2	2	1	3	2	1	1	0	0	1	0	0	0	1	0	3	2	4	0	0	0.3613549	0.361	**0.3613549**
3	2	1	2	1	0	1	0	1	0	1	0	0	0	0	2	1	1	0	0	0.3625848	0.363	**0.3625848**
1	1	3	3	1	0	0	0	0	0	0	0	1	1	0	1	0	0	1	1	0.3645886	0.365	**0.3645886**
1	2	2	3	2	0	1	1	0	1	0	0	0	1	0	3	2	4	0	0	0.3676414	0.368	**0.3676414**
1	3	3	2	2	0	0	0	1	1	0	1	1	0	0	3	1	1	1	1	0.3698894	0.370	**0.3698894**
1	2	3	2	3	0	1	0	1	0	0	0	1	0	1	3	1	1	1	1	0.3717719	0.372	**0.3717719**
2	3	2	2	2	1	0	1	1	1	0	1	0	0	0	4	3	9	0	0	0.3761496	0.376	**0.3761496**
2	2	2	3	1	1	1	1	0	0	0	0	0	1	0	3	2	4	0	0	0.3778484	0.378	**0.3778484**
2	2	2	2	3	1	1	1	1	0	0	0	0	0	1	4	3	9	0	0	0.3780321	0.378	**0.3780321**
3	2	1	1	2	0	1	0	0	1	1	0	0	0	0	2	1	1	0	0	0.3792525	0.379	**0.3792525**
2	3	3	2	1	1	0	0	1	0	0	1	1	0	0	3	1	1	1	1	0.3800964	0.380	**0.3800964**
3	1	1	2	2	0	0	0	1	1	1	0	0	0	0	2	1	1	0	0	0.3817043	0.382	**0.3817043**
3	2	2	1	1	0	1	1	0	0	1	0	0	0	0	2	1	1	0	0	0.395746	0.396	**0.395746**
2	3	3	1	2	1	0	0	0	1	0	1	1	0	0	3	1	1	1	1	0.3967641	0.397	**0.3967641**
2	1	2	3	2	1	0	1	0	1	0	0	0	1	0	3	2	4	0	0	0.3969679	0.397	**0.3969679**
1	3	3	2	1	0	0	0	1	0	0	1	1	0	0	2	0	0	1	1	0.3972043	0.397	**0.3972043**
3	1	2	2	1	0	0	1	1	0	1	0	0	0	0	2	1	1	0	0	0.3981978	0.398	**0.3981978**
2	2	3	1	3	1	1	0	0	0	0	0	1	0	1	3	1	1	1	1	0.3986466	0.399	**0.3986466**
1	2	1	3	2	0	1	0	0	1	0	0	0	1	0	2	1	1	0	0	0.3998364	0.400	**0.3998364**
2	1	3	2	3	1	0	0	1	0	0	0	1	0	1	3	1	1	1	1	0.4010984	0.401	**0.4010984**
3	2	1	1	1	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0.4065674	0.407	**0.4065674**
3	1	1	2	1	0	0	0	1	0	1	0	0	0	0	1	0	0	0	0	0.4090192	0.409	**0.4090192**
2	2	1	3	1	1	1	0	0	0	0	0	0	1	0	2	1	1	0	0	0.4100434	0.410	**0.4100434**
1	3	3	1	2	0	0	0	0	1	0	1	1	0	0	2	0	0	1	1	0.413872	0.414	**0.413872**

3	1	2	1	2	0	0	1	0	1	1	0	0	0	0	2	1	1	0	0	0.4148655	0.415	**0.4148655**
1	2	3	1	3	0	1	0	0	0	0	0	1	0	1	2	0	0	1	1	0.4157545	0.416	**0.4157545**
1	2	2	3	1	0	1	1	0	0	0	0	0	1	0	2	1	1	0	0	0.4163299	0.416	**0.4163299**
1	1	3	2	3	0	0	0	1	0	0	0	1	0	1	2	0	0	1	1	0.4182063	0.418	**0.4182063**
2	3	3	1	1	1	0	0	0	0	0	1	1	0	0	2	0	0	1	1	0.424079	0.424	**0.424079**
3	1	1	1	2	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0.4256869	0.426	**0.4256869**
1	2	1	3	1	0	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0.4271513	0.427	**0.4271513**
2	1	1	3	2	1	0	0	0	1	0	0	0	1	0	2	1	1	0	0	0.4291629	0.429	**0.4291629**
2	3	1	2	2	1	0	0	1	1	0	1	0	0	0	3	2	4	0	0	0.4297182	0.430	**0.4297182**
1	3	3	1	1	0	0	0	0	0	0	1	1	0	0	1	0	0	1	1	0.4305001	0.431	**0.4305001**
2	2	1	2	3	1	1	0	1	0	0	0	0	0	1	3	2	4	0	0	0.4316007	0.432	**0.4316007**
1	1	2	3	2	0	0	1	0	1	0	0	0	1	0	2	1	1	0	0	0.4354494	0.435	**0.4354494**
1	3	2	2	2	0	0	1	1	1	0	1	0	0	0	3	2	4	0	0	0.4360047	0.436	**0.4360047**
2	2	3	2	2	1	1	0	1	1	0	0	1	0	0	4	3	9	0	0	0.4374668	0.437	**0.4374668**
1	2	2	2	3	0	1	1	1	0	0	0	0	0	1	3	2	4	0	0	0.4378872	0.438	**0.4378872**
3	1	2	1	1	0	0	1	0	0	1	0	0	0	0	1	0	0	0	0	0.4421804	0.442	**0.4421804**
3	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0.442315	0.442	**0.442315**
2	1	3	1	3	1	0	0	0	0	0	0	1	0	1	2	0	0	1	1	0.445081	0.445	**0.445081**
2	1	2	3	1	1	0	1	0	0	0	0	0	1	0	2	1	1	0	0	0.4456564	0.446	**0.4456564**
2	3	2	2	1	1	0	1	1	0	0	1	0	0	0	3	2	4	0	0	0.4462117	0.446	**0.4462117**
1	1	1	3	2	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0.4462708	0.446	**0.4462708**
1	1	3	1	3	0	0	0	0	0	0	0	1	0	1	1	0	0	1	1	0.4515021	0.452	**0.4515021**
2	1	1	3	1	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0.4564778	0.456	**0.4564778**
1	1	2	3	1	0	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0.4627643	0.463	**0.4627643**
2	3	2	1	2	1	0	1	0	1	0	1	0	0	0	3	2	4	0	0	0.4628794	0.463	**0.4628794**
1	1	1	3	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0.4628989	0.463	**0.4628989**
2	2	2	1	3	1	1	1	0	0	0	0	0	0	1	3	2	4	0	0	0.4647619	0.465	**0.4647619**
2	1	2	2	3	1	0	1	1	0	0	0	0	0	1	3	2	4	0	0	0.4672137	0.467	**0.4672137**
1	3	1	2	2	0	0	0	1	1	0	1	0	0	0	2	1	1	0	0	0.4681997	0.468	**0.4681997**
1	2	1	2	3	0	1	0	1	0	0	0	0	0	1	2	1	1	0	0	0.4700822	0.470	**0.4700822**
2	3	1	2	1	1	0	0	1	0	0	1	0	0	0	2	1	1	0	0	0.4784067	0.478	**0.4784067**
1	3	2	2	1	0	0	1	1	0	0	1	0	0	0	2	1	1	0	0	0.4846932	0.485	**0.4846932**
2	3	1	1	2	1	0	0	0	1	0	1	0	0	0	2	1	1	0	0	0.4950744	0.495	**0.4950744**

1	3	1	2	1	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0	0.4955146	0.496	**0.4955146**
2	2	1	1	3	1	1	0	0	0	0	0	0	0	1	2	1	1	0	0	0.4969569	0.497	**0.4969569**
1	2	3	2	2	0	1	0	1	1	0	0	1	0	0	3	2	4	0	0	0.4973219	0.497	**0.4973219**
2	1	1	2	3	1	0	0	1	0	0	0	0	0	1	2	1	1	0	0	0.4994087	0.499	**0.4994087**
1	3	2	1	2	0	0	1	0	1	0	1	0	0	0	2	1	1	0	0	0.5013609	0.501	**0.5013609**
1	2	2	1	3	0	1	1	0	0	0	0	0	0	1	2	1	1	0	0	0.5032434	0.503	**0.5032434**
1	1	2	2	3	0	0	1	1	0	0	0	0	0	1	2	1	1	0	0	0.5056952	0.506	**0.5056952**
2	2	3	2	1	1	1	0	1	0	0	0	1	0	0	3	2	4	0	0	0.5075289	0.508	**0.5075289**
2	3	2	1	1	1	0	1	0	0	0	1	0	0	0	2	1	1	0	0	0.5115679	0.512	**0.5115679**
1	3	1	1	2	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	0.5121823	0.512	**0.5121823**
1	2	1	1	3	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0.5140648	0.514	**0.5140648**
1	1	1	2	3	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0.5165166	0.517	**0.5165166**
2	3	1	1	1	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0.5223893	0.522	**0.5223893**
2	2	3	1	2	1	1	0	0	1	0	0	1	0	0	3	2	4	0	0	0.5241966	0.524	**0.5241966**
2	1	3	2	2	1	0	0	1	1	0	0	1	0	0	3	2	4	0	0	0.5266484	0.527	**0.5266484**
1	3	2	1	1	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0.5286758	0.529	**0.5286758**
1	3	1	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0.5288104	0.529	**0.5288104**
2	1	2	1	3	1	0	1	0	0	0	0	0	0	1	2	1	1	0	0	0.5325699	0.533	**0.5325699**
2	1	1	1	3	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0.5433913	0.543	**0.5433913**
1	2	3	2	1	0	1	0	1	0	0	0	1	0	0	2	1	1	0	0	0.5460104	0.546	**0.5460104**
1	1	2	1	3	0	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0.5496778	0.550	**0.5496778**
1	1	1	1	3	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0.5498124	0.550	**0.5498124**
1	2	3	1	2	0	1	0	0	1	0	0	1	0	0	2	1	1	0	0	0.5626781	0.563	**0.5626781**
1	1	3	2	2	0	0	0	1	1	0	0	1	0	0	2	1	1	0	0	0.5651299	0.565	**0.5651299**
2	2	3	1	1	1	1	0	0	0	0	0	1	0	0	2	1	1	0	0	0.5728851	0.573	**0.5728851**
2	1	3	2	1	1	0	0	1	0	0	0	1	0	0	2	1	1	0	0	0.5753369	0.575	**0.5753369**
1	2	3	1	1	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0.589993	0.590	**0.589993**
2	1	3	1	2	1	0	0	0	1	0	0	1	0	0	2	1	1	0	0	0.5920046	0.592	**0.5920046**
1	1	3	2	1	0	0	0	1	0	0	0	1	0	0	1	0	0	0	0	0.5924448	0.592	**0.5924448**
2	2	2	2	2	1	1	1	1	1	0	0	0	0	0	4	4	16	0	0	0.5971891	0.597	**0.5971891**
1	1	3	1	2	0	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0.6091125	0.609	**0.6091125**
2	1	3	1	1	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0.6193195	0.619	**0.6193195**
1	1	3	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0.6257406	0.626	**0.6257406**

2	2	1	2	2	1	1	0	1	1	0	0	0	0	0	3	3	9	0	0	0.6721313	0.672	**0.6721313**
1	2	2	2	2	0	1	1	1	1	0	0	0	0	0	3	3	9	0	0	0.6784178	0.678	**0.6784178**
2	2	2	2	1	1	1	1	1	0	0	0	0	0	0	3	3	9	0	0	0.6886248	0.689	**0.6886248**
2	2	2	1	2	1	1	1	0	1	0	0	0	0	0	3	3	9	0	0	0.7052925	0.705	**0.7052925**
2	1	2	2	2	1	0	1	1	1	0	0	0	0	0	3	3	9	0	0	0.7077443	0.708	**0.7077443**
1	2	1	2	2	0	1	0	1	1	0	0	0	0	0	2	2	4	0	0	0.7319864	0.732	**0.7319864**
2	2	1	2	1	1	1	0	1	0	0	0	0	0	0	2	2	4	0	0	0.7421934	0.742	**0.7421934**
1	2	2	2	1	0	1	1	1	0	0	0	0	0	0	2	2	4	0	0	0.7484799	0.748	**0.7484799**
2	2	1	1	2	1	1	0	0	1	0	0	0	0	0	2	2	4	0	0	0.7588611	0.759	**0.7588611**
2	1	1	2	2	1	0	0	1	1	0	0	0	0	0	2	2	4	0	0	0.7613129	0.761	**0.7613129**
1	2	2	1	2	0	1	1	0	1	0	0	0	0	0	2	2	4	0	0	0.7651476	0.765	**0.7651476**
1	1	2	2	2	0	0	1	1	1	0	0	0	0	0	2	2	4	0	0	0.7675994	0.768	**0.7675994**
2	2	2	1	1	1	1	1	0	0	0	0	0	0	0	2	2	4	0	0	0.7753546	0.775	**0.7753546**
2	1	2	2	1	1	0	1	1	0	0	0	0	0	0	2	2	4	0	0	0.7778064	0.778	**0.7778064**
1	2	1	2	1	0	1	0	1	0	0	0	0	0	0	1	1	1	0	0	0.7806749	0.781	**0.7806749**
2	1	2	1	2	1	0	1	0	1	0	0	0	0	0	2	2	4	0	0	0.7944741	0.794	**0.7944741**
1	2	1	1	2	0	1	0	0	1	0	0	0	0	0	1	1	1	0	0	0.7973426	0.797	**0.7973426**
1	1	1	2	2	0	0	0	1	1	0	0	0	0	0	1	1	1	0	0	0.7997944	0.800	**0.7997944**
2	2	1	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0.8075496	0.808	**0.8075496**
2	1	1	2	1	1	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0.8100014	0.810	**0.8100014**
1	2	2	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0.8138361	0.814	**0.8138361**
1	1	2	2	1	0	0	1	1	0	0	0	0	0	0	1	1	1	0	0	0.8162879	0.816	**0.8162879**
1	2	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.8246575	0.825	**0.8246575**
2	1	1	1	2	1	0	0	0	1	0	0	0	0	0	1	1	1	0	0	0.8266691	0.827	**0.8266691**
1	1	1	2	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0.8271093	0.827	**0.8271093**
1	1	2	1	2	0	0	1	0	1	0	0	0	0	0	1	1	1	0	0	0.8329556	0.833	**0.8329556**
2	1	2	1	1	1	0	1	0	0	0	0	0	0	0	1	1	1	0	0	0.8431626	0.843	**0.8431626**
1	1	1	1	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0.843777	0.844	**0.843777**
2	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.853984	0.854	**0.853984**
1	1	2	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0.8602705	0.860	**0.8602705**
1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0.8604051	1.000	**1**

7.4 Step to identify the Day of baseline treatment increase/change:

[Step]

1. Identify “Relapse prevention therapy used at BL (i.e. Drug A)”.
2. Identify “Relapse prevention therapy* newly used from BL by the potential censored Day** other than the Day of increase/change of BL treatment (i.e. Drug B)”.
   - ✓ End if there is no Drug B.
3. Scientifically/medically evaluate if any of following information of Drug A are different from those of Drug B:
   i. Dose regimen
   ii. Drug name
   - ✓ End if not different.
   - ✓ If different, the earliest start Day of Drug B is the Day of dose increase/change of baseline treatment.

*; Including immunosuppressants and corticosteroids which were not used for relapse prevention (i.e. the indication is AE or Medical History etc). For them, route and duration of administration etc. will also be considered in step No.3 (e.g. temporal local administration will not be considered as increase/change of Drug A).

**; Including following days;

a. 1st Day of rescue therapy started in the double-blind period for this patient (if any)

b. The relapse onset Day of the event*** for this patient (if any)

c. Clinical cut-off Day (CCOD): the relapse onset day of the event*** with the 26th earliest onset date

d. Day of discontinuation from the double-blind period for this patient (e.g. Day of WD visit, Day of consent withdrawal) (if any)

***; the relapse adjudicated as protocol-defined relapse by Clinical Endpoint Committee (CEC) and EDSS/FSS assessed within 7 days from the date when the patient first reported symptoms to the site.

[Note]

- Day 1 = Baseline in the double blind period
- There may be more than one Drug B.
- Drug A must meet both of followings:
  - ✓ “Day of medication started” =< 1
  - ✓ “Day of medication stop” >= 1
- Drug B must meet both of followings:
  - ✓ “Day of medication started” >= 1
  - ✓ “Day of medication started” < “potential censored Day**”

7.5 Procedure to identify the clinical relapse of optic neuritis occurred in the double-blind period:

The clinical relapse of optic neuritis occurred in the double-blind period of SA-307JG study will be identified by satisfying with either or both of followings. The Relapse Assessment Form (RAF) completed by study sites will be used for the identification.

- Lower box "New or worsening neurological symptoms relating to this functional area reported by the patient at this visit. Please describe:" is ticked in the Section A-1 "Visual (optic) functions: *Symptoms*" of the RAF, and then the information is described per the instruction.
- The information on new or worsening neurological symptoms in visual (optic) functions are described in section B of RAF.

[Reference: Section A-1 of RAF]

1. Visual(optic)functions

➢ *Symptoms*

☐ No new or worsening neurological symptoms in this functional area from the previous assessment of EDSS/FSS

☐ New or worsening neurological symptoms relating to this functional area reported by the patient at this visit. Please describe:

7.6 Rule for summary of titer for anti AQP4 antibody status

Titer for anti AQP4 antibody status except screening visit will be replaced by following rule. This rule will apply to throughout TFL.

- If value is "<16", value will be replaced as 4.
- If titer is character (eg. ">16384", ">65536" except "<16") or titer is numeric more than 16384 (eg. "65536", "262144"), value will be replaced as 65536.

7.7 SAS Codes:

Log-rank test:

```
proc lifetest data=final;
   time DURATION*STATUS (0);
   strata ARR REGEON / group=TREATMENT;
   ods output test=_logrank;
run;
```

Cox Regression Model:

```
proc phreg data=final;
   class TREATMENT/descending;
   Model DURATION*STATUS(0)=TREATMENT / ties=exact rl;
   strata ARR REGION;
   ods output parameterEstimates=est;
run;
```

Mixed effect Model Repeat Measurement (MMRM)

```
proc mixed data=VAS method=REML;
   class REGION TREATMENT VISIT USUBJIDARR;
   model CHG = BASE TREATMENT REGION VISIT ARR
   TREATMENT*VISIT/ddfm=KR;
   repeated VISIT / type=un subject = USUBJID;
   lsmeans TREATMENT*VISIT / pdiff cl;
```

```
   ods output lsmeans = lsm; * contains the adjusted means;
   ods output diffs = dif; * contains treatment differences;
run;
```

ANCOVA;

```
proc mixed data=;
   class TREATMENT ARR REGION;
   model CHG_BL=TREATMENT BASELINE ARR REGION;
   lsmeans TREATMENT / pdiff cl;
run;
```