Official Title: **A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.**

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Protocol Title:

A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.

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Version: 1.0 **Date:** 3 February 2021

SPONSOR APPROVAL

The undersigned have reviewed and approved the format and content of this statistical analysis plan for Protocol TG1101-RMS201.

Protocol Title:	A Placebo-Controlled Multi-Center Phase IIa Dose Finding Study of Ublituximab, a Third-Generation Anti-CD20 Monoclonal Antibody, in Patients with Relapsing Forms of Multiple Sclerosis.
Protocol Number:	TG1101-RMS201
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List of Abbreviations and Definitions of Terms

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical Classification
BMI	Body mass index
BUN	Blood urea nitrogen
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
DILI	Drug-induced liver injury
DSMB	Data Safety Monitoring Board
DLT	Dose-limiting toxicity
ECG	electrocardiogram
eDISH	Evaluations of drug-induced serious hepatotoxicity
EDSS	Expanded Disability Status Scale
Gd	gadolinium
GGT	Gamma glutamyl transferase
INR	International normalization ratio
ITT	Intent-to-treat
MDRD	Modification of diet in renal disease formula
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MRI	Magnetic resonance imaging or magnetic resonance image
MS	Multiple sclerosis
NEDA	No evidence of disease activity
PK	Pharmacokinetic
PT	Preferred term
QTcF	QT Interval Corrected Using Fridericia's Formula
RMS	Relapsing forms of Multiple Sclerosis
RRR	Relapse rate reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGOT/AST	Serum glutamic oxaloacetic transaminase/aspartate aminotransferase
SGPT/ALT	Serum glutamic pyruvic transaminase/alanine aminotransferase
SIB	Suicidal ideation and Behavior
SMQ	Standardized MedDRA Queries

SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
UTX	Ublituximab
WHO-DD	World health organization drug dictionary

Contents

1 Overview and Investigational Plan

This statistical analysis plan (SAP) provides a detailed description of the statistical strategy for the "TG1101-RMS201" protocol Version 8.0 dated 10 October 2017. The goal of the SAP is to specify the statistical approaches to the analysis of study data.

1.1 Study Design and Randomization

This is a 52-week, phase IIa, placebo-controlled, multi-center study that is primarily designed to assess the optimal dosing, optimal infusion time as well as safety/tolerability of ublituximab (TG1101; UTX) in patients with RMS.

Subjects may be screened up to 4 weeks before first dosing date. Qualified subjects will receive ublituximab on Days 1, 15, and week 24. There will be at least four treatment cohorts in the study with 8 subjects (2 placebo and 6 ublituximab treatment; please see treatment schema) enrolled in each cohort.

A Data and Safety Monitoring Board (DSMB) will be established to safeguard the wellbeing of the subjects and to advise the Sponsor whether it is appropriate to expand the enrollment to a dosing cohort or to initiate next dosing cohort. Once a subject is qualified, the Site will contact the Sponsor or its designee for cohort assignment (treatment assignment). The Sponsor or its designee will issue the cohort assignment for the subject using the following procedures. If DSMB deems that a cohort is not appropriate (e.g., due to safety), enrollment to that cohort and all higher cohorts will be terminated and all future subjects will be enrolled to the lowest incomplete cohort. Upon completion of first two patients in each cohort (one on placebo and one on study drug) through 21 days, the DSMB will review safety data and assuming no safety concern is raised, the remaining qualified subjects will be enrolled into such cohort.

1.2 Objectives

1.2.1 Primary Objective

- To determine the level of B cell depletion by ublituximab in subjects with RMS
- To determine the optimal dose and infusion time for ublituximab in subjects with RMS

1.2.2 Secondary Objectives

- To examine the effect of ublituximab on the development of new Gadolinium- (Gd) enhancing lesions and new or enlarging T2 lesions at 24 and 48 weeks
- To evaluate the % of relapses in ublituximab-treated RMS subjects

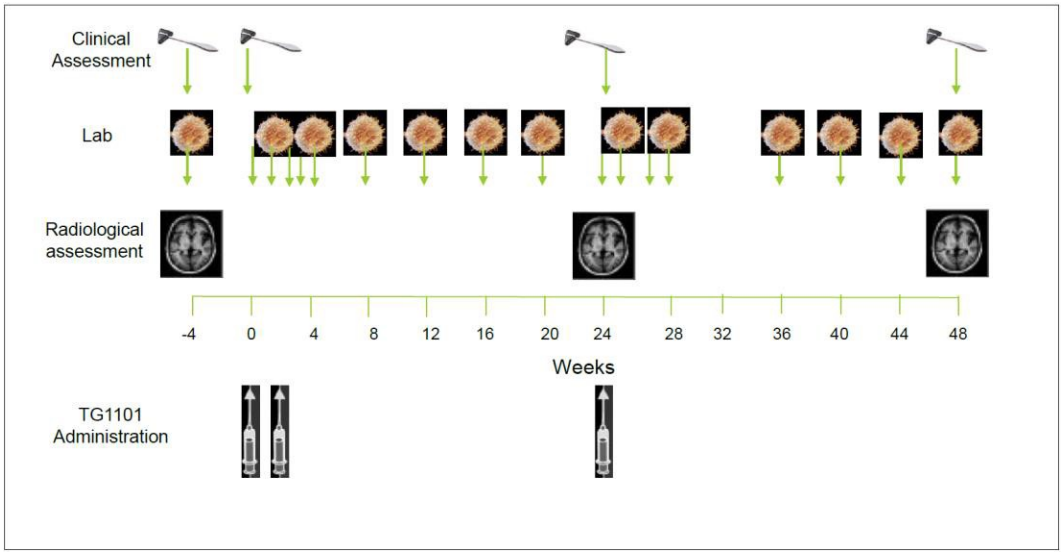
- To determine immunogenicity
- To evaluate the safety of ublituximab, as determined by adverse events (AEs) and serious adverse events (SAEs), including MS worsening

1.3 Determination of Sample Size

[redacted]

1.4 Study Plan

Refer to the study protocol for TG1101-RMS201 for study schedule for analysis variables.



- Ublituximab (IV): Infusions on Days 1 and 15 and week 24
- Placebo (IV): Infusions on Days 1 and 15

2 Statistical and Analytical Procedures

2.1 Analysis Variables

Baseline for both efficacy and safety variables are defined as the last non-missing value on or before the first dose of Ublituximab.

2.1.1 Demographics and Baseline Characteristics

Demographic and other baseline characteristics

Demographic variables are gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, or Not Applicable due to country's legislation), age in years (quantitative and categorical variable: <38, and ≥38 years) and Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

Medical and surgical history

Medical history data will be coded to "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

Disease characteristics at baseline

- Number of relapses experienced within past 1 year and 2 years (0, 1, 2, 3, and ≥4), respectively
- Time since first diagnosis of MS (in years) to be derived as (Day of randomization – Day of first MS diagnosis) / 365.25
- Time since first symptoms of MS (in years) to be derived as (Day of randomization – day of first symptoms of MS) / 365.25
- Time since most recent relapse onset (in months) to be derived as (Day of randomization – day of most recent relapse onset) / (365.25 / 12)
- Baseline EDSS score
- Baseline EDSS (≤3.5, >3.5)
- Number of baseline Gadolinium (Gd)-enhancing lesions (0, ≥1)
- Baseline T2 lesion count
- Baseline T2 lesion Volume
- Baseline brain volume

Multiple Sclerosis treatment history

- Received any MS therapy for at least 1 month (30 days) prior to enrollment (Yes, No)
- Prior Treatments for Current Diagnosis by Preferred Name
- Previous corticosteroid treatment for relapse
- Time since last corticosteroid treatment for relapse (months)

Vital signs and height

Vital signs are variables: weight in kg (quantitative variable and categorical variable: <50, ≥50 - <100, ≥100), height (m) and Body Mass Index (BMI) in weight[kg]/height[m^2] (<30, ≥30) calculated from weight and height.

Concomitant medications

All concomitant medications or concomitant medications (extension) are reported in the case report forms (CRF).

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

- Concomitant medications are those taken at any time during the study treatment period, from the first study treatment use to the day of last study drug treatment, started before or during study treatment.

- Concomitant medications (extension) are those taken at any time between last study treatment and end of extension.

Technical details related to calculating dates, imputation for missing dates, etc. are described in Section 2.5.

2.1.2 Study Treatment Exposure

Treatment exposure for ublituximab/placebo is summarized with following variables:

- The total number of infusions of placebo
- The total number of infusions of ublituximab received over the 3 expected infusions.
- The overall number of infusions of ublituximab, number and percentage (based on all infusions) of infusions completed with/without interruption and infusions not completed.
- The number and percentage of patients (based on all patients with at least one infusion) with and without any infusion complication (interruption or stop).
- The percentage of planned total infusion received.

2.1.3 Efficacy Variables

2.1.3.1 Primary Efficacy Variable

The primary efficacy variable will be responder rate at week 4 (2 weeks after W3D15, the second scheduled infusion of ublituximab), where responders are subjects who have reduced B-cell depletion by ≥95%.

2.1.3.2 Secondary Efficacy Variables

The secondary efficacy variables are as follows:

- Number of new Gd-enhancing lesions at 24 and 48 weeks
- Number of new or enlarging T2 lesions at 24 and 48 weeks
- Annualized relapse rate (ARR)
- Relapse rate reduction (RRR)
- Percent of relapse free subjects

- Reduction in B cells (CD19+), memory (CD19+CD27+) and naïve (CD19+CD27-) B cells at baseline, day 1 (pre dose) and 2; week 2; Day15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post-dose) 25, 28, 36, 40, 44 and 48
- To examine sustained B cell reduction during the first and third infusions
- Additional immune profiling (CD4+, CD8+, IL10 and NK cells) at baseline, day 1 (pre dose) and 2; week 2, Day 15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post dose) 25, 28, 36, 40, 44 and 48
- PK (ADME) profile of ublituximab at day 1 (pre-dose); week 2; day 15 (pre-dose); weeks 4, 24 (pre-dose) and 25

2.1.3.3 Exploratory Endpoints

- The proportion of subjects with confirmed disability progression/improvement for at least 24 weeks

Confirmed disability progression was defined as an initial increase of ⩾1.0 point from the baseline EDSS score (not attributable to another etiology, concurrent illness, or concomitant medication) when the baseline score was ⩽5.5, and of ⩾0.5 point when the baseline score was >5.5, confirmed in a subsequent EDSS assessment 24 weeks later. Confirmed disability improvement followed the same criteria, but with a sustained decrease of ⩾1.0 EDSS point from baseline.

- No evidence of disease activity (NEDA)

No evidence of disease activity (NEDA) was defined as no evidence of clinical (relapse, confirmed disability progression for 24 weeks) or MRI (T1-weighted gadolinium-enhancing or new/enlarging T2 lesions) disease activity.

2.1.4 Safety Variables

The safety analysis will be based on the reported DLTs, AEs and other safety information, such as clinical laboratory data, electrocardiogram (ECG), physical examination, and vital signs.

2.1.4.1 Adverse Events

Adverse events will be coded and classified according to the System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The occurrence of AEs (including SAEs and adverse events of special interest [AESIs]) will be captured from the time the informed consent is obtained until the participant terminates participation in the study.

AESI will be categorized using a grouped set of MedDRA terms based on Standardized MedDRA Queries (SMQs) and clinical concept, as determined by the Sponsor. The MedDRA terms selected for AESI analysis will be provided in the Clinical Study Report (CSR).

Suicidal ideation and behavior will be identified by the AE preferred terms included in MedDRA SMQ "Suicide/self-injury".

2.1.4.2 Laboratory Safety Variables

Clinical laboratory data consist of hematology, serum chemistry and coagulation. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The laboratory parameters will be classified as follows:

Hematology

Hematology and differential panel: hemoglobin, hematocrit, red blood cell count, mean corpuscular hemoglobin, white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets

Serum chemistry/ Pancreatic enzyme panel
The serum chemistry to be analyzed are presented in the table below.

Serum Chemistry		
Albumin	Creatinine	SGOT [AST]
Alkaline phosphatase	Glucose	SGPT [ALT]
Bicarbonate	LDH	Sodium
BUN	Magnesium	Total bilirubin
Calcium	Phosphorus	Total Protein
Chloride	Potassium	Uric acid

Coagulation
PT/INR and Fibrinogen

All observations of these tests including unscheduled measurements will be assigned to the appropriate safety analysis visit window, as defined in Section 2.5.3. In the presence of multiple measurements of the same laboratory test in the same window, the one closest to the targeted visit date will be used for the by-visit summaries. In case of equal distance, the later observation will be selected. All other lab results will only be listed.

2.1.4.3 Vital Signs

The following vital sign parameters will be analyzed:

- Systolic and diastolic blood pressures (mmHg)
- Heart Rate (beats/min)
- Weight (kg)
- Body Temperature (All results will be converted to Celsius)

2.1.4.4 Physical Examination

Physical examination is assessed per visit and body system, with possible outcomes normal and abnormal (plus free text for specification if abnormal).

2.1.4.5 ECG

ECG interpretation (normal/abnormal) and QTcF interval will be collected by visit and - where applicable - time point (pre-/post-dose).

2.1.5 Pharmacokinetic Variables

To characterize population PK of ublituximab, blood samples will be drawn from all subjects at pre-infusion and 15-30 minutes after the completion of the infusion on Day 1 and 15 and 180 (week 24); three additional sample will be taken at week 2, 4 and 25. [redacted]

2.2 Analysis Populations

2.2.1 Safety Population

The Safety Population will include all subjects who receive at least one dose of Ublituximab. All safety assessments for Ublituximab including toxicity will be performed on the Safety Population.

The Placebo Safety Population will include all subjects who receive at least one dose of Placebo. All safety assessments for Placebo including toxicity will be performed on the Placebo Safety Population.

2.2.2 Intent-to-Treat (ITT)

The Intent-to-Treat (ITT) population will consist of all subjects who receive at least one dose of Ublituximab. The primary efficacy analyses will be performed based on the ITT population.

2.2.3 Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat Population (mITT) will consist of all subjects who have received ublituximab and have one baseline and post-baseline MRI.

2.2.4 Other Analysis Population

The PK Population will be a subset of the Safety Population containing subjects who participate in the population PK subset and have at least one baseline and one post-baseline PK sample taken.

2.3 Disposition of Subjects

Subject disposition will be tabulated as follows:

- Screened subjects defined as subjects who signed the informed consent;
- Screened but not randomized subjects and reasons for not randomized (screen failure etc.);
- Randomized subjects and corresponding treatment;
- Subjects who completed the 48-week study treatment period
- Subjects who discontinued study treatment and reasons for discontinuation but continue to allow assessments in the study after stopping study medication;

For all categories of subjects (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized subjects per cohort as the denominator.

Additionally, the analysis populations for safety, ITT and mITT will be summarized in a table by subject counts on the randomized population.

2.4 Statistical Methods

Unless otherwise stated, all analyses will be performed using SAS Version 9.2 or higher. All hypothesis tests will be descriptive and conducted at a two-sided significance level of 0.05; no

multiplicity adjustment will be done. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

2.4.1 Demographics and Baseline Characteristics

Continuous data will be summarized using number with available data: mean, standard deviation (SD), median, minimum, and maximum, and 1st and 3rd quartile for each treatment group. Categorical or ordinal data will be summarized using the number and percentage of subjects within each treatment group. Summaries will be presented for the ITT population.

Demographics and Baseline Characteristics

Demographic and baseline characteristics as described in Section 2.1.1 will be summarized by treatment cohort and overall using descriptive statistics.

Medical and surgical history

Medical history and concurrent medical conditions (ongoing at screening) will be summarized by primary system organ class (SOC) and preferred term for each treatment cohort. The table will be sorted alphabetically by SOC and by decreasing frequency in the total column.

Concomitant/follow-up medications

The concomitant and follow-up medications will be presented on the safety population.

Medications will be summarized by treatment cohort, according to the international classification of medicines (WHO-DD dictionary), using the terms corresponding to the ATC class level 4 and Preferred Name. All ATC codes corresponding to a medication will be summarized. Subjects will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication.

The tables for concomitant and follow-up medications will be sorted by decreasing frequency of anatomic category followed by all other therapeutic classes based on the incidence in the total column. In case of equal frequency regarding anatomic categories or therapeutic categories, alphabetical order will be used.

Previous MS treatment

Variables related to previous MS treatment will be summarized per treatment cohort.

No statistical tests will be performed on demographic and baseline characteristic data.

2.4.2 Primary Efficacy Variable

The primary efficacy variable will be responder rate of B-cell depletion at week 4, which is the proportion of subjects who have reduced B-cell depletion at week 4 (2 weeks after W3D15 administration of ublituximab) in the ITT population. The percentages of the responders and its 95% confidence intervals will be presented by cohort and total, if appropriate, using exact method due to small sample size. The B-cell count in % and its change from baseline will be summarized by visit. Logistic analysis may be used to perform trend tests to assess dose response.

2.4.3 Secondary Endpoints

MRI count variables:

- Number of new Gd-enhancing lesions at 24 and 48 weeks
- Number of new or enlarging T2 lesions at 24 and 48 weeks

The MRI count variables will be summarized by visit (baseline, 24 and 48 weeks) using descriptive statistics.

The Volume of Gd-enhancing lesions and T2 lesions at 24 and 48 weeks and the change from baseline will be summarized using descriptive statistics.

- Annualized relapse rate (ARR)
- Relapse rate reduction (RRR)
- Percent of relapse free subjects

ARR at week 48 is calculated as the ratio of the sum of all patients' confirmed relapse counts divided by the sum of all patients' treatment duration (in years). The confirmed relapses count includes the confirmed relapses starting (Start Date of Suspected Relapse Symptoms) on or after the day of first dose date of ublituximab and up to date of Week 48 visit or the early withdraw date, whichever occurs earlier. If the exact start date of relapse symptoms is unknown, the relapse will be assumed to have started during this period unless sufficient information is available to conclude that the symptoms started before or after (e.g. in case of missing start day, the symptoms start month is after the month of treatment end). ARR will be summarized by cohorts and total in ITT population.

Years under treatment will be derived as:
Treatment years = (date of Week 48 visit or early withdraw date – date of first dose of ublituximab + 1) / 365.25.

RRR will be calculated as the percentage reduction from baseline ARR to ARR at week 48. Baseline ARR will be the sum of (Total # of Relapses Within 1 Year Prior to Screening collected from CRF) divided by the number of subjects.

The percent and its 95% CI of relapse free subjects during the treatment period in ITT population will be presented.

- Reduction in B cells (CD19+), memory (CD19+CD27+) and naïve (CD19+CD27-) B cells at baseline, day 1 (pre dose) and 2; week 2; Day15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post-dose) 25, 28, 36, 40, 44 and 48
- To examine sustained B cell reduction during the first and third infusions

The reduction in B cells (%) will be summarized and plotted by visit using descriptive statistics.

- Additional immune profiling (CD4+, CD8+, IL10 and NK cells) at baseline, day 1 (pre dose) and 2; week 2, Day 15 (pre-dose); week 4 and every 4 weeks thereafter until the next infusion at week 24 (pre-dose and 2 days post dose) 25, 28, 36, 40, 44 and 48

Descriptive statistics will be presented by visit.

2.4.4 Exploratory Endpoints

- The proportion of subjects with confirmed disability progression/improvement at 48 weeks

The EDSS score will be summarized by visit using descriptive statistics. The proportion of subjects with confirmed disability progression or improvement at 48 weeks will be presented.

- No evidence of disease activity (NEDA)

The proportion of subjects who have no evidence of disease activity, no evidence of clinical and no evidence of MRI disease activity will be reported.

2.4.5 Analyses of Safety Data

Safety results will be summarized and presented by cohort and total in safety population.

General common rules

All safety analyses will be performed on the Safety Population as defined in Section 2.2.1, unless otherwise specified, using the following common rules:

1. For quantitative safety parameters based on central laboratory/ reading measurements, visit and cohort will use descriptive statistics to summarize results and change from baseline values. Summaries will include the value and/or the worst value of the observation period.

2. All of the values including unscheduled measurements will be assigned to the appropriate safety analysis visit window. The safety analysis visit window is defined in Section 2.5.2. In the presence of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summaries.
3. The analysis of the safety variables will in general be descriptive and no systematic statistical testing is planned.

2.4.5.1 Analysis of Adverse Events

The Treatment-Emergent Adverse Events (TEAE) is defined as any AE that:

- Occurs after first dosing of study medication and through the end of the study or up through 30 days after the last dose of study treatment, or
- Is considered treatment-related regardless of the start date of the event, or
- Is present before first dosing of study medication but worsens in intensity or the investigator subsequently considers treatment related.

Dose-limiting toxicity (DLT) is defined in protocol section 5.1.1 and collected in eCRF.

Adverse event incidence tables will be presented by cohort and total, the number (n) and percentage (%) of subjects experiencing an AE. In a subset of tables, also all occurrences will be counted providing a severity of occurrence of the AE. The denominator for computation of percentages is the Safety Population within each cohort.

Not treatment emergent AE(s) summary:

- Listing of (not treatment emergent) AEs showing cohort, subject identifier, SOC, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

TEAE(s) summaries:

The following TEAE summaries will be generated for the Safety Population.

Overview of TEAEs, summarizing number (%) of subjects with any

- (related/all) TEAE
- (related/all) Serious TEAE
- DLT
- (related/all) TEAE leading to death
- (related/all) TEAE of grade 3 or higher
- (related/all) TEAE leading to drug interruption
- (related/all) TEAE of special interest (AESI)
- (related/all) TEAE leading to permanent discontinuation

- TEAEs by primary SOC and PT, showing number (%) of subjects with at least one TEAE, sorted alphabetically by SOC and decreasing incidence of PTs within SOC for the total column. This sorting order will be applied to all other tables, unless otherwise specified.

- TEAEs by PT, sorted by decreasing frequency in the total column.
- All at least possibly drug related TEAEs by primary SOC and PT, showing number (%) of subjects with at least one possibly related TEAE, sorted by sorting order defined above.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing number (%) of subjects with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by sorting order defined above.

- Listing of TEAEs showing treatment group, subject identifier, SOC, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

DLT summaries:

- DLTs by SOC and PT, showing number (%) of subjects with at least one DLT, sorted by sorting order defined above.

- Listing of DLTs showing cohort, subject identifier, SOC, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

AESI summaries:

- Treatment-emergent AESI by category and PT, showing number (%) of subjects with at least one TEAE, sorted alphabetically by category and decreasing incidence of PTs within category for the total column. This sorting order will be applied to all other tables, unless otherwise specified.

- Listing of treatment-emergent AESI showing cohort, subject identifier, category, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

Treatment-Emergent Suicidal Ideation and Behavior (SIB)

- Treatment-emergent SIB events will be summarized by treatment group, showing number (%) of subjects with at least one TEAE of suicidal ideation and behavior, and number (%) of subjects for each PT.
- A listing of suicidal ideations and behaviors will also be presented.
- Additional SIB analyses may be conducted as needed, such as follow-up time adjusted incidence rates of SIB event.

Serious TEAE(s) summaries:

- All serious TEAEs by primary SOC and PT, showing number (%) of subjects with at least one serious TEAE, sorted by sorting order defined above.
- All at least possibly related to ublituximab serious TEAEs by primary SOC and PT, showing number (%) of subjects with at least one possibly related serious TEAE, sorted by sorting order defined above.
- All serious TEAEs by seriousness criteria, presented by primary SOC and PT, showing number (%) of subjects with at least one serious TEAE by seriousness criteria.
- Listings of SAEs showing treatment group, subject identifier, SOC, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

TEAE(s) leading to treatment discontinuation summaries:

- All TEAEs leading to treatment discontinuation, by primary SOC and PT, showing number (%) of subjects with at least one TEAE sorted by sorting order defined above.
- Listings of TEAEs leading to treatment discontinuation showing treatment group, subject identifier, SOC, PT, verbatim term, date and day of onset, end date/time, duration, outcome, severity, date of death (if relevant), relationship to study treatment, action taken, AE seriousness and criteria.

Deaths summaries:

- Number (%) of subjects who died during the study period will be presented by cohort and total.
- All TEAEs leading to death, by primary SOC and PT, showing number (%) of subjects sorted by sorting order defined above.
- Listings of deaths showing cohort, subject identifier, gender, race, age, date of death (if relevant), study day relative to first dose date, primary cause of the death

2.4.5.2 Analysis of Laboratory Variables

Clinical laboratory variables that will be analyzed include hematology tests, serum chemistry tests and coagulation tests (see Section 2.1.4.2 for the complete list of parameters).

Laboratory data for hematology and serum chemistry tests will be reported in summary tables and listings. Laboratory data for coagulation and serology tests will be presented in listings. Individual values outside the laboratory reference ranges will be identified (by “H” for high and “L” for low) in the data listings displaying the absolute values for each subject.

Continuous laboratory test results will be summarized descriptively by cohort for actual values and for changes from baseline. Number and percentage of subjects with laboratory abnormalities (H/L) will be presented. Visits to be summarized include all scheduled post-baseline visits.

Shift table from baseline to the worst post-baseline tests will be presented based on laboratory abnormalities (H/L). Laboratory tests that have high and low abnormalities will be summarized separately for each direction (e.g., hypocalcemia and hypercalcemia).

Drug-Induced Liver Injury (DILI)
The liver function tests, namely AST, ALT, total bilirubin (TBL), and alkaline phosphatase are used to assess possible drug induced liver injury. Evaluations of drug-induced serious hepatotoxicity (eDISH) plot (Hy's Law graphs) of distribution of peak values of ALT, AST and the maximum of ALT and AST versus peak values of total bilirubin will also be presented. Similarly, a graph for ALT vs. TBL and a graph for AST vs. TBL will be provided.

2.4.5.3 Analyses of Vital Sign Variables

Summary tables of vital signs and change from baseline will be presented for all scheduled visits where vital signs were assessed. All recorded vital sign data will be listed.

2.4.5.4 Analysis of Physical Examination Variables

Physical examination data will be presented in a data listing.

2.4.5.5 Analysis of Electrocardiogram Variables

ECG interpretation will be tabulated as frequencies by visit and time point, and in a shift table of baseline vs. worst post-baseline observation. Results per time point and free-text specifications of abnormalities will be listed.

2.4.6 Study Treatment Exposure and Compliance

Treatment exposure and compliance variables will be summarized as quantitative variables (N, mean, SD, median, Q1, Q3, minimum, and maximum). The percentage of subjects who have a compliance of <80%, 80% to <100%, and >=100% will be tabulated by cohort.

2.4.7 Analyses of Pharmacokinetics

Pharmacokinetics for ublituximab

An independent SAP will be issued to detail the conduct of population PK and exposure-response analyses.

2.4.8 Analyses of Anti-Drug Antibody (ADA)

The percentage of subjects developing ADA will be summarized by cohort. A listing will be provided for ADA data.

2.4.9 Analyses of Immunoglobulins

The descriptive summary and change from baseline of Immunoglobulins will be summarized by cohort. A listing will be provided for Immunoglobulins data.

2.5 Data Handling Conventions

Data handling discussions for the primary efficacy is included in Section 1.2.1. The further discussion for the data handling conventions for other variables will be included in this section.

General conventions

The following formulas will be used for computations of parameters.

Demographic formulas:

The age variable recorded in the eCRF will be used for analysis, no derived age variable is planned as only the year of birth is reported.

$$\text{BMI (in kg/m}^2) = \frac{\text{weight in kg}}{\text{height (in cm)} \times \text{height (in cm)}} \times 10000$$

Renal function formulas:

Creatinine clearance value will be derived using the equation of Cockroft and Gault. The calculation requires body weight and age. The last weight measurement on or before the visit of the creatinine measurement will be used. If available, the age used by central lab at the visit will also be used for this derivation, otherwise the age at informed consent will be used. Additionally, eGFR based on MDRD will be calculated.

$$crcl\ (mL/\min) = \frac{(140 - age) \times weight(kg)}{0.814 \times creatinine(umol/L)} \quad \text{(For males)}$$

$$crcl\ (mL/\min) = \frac{(140 - age) \times weight(kg)}{0.814 \times creatinine(umol/L)} \times 0.85 \quad \text{(For females)}$$

2.5.1 Missing Data

For categorical variables, subjects with missing data are not included in calculations of percentages unless otherwise specified. The number of subjects with missing data will be presented.

For data listings, the character date will always be used to present the date collected in the eCRF, which allows the actual recorded date to be shown if elements are unknown/missing.

2.5.1.1 Multiple sclerosis medical history variables

If the date of first MS diagnosis, first symptoms of MS, most recent relapse onset or start and end of previous MS treatments are incomplete, (i.e., month is unknown or day is unknown), unknown month/day will be set to July 1st, an unknown day will be set to the 15th.

2.5.1.2 Adverse event information

Adverse event start date
AE start date will be used for AE classification and analysis. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing:
If AE start year is the same as first dose year and the AE start month is the same as the first dose month) then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise (AE start year is not the same as first dose year and/or AE start month is not the same as the first dose month) impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is 'D'.

If AE start month is missing, and AE start year is not missing:
If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 1 January. Imputation flag is 'M'.

If AE start year is missing:
Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date
The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, In order to carry through the logic for programming, the following intermediate step will be used. Afterwards, the original character/numeric date recorded in CRF and supportive imputed end date will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing:
Impute AE end date using the last day of the month. If this leads to a date after end of follow-up date, use end of follow-up date instead.

If AE end month is missing, and AE end year is not missing:
Impute AE end date using 31 December as the day and month. If this leads to a date after end of follow-up date, use the end of follow-up date instead.

If AE end year is missing:
Impute AE end date using the end of follow-up date.

Severity of adverse event

If the severity is missing for one of the treatment emergent occurrences of an AE (the same SOC/PT), the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences a "missing" category will be added in summary table.

Relationship to investigational product

If the assessment of the relationship to investigational product is missing, then the relationship to investigational product has to be assumed as related and the AE considered as such in the derived analysis variable.

Adverse event Listings

For date variables, only character date variables will be presented, and no imputed dates will be printed in the listings. If the AE start date is imputed, then the onset relative day will be empty; if the AE start date or end date is imputed, then AE duration will be empty.

2.5.1.3 Prior and concomitant medication date

Medication start and end date will be used for prior, concomitant and follow up medication classification and potential analysis for specific medications. To keep the data integrity, if the date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed (impute the end date first) and an imputation flag will indicate which date component is missing. Only the character variable will be used in data listing.

As prior and concomitant medications are flagged using the recorded start and end dates, it is not possible to apply different imputation rules based on the prior/concomitant status of a record. So the same algorithm will be used for all records made in the "prior/concomitant medication" section of the eCRF.

Prior/Concomitant medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D'.

If start month is missing, and start year is not missing: Impute the start day using 1 January. Imputation flag is 'M'.

If start year is missing: No imputation will be done.

Prior/Concomitant medication end date

If end day is missing, and end month and year are not missing:
Impute end date using the last day of the month. If this leads to a date after end of study date, use end of study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing:
Impute end date using 31 December as the day and month. If this leads to a date after end of study date, use the end of study date instead. Imputation flag is 'M'.

If end year is missing:
Impute date using the end of study date. Imputation flag is 'Y'.

2.5.2 Windows for Time Points

MRIs are linked to specific visits, so it is not necessary to assign visits based on relative timing. Other efficacy assessments will be summarized by the nominal visit as well and no visit window will be defined.

For safety assessments, the reference date for the derivation of relative days of events or findings will be the date of first dose as documented in the eCRF. All available values obtained between 2 visits including unscheduled measurements will be assigned to the appropriate visit window as specified in section 2.5.3. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary, in case of equal distance the later observation will be selected. For further details please see the section "Unscheduled Visits" as well.

2.5.3 Unscheduled Visits

Only scheduled visit efficacy measurements will be used for analyses visit to exclude the temporary fluctuations in the clinical status that may occur with a relapse.

Safety data from unscheduled visits will be used in in all safety analyses. The unscheduled visits will be assigned to the appropriate analysis time window. The one closest to the targeted visit date will be used in the presence of multiple measurements within the same time window. If two observations within a window have the same target distance, the later one will be used for analysis. The following windows will be used:

Week of study	Target day	Minimal days	Maximum days
1 (day 1)	1	1	1
1 (day 2)	2	2	4
2	8	5	W3-1 (11)
3	15	W3 (12)	W3 +6 (21)
4	28	W3+7 (22)	42
8	56	43	70
12	84	71	98
16	112	99	126
20	140	127	W24-1 (154)
24	168	W24 (155)	W24+6 (172)
2 days after w24	170	W24+2 (NA)	W24+4 (NA)
25	175	W24+5 (173)	W24+17 (185)
28	196	W24+18 (186)	224
36	252	225	294
48	336	295	378

Note: w3 and w24 refer to the actual date of 2nd and 3rd administration of ublituximab; the days in () are the alternative window if there is no 2nd or 3rd administration of ublituximab.

3 Interim Analysis

There are no interim efficacy analyses planned for this study.