COVER PAGE

Official Title:	A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis Via a Subcutaneous Route of Administration
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STATISTICAL ANALYSIS PLAN

Version No.: 1.0

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Study Title: A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants with Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of Administration

Name of Study Treatment: Tysabri

Protocol No.: 101MS330

Study Phase: 3

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APPROVAL

This document has been reviewed and approved by:		
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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Stable SAP, V0.1	04 May 2022	Not applicable
SAP V1.0	05 June 2024	Final, Approved

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LIST OF ABBREVIATIONS

Abbreviation	Definition
3T	3 Tesla
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	anti-natalizumab antibodies
ARR	annualized relapse rate
AST	aspartate aminotransferase
CI	confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough concentration
CV	coefficient of variation
DMT	disease-modifying therapy
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
EOS	end of study
ET	early termination
FAS	Full analysis set
GGT	gamma glutamyl transferase
[redacted]	[redacted]
ICH	International Council for Harmonisation
IV	intravenous(ly)
JCV	John Cunningham virus (human polyomavirus)
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Abbreviation	Definition
MS	multiple sclerosis
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PT	preferred term
Q4W	every 4 weeks
RBC	red blood cell
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SMQs	standardized MedDRA queries
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1

1 Introduction

Natalizumab (Tysabri) is a recombinant, humanized, anti-α4-integrin monoclonal antibody currently approved as a disease-modifying therapy (DMT) for the treatment of multiple sclerosis (MS). The Sponsor has developed a pharmaceutical formulation for subcutaneous (SC) administration in a prefilled syringe (PFS) that delivers natalizumab at a dose of 150 mg (in 1 mL), enabling a total dose of 300 mg to be delivered by 2 consecutive injections, every 4 weeks (Q4W). Studies in cohorts of participants with MS have shown that this product is similar to the intravenously (IV) formulation with respect to its pharmacokinetic (PK), and pharmacodynamic (PD) profile as well as its efficacy and safety (Studies 101MS102 and 101MS206).

This Phase 3 study is aimed to evaluate the efficacy, safety, PK and PD of natalizumab 300 mg Q4W administered to Japanese participants with relapsing-remitting multiple sclerosis (RRMS) via a SC route of administration.

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses as outlined in the study protocol. This SAP is written based on the following documentation under the guidance of International Council for Harmonisation (ICH) documents:

Document	Date	Version
Protocol	21 Feb 2022	3.0
eCRF	15 Mar 2023	4.0

2 Study Overview

2.1 Study Objectives and Endpoints

Primary Objective	Primary Endpoint
To evaluate the efficacy of natalizumab 300 mg SC Q4W administrations up to 24 weeks in Japanese participants with RRMS	Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans

Secondary Objectives	Secondary Endpoints
To evaluate other clinical and MRI measures of efficacy of natalizumab 300 mg SC Q4W administrations in Japanese participants with RRMS	• Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Change from baseline in number of gadolinium-enhancing lesions at Week 24 and Week 48 • The number of non-enhancing new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 • The number of new T1 hypointense lesions at Week 24 and Week 48 • ARR at Week 24 • ARR at Week 48 • ARR at Week 52 • Proportion of relapse-free participants at Week 24 and Week 52 • VAS assessing the participant's global impression of their well-being at Week 24 and Week 48
To evaluate the safety, tolerability, and immunogenicity of natalizumab 300	• Incidence of treatment-emergent AEs and SAEs from baseline to end of study

mg SC Q4W administrations up to 48 weeks in Japanese participants with RRMS	• Anti-JCV antibody status as measured by anti-JCV antibodies • Incidence of injection site reactions and injection reactions • Immunogenicity as measured by the incidence of anti-natalizumab antibodies • Change in EDSS score from baseline to Week 24 • Change in EDSS score from baseline to Week 48
To evaluate the PK and PD of natalizumab 300 mg SC Q4W administrations up to 24 weeks and for an additional 24 weeks in Japanese participants with RRMS	• Serum natalizumab concentrations (C_{trough}) at each visit until Week 48 • Serum natalizumab concentration between Day 6 and Day 8 • α4-integrin saturation and serum soluble VCAM-1 concentrations at each visit until Week 48 (excluding Week 1 [Day 6 to Day 8] visit)
[redacted]	

2.2 Study Design

This is a multicenter, open-label, single-arm Phase 3 study to evaluate the efficacy, safety, tolerability, PK, and PD of natalizumab SC formulation in Japanese participants with RRMS. The study will be conducted at approximately 10 sites in Japan. The study will have 2 parts and enroll approximately 20 participants, who will receive natalizumab 300 mg SC Q4W.

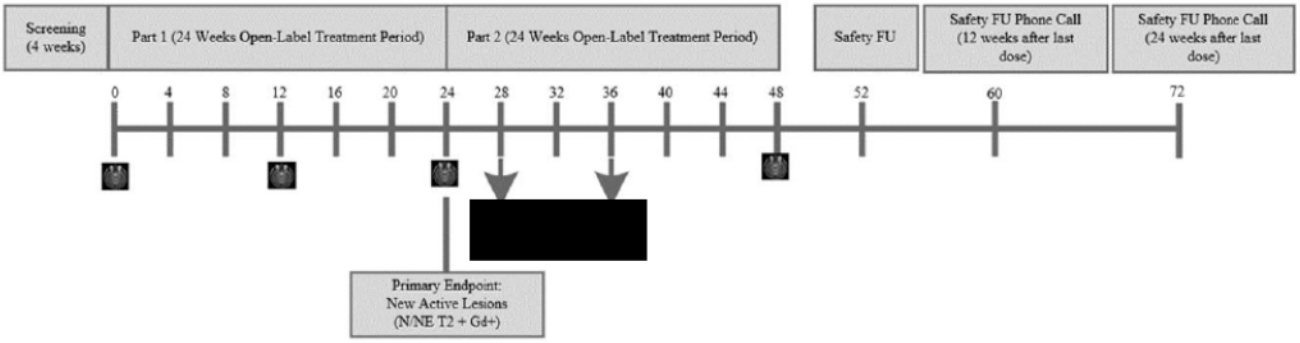
Part 1 is designed for a period of 24 weeks to include the efficacy, safety, tolerability, PK, and PD evaluation of natalizumab SC formulation.

Part 2 is designed for an additional period of 24 weeks to include efficacy and safety assessments. Additionally, similar assessments, including safety, PK, and PD, will be assessed after [redacted] in Part 2 to confirm the usability of a [redacted] of natalizumab SC.

At the completion of their 48-week Treatment Period, participants will have Safety Follow Up Visit at Week 52 and will receive a follow-up safety phone call at Week 60 and Week 72 (i.e., 12 weeks and 24 weeks after the last dose of study treatment on Week 48) before completing the study.

See

Figure 1: Study Design Schematic

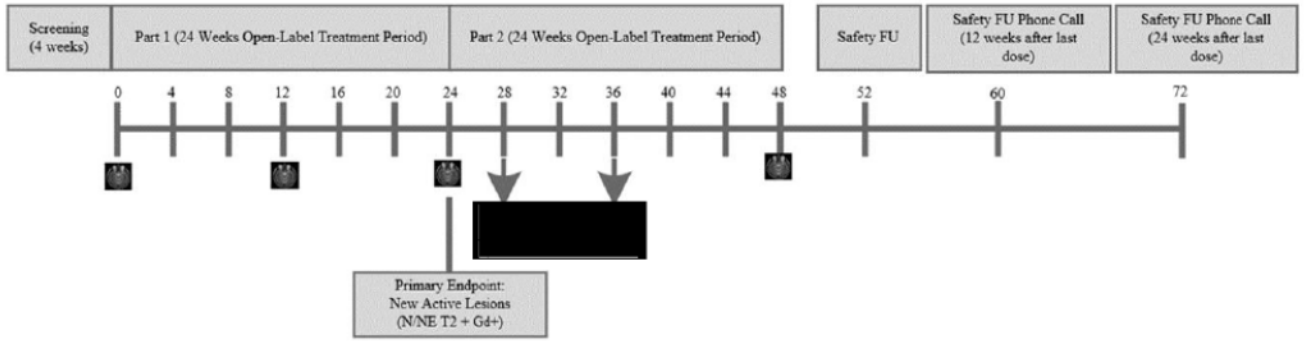


Note: Note: An additional visit will occur between Day 6 and Day 8 to collect a blood sample for C_{trough}.

for a schematic of the study design.

The total duration of study participation for each participant will be up to 76 weeks; this consists of a screening period of up to 4 weeks, a treatment period of 24 weeks in Part 1, a treatment period of 24 weeks in Part 2, and safety follow-up period of 4 weeks. A follow-up safety phone call will be performed 24 weeks after the last dose of study treatment.

Figure 1: Study Design Schematic



Note: Note: An additional visit will occur between Day 6 and Day 8 to collect a blood sample for C_{trough}.

2.3 Schedule of Activities

See Protocol section 1.3.

2.4 Sample Size Considerations

The study plans to enroll approximately 20 participants which was based on feasibility. Approximately 15 through 17 evaluable participants are deemed sufficient to characterize the efficacy profile of natalizumab SC.

The margin in Study 101MS330 showing comparability of the natalizumab SC to IV is set at 2.32, which is one-third of the mean difference (1.53 and 8.49) between the natalizumab and placebo groups in new active lesions at Week 24 in Japanese natalizumab IV study 101MS203. To demonstrate the comparability of natalizumab SC to IV, 15 evaluable participants allow at least 80% probability that the upper limit of the 95% CI for mean new active lesions at Week 24 in natalizumab SC is lower than 3.85 (i.e., 2.32 plus 1.53), assuming similar field MRI machines are used for Studies 101MS203 and 101MS330 and the true mean of new active lesions for the natalizumab SC is 1.53. In addition, assuming 70% of participants will have MRIs using 3T machines in Study 101MS330, compared to approximately 13% in Study 101MS203, and the true mean of new active lesions is 1.73, 17 evaluable participants allow 80% probability that observing the upper limit of 95% CI for new active lesions at Week 24 in natalizumab SC is lower than 3.85 [Shilane and Bean 2013].

3 Definitions

3.1 Dates and Points of Reference

3.1.1 Study Baseline

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first dose of study treatment (SC injection). Change from baseline will be defined as the post baseline value minus the baseline value.

- Study day 1: the day of the first study treatment injection
- Study day for a date on or after study day 1:

  Study day = (date of Interest) – (date of first study treatment injection) + 1
- Study day for a date before study day 1:

Study day = (date of Interest) – (date of first study treatment injection)

3.1.2 End of Study

The end of study date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed, up to the date of AE resolution or until the last safety follow up phone call (24 weeks after last dose of study medication), whichever occurs first.

Test data will be analyzed using the nominal visit as reported. Visit windows for unscheduled visits will be specified in Appendix B for safety endpoints.

3.2 Study Treatment

Natalizumab 300 mg SC will be administered as a Q4W regimen over 48 weeks.

3.3 Definition of Alternative Treatment for MS

Alternative treatment for MS is defined as any non-study treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments, as described in Section 7.7.1.2 of the protocol.

3.4 Treatment Period

Treatment period is defined as from the day of the first study treatment injection to the day of the last study treatment injection (Week 48) for participants who completed study treatment, or the day of early termination (ET) visit for participants who discontinued study treatment.

3.5 Study Periods

The total study duration for each participant will be up to 76 weeks and will consist of the following:

- 4-week Screening Period
- 24-week Treatment Period in Part 1
- 24-week Treatment Period in Part 2
- 4-week Safety Follow-Up Period after last dose of study medication
- Follow-up safety phone calls 12 and 24 weeks after the last study treatment injection

Participants will have up to 16 scheduled visits during the study and 2 safety follow-up phone calls. All visits should be performed ± 3 to 10 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the day of first study treatment injection).

3.6 Key Derived Variables

3.6.1 Definition of a treatment-emergent adverse event

A treatment-emergent AE (TEAE) is defined as any AE that has an onset date and time that is on or after the date and time of the first study treatment injection, or that has worsened on or after the date and time of the first study treatment injection through 84 days (or 168 days for PML cases) after the last study treatment injection. If only the AE onset or worsening date is available, it will be compared with the date of the first injection to determine a TEAE.

In order to define treatment emergence for AE with missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates for a particular event are missing, then the event is considered treatment emergent;
- If the start date for a particular event is missing and the stop date/time falls after the first injection date/time, then the event is considered treatment emergent;
- If the start date was the same as the first injection date, and the start time was missing, then the event is considered treatment emergent.

For events with a partial start date, the year/month of the event date will be compared to that of the first dosing date to determine whether the event is treatment emergent. If it cannot be determined whether an event is treatment emergent due to a missing or partial date, then the event will be tabulated as treatment emergent.

3.7 Stratification Factors and Subgroup Variables

Not Applicable

3.8 Analysis Sets

The following definitions describe the planned analysis sets for specific study analyses:

3.8.1 Full analysis set

The full analysis set (FAS) is defined as all participants who receive at least 1 study treatment injection and have at least 1 post baseline efficacy assessment from the efficacy assessments below:

- MRI Efficacy Assessments (not include locally read MRIs)
- Relapses (An MS relapse will be defined as the onset of new or recurrent neurological symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological examination, and not explained solely by non-MS processes such as fever, infection, severe stress, or drug toxicity; see protocol section 5.4 for further details)
- Neurological examination and EDSS
- VAS assessing the participant's global impression of their well being

The primary and secondary efficacy endpoints will be evaluated on the FAS. Participants will be analyzed according to their planned treatment assignment.

3.8.1 Week 48 analysis set

The Week 48 analysis set includes all participants in the full analysis set but will exclude participants who withdrew from study due to termination of study by Sponsor.

3.8.2 Safety analysis set

The safety analysis set is defined as all participants who receive at least 1 study treatment injection. Participants will be analyzed based on the treatment they receive.

3.8.3 Immunogenicity analysis set

The immunogenicity analysis set is defined as all participants who receive at least 1 study treatment injection and have at least 1 postbaseline assessment for the specific parameter.

3.8.4 PK analysis set

The PK analysis set is defined as all participants who receive at least 1 study treatment injection and have at least 1 measurable serum natalizumab concentration.

3.8.5 PD analysis set

The PD analysis set is defined as all participants who receive at least 1 dose of study treatment and have at least 1 assessment for α4-integrin saturation, serum soluble VCAM-1 concentration, and [redacted]

Participants will be analyzed based on actual treatment received for Immunogenicity, PK and PD analysis sets.

4 List of Planned Study Analyses

4.1 Interim Analysis

Interim analysis as described in Section 12.8 of the protocol was not performed for this study.

4.2 Final Analysis

Final analysis will be performed after the last participant completes the 24-week safety follow-up after the last dose on the study. Refer to Section 5 for the analyses for all study endpoints.

5 Statistical Methods for Planned Analyses

5.1 General Principles

Summary tables will be presented using descriptive summary statistics. For continuous variables, summary statistics will generally include number of participants with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include number of participants dosed, number with data, and the percent of those with data in each category.

For summary of PK and PD parameters, refer to sections 5.8 and 5.9.

In the analysis using negative binomial regression model, if the data are underdispersed, or if the negative binomial regression model does not converge, a Poisson regression model with the same covariates will be used instead of the negative binomial regression model. Dispersion will be evaluated from the Pearson Chi-Square statistic. If the ratio of the Pearson Chi-Square statistic to the degrees of freedom is ≤ 1 which indicates no overdispersion, then a Poisson regression model with adjustment for under dispersion will be used.

Unless stated otherwise, all statistical tests will be 2-sided with statistical significance level of 0.05.

The statistical analysis will be performed using the software package SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

5.2 Missing Data and Outliers Handling Conventions

Missing gadolinium-enhancing or new or newly enlarging non-enhancing T2 hyperintense lesions at Week 12 or 24 will be imputed using last observation carried forward on-treatment.

To define concomitant use for medications and procedures with missing start or stop dates, the additional criteria are defined in Section 5.6.4. The imputation rules for missing or partially missing start and end dates are defined in Appendix A.

For AEs with missing or partial start date, if there is no clear evidence that the AEs started or increased in severity before the initial dosing of study treatment in the study, the start date will be imputed to the initial study treatment injection date and the AEs will be regarded as TEAEs in the treatment period. The imputation rules for missing or partially missing AE start and end dates are defined in the Appendix A.

No formal statistical analyses will be performed to detect or remedy the presence of outliers, unless otherwise specified.

5.3 Participant Accountability

Disposition of participants will be summarized, and the summary data will include:

- Number of participants enrolled
- Number of participants dosed
- Number of participants who completed the Week 24 treatment
- Number of participants who completed the Week 48 treatment
- Number of participants who completed Week 52 visit
- Number of participants who completed the study including Week 72 safety phone call follow-up
- Number of participants who discontinued treatment and/or withdrew from study
- Number of participants in each analysis set
- Number of participants dosed by site
- Number of participants who completed the treatment period (up to Week 48) and who completed the study (up to 24-week safety follow-up) by site.

For participants who discontinued treatment and/or withdrew from study, the reasons for discontinuation and/or withdrawal, and days on treatment and days on study will be summarized and listed.

5.4 Demographic and Baseline Characteristics

Demographic data will be summarized, and the summary data will include:

- age (years) and age category (<40 and ≥ 40)
- sex
- ethnicity
- race
- country
- height
- weight and baseline body weight category (≤ 80 kg and > 80 kg)
- body mass index (BMI)

Baseline disease characteristics will also be summarized using descriptive statistics and the summary data will include:

- EDSS
- years since disease (MS) onset
- years since MS diagnosis
- the number of relapses during the years (1, 2, and 3 years) prior to first injection of Tysabri in current study

In addition, summary statistics for following baseline MRI assessments will also be presented.

- Gadolinium-enhancing lesion number
- T2 hyperintense lesion number
- T1 hypointense lesion number

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 27.0 or later). The number and percentage of participants with medical history (including both ongoing and past medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Number and percentage of participants with previous MS treatments will be summarized by medications. Prior MS treatments will also be listed.

5.5 Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. The major protocol deviations will be summarized. Listings will be generated for both major and minor protocol deviations, respectively.

5.6 Study Treatment Exposure and Concomitant Medications

5.6.1 Study Treatment Exposure

Participants will receive each dose of natalizumab 300 mg SC administered via two pre-filled syringes of 150 mg/mL (total of 300 mg/2 mL).

Number of complete doses = number of injections / 2 (if the value is not a whole number, the lowest integer will be taken, e.g., if number of injections / 2 is 12.5 then the number of complete doses is 12).

The number of participants who received a complete dose at each dosing visit will be presented.

5.6.2 Compliance

Compliance up to Week 24 and Week 48 will be calculated as follows:

Overall compliance (%) will be calculated regardless of treatment completion for all subjects as (number of complete doses received / total planned doses for 24 or 48 weeks [7 and 13 doses respectively]) * 100.

Compliance up to the last dose (%) is calculated as (number of complete doses received / number of doses the subject is expected to receive while on study) * 100.

Number of doses expected while on study is calculated using the protocol-specified dosing visit windows, as follows:

Number of doses expected	Treatment duration (days)	Protocol-defined visit window
1	[1, 25]	Week 4 minus 3 days
2	[26, 53]	Week 8 minus 3 days
3	[54, 81]	Week 12 minus 3 days

4	[82, 109]	Week 16 minus 3 days
5	[110, 137]	Week 20 minus 3 days
6	[138, 165]	Week 24 minus 3 days
7	[166, 193]	Week 28 minus 3 days
8	[194, 221]	Week 32 minus 3 days
9	[222, 249]	Week 36 minus 3 days
10	[250, 277]	Week 40 minus 3 days
11	[278, 305]	Week 44 minus 3 days
12	[306, 333]	Week 48 minus 3 days
13	≥ 334	Week 52 minus 3 days

Study drug compliance, the total number of doses received, and the number of doses missed based on the protocol-defined dosing visit window will be summarized.

5.6.3 Time on study, time on treatment, time exposed to study treatment

Time on study, time on treatment and time exposed to study treatment will be summarized using descriptive statistics:

- Time on study (in days) is defined as (last date on study - date of the first study treatment injection) + 1. The last date on study will be taken as the last visit / evaluation from all available data for the participant.
- Time on treatment (in days) is defined as (last study treatment injection - date of the first study treatment injection) + 1 and will be summarized using descriptive statistics and categorized for number of subjects on treatment up to Week 24, Week 24 to Week 48, Week 48 to Week 52, and Week 52 onwards.
- Time exposed to study treatment (in days) is based on number of days from the date of the first study treatment injection to the 28 days after the date of the last study treatment injection, e.g., (last study treatment injection - date of the first study treatment injection) + 29.

5.6.4 Concomitant Medications

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary (WHODD GLOBAL version B3 March 2024 or later if updated). All concomitant non-drug therapies will be coded using the latest version of MedDRA (version 27.0 or later if updated). A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first study treatment injection. This includes therapies that start prior to the initiation of the first injection if their use continues on or after the date of first injection. To define concomitant use for therapies with missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates of a therapy are missing, that therapy will be considered concomitant.
- If the start date of a therapy is missing and the stop date of that therapy fall on or after the date of the first injection, that therapy will be considered concomitant.
- If the start date of a therapy is prior to the date of the first injection and the stop date of that therapy is missing and the therapy is listed as continuing, that therapy will be considered concomitant, or
- If the start date of a therapy is prior to the date of the first injection and the stop date of that therapy is missing and the therapy is not listed as continuing, that therapy will be considered non-concomitant.

For a therapy with a partial start date, the year/month of the therapy date will be compared to that of the first dosing date to determine whether the therapy is concomitant. If the date of the therapy is missing and the year/month of the therapy date is same as the first injection, that therapy will be considered as concomitant.

The number and percentage of participants taking concomitant medication and non-drug therapies will be summarized. Concomitant medications and non-drug therapies will be listed.

The number and percentage of participants taking (switching to) an alternative treatment for MS will also be summarized.

5.7 Efficacy Endpoints

5.7.1 General Analysis Methods for Efficacy Endpoints

All efficacy analyses will be performed on the full analysis set.

All efficacy data collected at scheduled, unscheduled or ET visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Appendix B: Visit Window Mapping. If there

are 2 or more assessments available in the same analysis window for a participant, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

MRI assessments collected within 4 weeks after the last dose of steroid treatment for relapse will not be included in the efficacy analysis.

5.7.2 Primary Efficacy Endpoint

5.7.2.1 Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain scan

The primary endpoint of cumulative number of new active lesions (gadolinium enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) at Week 24 (Part 1) will be calculated as the sum of the new active lesions over the postbaseline scans at Weeks 12 and 24 for all treated participants with at least 1 postbaseline efficacy assessment, excluding participants with persistent anti-drug antibodies (ADA) or progressive multifocal leukoencephalopathy (PML). The cumulative number will be summarized using descriptive statistics. The primary analysis will be based on a negative binomial distribution model with no explanatory variables. The mean cumulative number of new active lesions (gadolinium enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) at Week 24 will be derived from the model with a 95% CI.

The proposed primary and [redacted] estimands will be based on a hypothetical strategy and/or the treatment policy strategy, as follows:

Population: All treated participants with at least 1 postbaseline efficacy assessment, excluding participants with persistent anti-drug antibodies (ADA) or progressive multifocal leukoencephalopathy (PML).

Subject level outcome: The cumulative number of new active lesions at Week 24 will be calculated as the sum of gadolinium enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions over the postbaseline scans at Weeks 12 and 24.

Intercurrent event handling: Intercurrent events include the start of alternative medication for MS, or early discontinuation of treatment due to safety or lack of efficacy.

The proposed primary estimand will be based on the treatment policy strategy, therefore, the primary analysis will utilize all measurements regardless of whether subjects remain on treatment.

For subjects who withdraw from the study due to lack of efficacy or an AE, missing values will be imputed using last observation carried forward on-treatment as specified below.

The secondary estimand will be based on a hypothetical strategy, in which the treatment effect will be estimated in the hypothetical scenario that the intercurrent event did not occur. The analysis for this estimand will treat the data obtained post-intercurrent event as missing values.

Missing gadolinium-enhancing or new or newly enlarging non-enhancing T2 hyperintense lesions at Week 12 or 24 will be imputed using last observation carried forward on-treatment as follows:

- If Week 24 data is missing, and Week 12 data is present, then the Week 24 data will be imputed to the value at Week 12.
- If Week 12 data is missing, and Week 24 data is present, then no imputation will be applied.
- If both Week 12 and Week 24 data are missing, the participant will not be included in the analysis.

Population-level summary measure: The LS mean and 95% CI of the cumulative number of new active lesions at Week 24 will be derived from a negative binomial distribution model with no explanatory variables. The cumulative number of new active lesions will also be summarized using descriptive statistics (number of participants with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum).

5.7.2.2 Sensitivity analysis

The sensitivity analysis will repeat the primary analysis as specified in Section 5.6.2 based on the observed data only.

5.7.3 Secondary Efficacy Endpoints

Secondary endpoints will be summarized using descriptive statistics as defined in 5.1, unless otherwise specified:

5.7.3.1 Cumulative number of new active lesions (sum of gadolinium enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans

Summary statistics including percentages will be calculated based on the Week 48 analysis set.

5.7.3.2 Proportion of participants with any new active lesions (gadolinium enhancing lesions or non-enhancing new or newly enlarging T2 hyperintense lesions)

Proportion of subjects with any new active lesions at Week 24 and Week 48 will be presented.

5.7.3.3 Number of lesions at Week 24 and Week 48

Descriptive statistics for the number of lesions at Week 24 and Week 48 will be provided for the following:

- Change from baseline in number of gadolinium-enhancing lesions
- The number of non-enhancing new or newly enlarging T2 hyperintense lesions
- The number of new T1 hypointense lesions

5.7.3.4 Annualized relapse rates

Only relapses prior to Week 52 will be included in the analysis for this endpoint. Relapses that occur after subjects receive an alternative medication for MS will be excluded from the analyses of relapse rate, and the subject's time on study will be censored at the time the alternative medication is started.

The unadjusted relapse rate is defined as the total number of relapses experienced divided by the total number of patient-years on study at Weeks 24, 48, and 52 or at the last dose.

The subject relapse rate is defined as the number of relapses for that subject divided by the duration of the subject on study in years at Weeks 24, 48, and 52 or at the time of censoring.

The annualized relapse rate at Weeks 24, 48 and 52 will be analyzed using negative binomial regression models with baseline body weight ($\leq$ 80 kg versus > 80 kg) and site as covariates. The logarithmic transformation of the number of years in the study at the time of the last treatment injection (Week 48) or at the time of censoring will be included in the model as the "offset" parameter. The mean annualized relapse rate will be derived from the model with a 95% CI.

5.7.3.5 Proportion of relapse-free participants

The proportion of participants free of relapse at Week 24, Week 48, and Week 52 will be summarized.

5.7.3.6 Participant global impression of well-being

The participant's global impression of well-being will be assessed using a visual analogue scale (VAS) at Baseline, Week 24, and Week 48. The VAS at each visit and the change from baseline to each post-baseline visit will be summarized using descriptive statistics as defined in 5.1.

[redacted]

5.9 Safety Endpoints

All safety analyses will be performed on the safety analysis set.

All adverse events (AEs) and serious adverse events (SAEs), clinical laboratory abnormalities, vital sign measurements, 12-lead ECG, physical and neurological examination, Columbia Suicide Severity Rating Scale (C-SSRS), anti-drug [natalizumab] antibodies (ADA), anti-JCV antibodies, and EDSS will be summarized using descriptive statistics. Unless otherwise specified, no formal statistical testing will be performed on the safety data.

For safety data that are summarized by visit, assessment from all scheduled visits, ET visit, EOS visit, follow-up safety phone call visits and any unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme (Appendix B).

5.9.1 Clinical Adverse Events

Any AE experienced by the participant on or after the first injection in this study (Day 1/Baseline visit) through the 24-week follow-up safety phone call will be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

Any SAE experienced by the participant between the time of informed consent and 24-week follow-up safety phone call will be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment.

Unless otherwise specified, only TEAE will be presented in the summary tables.

The overall summary table of TEAEs will present the number and percentage of participants with the following events. A participant is counted only once in each category.

- Any TEAE
- TEAEs by severity (mild, moderate, or severe)
- TEAEs related to natalizumab
- Serious TEAEs
- Serious TEAEs related to natalizumab
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to withdrawal from study
- Any fatal events
- Any TEAE of special interest

For each category of AEs listed above, a summary table will be created which presents the number and percentage of participants by the following categorizations:

- preferred term (PT);
- primary system organ class (SOC);
- primary SOC and PT;
- severity, primary SOC and PT; and
- relationship to study treatment, primary SOC and PT.

Corresponding to the five categorizations above, the data will be processed as follows,

- a participant will be counted only once within each PT, and PTs will be ordered by decreasing frequency;
- a participant will be counted only once within each primary SOC, and primary SOCs will be ordered by decreasing frequency;
- a participant will be counted only once within each primary SOC/PT, and PTs will be ordered by decreasing frequency within each primary SOC.
- a participant will be counted only once within each primary SOC/PT, and the AE with the greatest severity will be used. PTs will be ordered by decreasing frequency within each primary SOC.
- a participant will be counted only once within each primary SOC/PT, and the AE with the relationship to study treatment will be used. PTs will be ordered by decreasing frequency within each primary SOC.

Adverse events of special interest

The number and percentage of treatment emergent adverse events of special interest (AESI) will also be presented. An AESI is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required. The AESI categories are defined mainly based on Standardized MedDRA Queries (SMQs), SOCs, and/or PTs.

The AESI categories may include but are not limited to the following:

- PML (all events that occur before the end of the study or up to 24 weeks after Tysabri discontinuation) [Serum anti-JCV antibody positive status alone without signs/symptoms does not necessarily indicate PML (recognizing that asymptomatic PML can occur)].
- Injection site pain
- Opportunistic infections other than PML
- Serious herpes infection (defined based on SMQs)
- Drug-induced liver injury
- Hypersensitivity reactions
- Malignancies

Other adverse events of interest

- Injection site reactions (defined based on SMQs)
- Injection reactions (defined as any events occurring within 2 hours of the injection).
- [redacted]
- [redacted]

Adverse events by ADA status

The number and percentage of participants with TEAE, SAE, hypersensitivity or injection site pain by ADA status will also be presented, as described in Section 5.12.1.

Adverse events listings

In addition, listings will be provided for the following:

- Adverse events
- Treatment-emergent adverse events
- Serious adverse events
- Treatment-emergent serious adverse events
- Adverse events that led to discontinuation of study drug
- Adverse events that led to withdrawal from study
- Adverse events of special interest
- Treatment-emergent adverse events with special interest
- [redacted]
- [redacted]
- Deaths

5.9.2 Clinical Laboratory Data

The following clinical laboratory parameters are assessed as stated in protocol Section 10.2:

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count.
- Blood chemistry: sodium, potassium, chloride, alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), lactate dehydrogenase, gamma glutamyl transferase (GGT), glucose, calcium, phosphorus, blood urea nitrogen, creatinine, uric acid, bilirubin (total and direct), total protein, albumin, and bicarbonate
- Urinalysis: color, protein, blood, glucose, ketones, pH, specific gravity, and microscopic examination if abnormal.

5.9.2.1 Quantitative laboratory analysis

Actual laboratory values, changes from baseline and percent changes from baseline in the selected quantitative laboratory values will be summarized using descriptive statistics by visit. Number of evaluable participants, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum values will be presented at each visit.

Plots of mean values (with standard deviation) for the key numeric laboratory parameters by visit will be provided.

Visit windows for by visit summaries

For laboratory by visit summaries, the analysis visit should be defined using visit windows (Tables 4 in Appendix B). If there is more than 1 value in the same analysis visit window (>1 value for the same analysis visit) for a certain parameter for a participant, then the closest record to the target visit day will be used for the by visit analysis. If there are 2 values in the same analysis visit window with the same distance from the target visit day for a certain parameter for a participant, then the record with the later date will be used for the by visit analysis. If there are 2 values on the same day for a certain parameter for a participant, then the record with the later time will be used for the by visit analysis.

5.9.2.2 Qualitative laboratory analysis

For all qualitative analyses, all values will be included (not just the "analyzed record" within each visit window in the quantitative analyses).

Shift analyses

Laboratory data will be summarized using shift tables where appropriate. Each participant's hematology and blood chemistry values will be flagged as "low", "normal", or "high" based on the normal ranges of the central laboratory or as "unknown" if no result is available. Shifts from baseline to high or low status for hematology and blood chemistry parameters will be presented.

In the hematology and blood chemistry shift summary tables, entries are numbers of participants shift to low (or high) divide by number of participants at risk followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of participants whose baseline value was not low (or high) and who had at least one post-baseline evaluation. Shift to low includes normal to low, high to low, and unknown to low. Shift to high includes normal to high, low to high, and unknown to high.

Potentially clinically significant (PCS) abnormalities

For hematology and blood chemistry, the number and percentage of participants with any post-baseline PCS laboratory abnormalities will be summarized for the parameters provided in Table 1.

Listings will also be presented for all participants with any PCS laboratory abnormalities. In these listings, each participant's complete history from screening to last study visit for that specific laboratory test meeting the PCS criteria will be listed; any abnormal values based on the normal ranges of the central laboratory and abnormal values based PCS criteria will be separately flagged in the same listing.

Table 1 Criteria to Determine Clinically Relevant Abnormalities in hematology and blood chemistry

Parameter Name	Unit	PCS Low	PCS High
Blood hematology			
White Blood Cells	$x10^9$ cells/L	< 3.0	>16
Neutrophils	$x10^9$ cells/L	< 1.5	>13.5
Lymphocytes	$x10^9$ cells/L	< 0.8	>12
Monocytes	$x10^9$ cells/L	N/A	>2.5
Eosinophils	$x10^9$ cells/L	N/A	>1.6
Basophils	$x10^9$ cells/L	N/A	>1.6

Hemoglobin for females for males	g/L	<= 95 <= 115	>=175 >=190
Hematocrit for females for males	%	<= 32 <= 37	>=54 >=60
Red Blood Cells (RBC)	$x10^{12}$ cells/L	<= 3.5	>=6.4
Platelet count	$x10^{9}$ cells/L	<= 75	>=700
Blood chemistry			
Sodium	mmol/L	<= 126	>= 156
Potassium	mmol/L	<= 3	>= 6
Chloride	mmol/L	<= 90	>= 118
Bicarbonate	mmol/L	<= 16	>= 35
Calcium	mmol/L	<= 2	>= 3
Phosphorus	mmol/L	<= 0.5491	>= 1.7119
Aspartate aminotransferase (AST)	IU/L	N/A	>= 3x ULN
Alanine Aminotransferase (ALT)	IU/L	N/A	>= 3x ULN
Alkaline phosphatase	IU/L	N/A	>= 3x ULN
Creatinine	umol/L	N/A	>= 1.5x ULN
Total Bilirubin	umol/L	N/A	>= 1.5x ULN
Total Protein	g/L	<= 45	>= 100
Albumin	g/L	<= 25	N/A

Uric Acid for females for males	umol/L	N/A N/A	>= 501.5 >= 619.5
Glucose (non-fasting)	mmol/L	<= 2.2	>= 13.75
Blood urea nitrogen	Mg/dl	<6	>20
Gamma-glutamyl transferase	Units/litre	<9	>48

Liver function laboratory tests

For liver function laboratory tests (ALT, AST, and total bilirubin), counts and percentages of maximal post-baseline values by following categories will be provided:

For ALT or AST,

- <= Upper Limit of Normal (ULN),
- > ULN,
- >= 3x ULN,
- > 5x ULN,
- > 10x ULN,
- > 20x ULN.

For total bilirubin,

- <= ULN,
- > ULN,
- >= 1.5x ULN,
- > 2x ULN,
- > 3x ULN,
- > 10x ULN.

A listing of the liver function test parameters will be provided.

5.9.3 Vital Sign Measurements

Vital signs collected in this study include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. All measurements are collected at all study visits except Week 1 visit until Week 52 visit and all measurements are collected at unscheduled visits. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities from Day 1/Baseline to the Week 52 and unscheduled visit, based on the following criteria in Table 2.

Table 2 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C and an increase from predosing of at least 1°C
Pulse rate	> 120 beats per minute and an increase from predosing of more than 20 beats per minute, or < 50 beats per minute and a decrease from predosing of more than 20 beats per minute
Systolic Blood Pressure	> 180 mmHg and an increase from predosing of more than 40 mmHg, or < 90 mmHg and a decrease from predosing of more than 30 mmHg
Diastolic Blood Pressure	> 105 mmHg and an increase from predosing of more than 30 mmHg, or < 50 mmHg and a decrease from predosing of more than 20 mmHg
Respiratory rate	>=20 breaths per minute with a pre-dose rate of < 20 breaths per minute <= 10 breaths per minute with a pre-dose rate of > 10 breaths per minute

A summary table for participants with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of participants with an abnormality divided by number of participants evaluated followed by corresponding percentages. Number evaluated is the number of participants who had a baseline assessment and at least one post-baseline assessment for that vital sign.

For each vital sign parameter, actual values and changes from baseline will be summarized using descriptive statistics by visit.

A participant listing will be presented for participants with any post-baseline clinically relevant abnormalities in vital signs. In this listing, each participant's complete vital sign values from screening visit to Week 52 and unscheduled visit will be listed with abnormalities labeled.

For vital sign visit summaries, the analysis visit will be defined by visit window in Appendix B. For the same parameter for a participant, if there is more than 1 record in the same analysis visit window, then select the record closest to the target visit day. If there are 2 records in the same analysis visit window with the same distance from the target visit day, then select the record with the later date. If there are 2 records on the same date, then use the average value for quantitative parameters and the worse value for qualitative parameters.

5.9.4 12-Lead ECG

ECG is performed at Screening, Week 24, and Week 52 (or Early Termination visit, if applicable) and will be summarized by visit. Overall interpretation (Normal/Abnormal, not AE/Abnormal, AE) will also be summarized. A listing of ECG data will be presented.

5.9.5 Physical and Neurological Examination

New abnormalities in physical and neurological assessments will be reported as AEs and presented in the AE summaries.

5.9.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The following analyses on C-SSRS measurements will be conducted:

- Descriptive summary of participants who answered "Yes" to any question 1-12 as well as participants who had suicidal ideation or suicidal behavior at screening visit and at any post-screening visits. The denominator for baseline summary is the number of participants who were dosed and had assessment at screening visit; the denominator for post-baseline summary is the number of participants who were dosed and had at least one assessment at the post-screening visits for each question.
- Descriptive summary of participants who had treatment-emergent suicidal ideation, participants who had new suicidal ideation as well as participants who had worsening suicidal ideation. The denominator is the number of dosed participants with suicidal ideation assessment at both screening visit and at least one post-screening visit.
- Descriptive summary of participants who had treatment-emergent suicidal behavior. The denominator is the number of participants who answered "No" to all suicidal behavior questions at screening visit and had suicidal behavior assessment at least one post-screening visit.
- Descriptive summary of participants who answered "Yes" to any question 1-12 at screening visit and at any post-screening visits by group: less risky (self injurious behavior without suicidal intent-Q12), moderate risky (suicidal ideation-Q1-5), most risky (suicidal behavior-Q6-11), and summary of participants by each of the questions within each group. The denominator for baseline summary is the number of participants who were dosed and had assessment at screening visit; the denominator for post-baseline summary is the number of participants who were dosed and had at least one assessment at the post-screening visits for each question.

Listing of participants having treatment-emergent suicidal ideation will be provided. participants who had new suicidal ideation and participants who had worsening suicidal ideation will be flagged. The listing will display both baseline (collected at screening visit) and post-baseline (collected at all post-screening visits) Suicidal Ideation Scores for each participant. Listing of participants having treatment-emergent suicidal behavior will also be provided.

5.9.7 EDSS

Change in EDSS score from Baseline to Week 24 and Week 48 will be summarized descriptively.

5.10 Pharmacokinetic Endpoints

The PK analysis set will be used for pharmacokinetics analysis. For pharmacokinetics data that are summarized by visit, measurement taken from ET visit will be assigned to the next scheduled visit.

Serum natalizumab concentrations (C_{trough}) will be measured Q4W (just prior to dose administration) until Week 48 and 1 serum natalizumab concentration will be measured between Day 6 and Day 8 to obtain absorption information for SC administration. These serum concentration data will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, maximum, geometric mean, 95% CI of geometric mean, and geometric CV%) at each timepoint. Mean trough serum natalizumab concentrations (+/- standard deviation) will be plotted over time.

All measured serum natalizumab concentrations in this study will be combined with other natalizumab study data for population PK analysis to evaluate absorption profile after natalizumab SC administration. The analysis plan and reports will be prepared separately from this study.

5.11 Pharmacodynamic Endpoints

The PD analysis set will be used for pharmacodynamics analysis. For pharmacodynamics data that are summarized by visit, measurement taken from ET visit will be assigned to the next scheduled visit.

The PD properties of natalizumab will be evaluated using the α4-integrin saturation and serum soluble VCAM-1 concentrations which will be measured Q4W (just prior to study treatment administration) until Week 48.

The data will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, maximum, geometric

mean, 95% CI of geometric mean, geometric CV%) at each timepoint, and mean values will be plotted over time for each parameter.

5.12 Immunogenicity Endpoints

5.12.1 Anti-Natalizumab Antibody Analysis

The immunogenicity analysis set will be used for immunogenicity analysis. Immunogenicity data will be mapped to the closest analysis visit using the visit window scheme described in Appendix B.

Immunogenicity is measured by the incidence of anti-natalizumab antibodies (anti-drug antibodies [ADA]). Incidence of ADAs will be summarized descriptively.

Serum samples for ADA analysis will be collected immediately prior to the natalizumab injection at Screening, Week 12, 24, 36, 48 and unscheduled visit for neurological worsening and early termination visit.

The percentage of participants who develop antibodies will be determined and summarized by visit.

The baseline value is defined as the latest immunogenicity data collected at any time prior to the first study treatment injection. If no immunogenicity data are collected prior to the first study treatment injection, the baseline value is missing and will be imputed as ADA negative for immunogenicity analyses.

A summary of negative and positive will also be presented using the following definitions:

- Participants with no positive post-treatment samples for ADA will be considered negative regardless of their baseline result.
- Participants with at least one confirmed post-treatment positive result will be considered positive for ADAs if their baseline result is negative.

In addition, for participants that are considered ADA positive, the following may be evaluated:

- Persistent ADA response:
  - Persistent positivity is defined as 2 positive results separated by at least 12 weeks, with 1 of the positive results occurring when the subject had received at least 24 weeks of treatment.
- Transient ADA response:
  - Transient Positive is defined as a positive at one timepoint but negative upon re-test at least 12 weeks later.

Any impact on efficacy and safety may be conducted by considering antibody status (negative, positive, transient positive, persistent positive).

The number and percentage of participants will be summarized by ADA status for the following categories/endpoints:

- Participants with hypersensitivity reactions
- Participants with relapse
- Participants with injection site pain
- Summary of cumulative number of new active lesions (gadolinium-enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions) relative to study baseline
- Treatment emergent adverse events
- Treatment emergent adverse events that led to discontinuation of study drug
- Treatment emergent adverse events that led to withdrawal from study
- Serious adverse events

A listing will be generated for participants determined to be persistent positive including ADA status, EDSS score, presence of new active lesions (gadolinium-enhancing lesions and non-enhancing new or newly enlarging T2 hyperintense lesions), and on study relapse status by visit.

In the event of very few subjects (less than 3) with transient or persistent positive ADA, only the listing will be provided.

5.13 Anti-JCV Antibody Analysis

The number and percentage of participants will be summarized for serum anti-JCV antibody status (positive/negative/indeterminate) by visit (Baseline, Week 24, and Week 48).

Serum anti-JCV antibody status, anti-JCV antibody index and the number of subjects in each anti-JCV antibody index category (≤ 0.9, >0.9 and ≤ 1.5 and > 1.5), as well as the number and percentage of subjects who have positive serum anti-JCV antibodies at any time will be summarized.

6 Statistical Considerations for Interim Analysis

Since no decision will be made from the interim analysis, there is no statistical impact to the study analysis.

7 Changes from Protocol-Specified Analyses

Interim analyses as described in Section 12.8 of the protocol were not performed for this study. Final analysis of all endpoints will be performed after the last participant completes the 24-week safety follow-up after the last dose on the study.

8 Summary of Changes from the Previous Version of the SAP

Not Applicable

9 References

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10 Appendix A: Imputation Rules for Missing AE dates and Concomitant Medications

Partial start dates (of intervention or event):

- Case 1, day is missing (only month and year are present):
  - If year and month are same as treatment period start date, then assign the day of treatment period start date to the partial date. **[worst case scenario (WCS)]**
    - However, if end date of event or intervention is clearly before treatment period start date, assign day '01' to partial start date. **[Max Duration]**
  - Otherwise, assign day of '01' to partial start date. **[Max Duration]**
- Case 2, only year is present:
  - If year is same as treatment period start date, then assign the month and day of the treatment period start date to the partial date. **[WCS]**
    - However, if end date of event or intervention is clearly before treatment period start date, assign 'Jan. 01' to partial start date. **[Max Duration]**
  - Otherwise, assign the month and day of 'Jan. 01' to partial start date. **[Max Duration]**
- Case 3, completely missing date, no imputation is performed.

Partial end dates (of intervention or event):

- Case 1, day is missing (only month and year are present):
  - If year and month are same as study end date then assign the day of the study end date to the partial date. **[Do not exceed study end]**
  - Otherwise, assign day of last day of the month (28, 29, 30 or 31) to the partial end date **[Max Duration]**
- Case 2, only year is present:
  - If year is same as study end date then assign the month and day of the study end date to the partial date. **[Do not exceed study end]**
  - Otherwise, assign 'Dec. 31' to the partial end date. **[Max Duration]**
- Case 3, completely missing date, no imputation is performed.

If any partial dates have missing month, with day present, then day is ignored and also considered missing. The year-only scenario is considered for imputation purposes.

Also, if the study is ongoing (e.g., interim analysis) and study end date is not available then the cut-off date will be used in the place of study end date. If both a cut-off date and study end date are present for a participant, then the minimum of the two dates will be used as the study (or reference) end date.

11 Appendix B: Visit Window Mapping

For data that are summarized by visit for longitudinal analysis, assessment from all scheduled visits including ET visit and EOS visit, and all unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme, unless otherwise specified.

Analysis visit windows are defined in Table 2 – Table 9 for different endpoints.

To define analysis visit window, the target visit day is calculated as (week number*7+1). The lower bound of visit window is calculated as target day−(target day−target day of previous visit)/2+1, except for the first post-baseline visit window whose lower bound is set as Day 2; the upper bound of visit window is calculated as target day+(target day of next visit−target day)/2.

If there are 2 or more assessments from visits other than ET or EOS visits mapped to the same analysis visit for a participant, the assessment that is closest to the target visit day will be used for analysis. If there are 2 or more assessments from visits other than ET or EOS visits mapped to the same analysis visit with the same distance from the target visit day, then select the later one(s) for the analysis. If there are 2 or more assessments from visits other than ET or EOS visits mapped to the same analysis visit and on the same day, use the average value for quantitative parameters and the worst value for qualitative parameters for analysis.

If ET visit is mapped to an analysis visit and a prior visit (either scheduled or unscheduled visit) is mapped to the same analysis visit, then ET visit will be remapped to the next analysis visit. If EOS visit is mapped to an analysis visit and a prior visit, e.g., ET visit, is mapped to the same analysis visit, then EOS visit will be remapped to the next analysis visit. The latest analysis visit for ET visit can be up to Week 48 and for EOS visit can be up to Week 72.

Visit Mapping for MRI Brain Scan

MRI assessments collected within 4 weeks after the last dose of steroid treatment for relapse will not be included in the efficacy analysis. MRI data collected at unscheduled visit for safety monitoring will not be included in the efficacy analysis. Assessments from ET visit will be mapped to the next scheduled visit as described above.

Table 2: Visit Windows for Hematology, Blood Chemistry and Urinalysis

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 4	29	[2,57]
Week 12	85	[58,127]

Analysis visit	Target visit day	Analysis visit window
Week 24	169	[128,183]
Week 28	197	[184,225]
Week 36	253	[226,295]
Week 48	337	[296, 351]
Week 52	365	≥ 352

Table 3: Visit Windows for Vital Signs Measurements

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 4	29	[2,43]
Week 8	57	[44,71]
Week 12	85	[72,99]
Week 16	113	[100,127]
Week 20	141	[128,155]
Week 24	169	[156,183]
Week 28	197	[184,211]
Week 32	225	[212,239]
Week 36	253	[240,267]
Week 40	281	[268,295]
Week 44	309	[296,323]
Week 48	337	[324,351]
Week 52	365	≥ 352

Table 4: Visit Windows for Physical Examination/Weight Measurements

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 4	29	[2,57]
Week 12	85	[58,127]
Week 24	169	[128,211]
Week 36	253	[212,295]
Week 48	337	[296, 351]

Analysis visit	Target visit day	Analysis visit window
Week 52	365	≥352

Table 5: Visit Windows for Anti-natalizumab Antibodies

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 12	85	[2,127]
Week 24	169	[128,211]
Week 36	253	[212,295]
Week 48	337	≥296

Table 6: Visit Windows for Anti-JCV Antibodies, EDSS and Neurological Assessment

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 24	169	[2, 253]
Week 48	337	≥254

Table 7: Visit Windows for ECG

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 24	169	[2, 267]
Week 52	365	[≥ 268]

Table 8: Visit Windows for PD Assessments

Analysis visit	Target visit day	Analysis visit window
Day 1	1	≤ 1
Week 4	29	[26,32]
Week 8	57	[54, 60]
Week 12	85	[82, 88]

Analysis visit	Target visit day	Analysis visit window
Week 16	113	[110, 116]
Week 20	141	[138, 144]
Week 24	169	[166, 172]
Week 28	197	[193, 200]
Week 32	225	[222, 228]
Week 36	253	[250, 256]
Week 40	281	[278, 284]
Week 44	309	[306, 312]
Week 48	337	[334, 340]

Table 9: Visit Windows for PK Assessments

Analysis visit	Target visit day	Analysis visit window
Day 1	1	≤ 1
Day 6-8	7	[4, 10]
Week 4	29	[26,32]
Week 8	57	[54, 60]
Week 12	85	[82, 88]
Week 16	113	[110, 116]
Week 20	141	[138, 144]
Week 24	169	[166, 172]
Week 28	197	[193, 200]
Week 32	225	[222, 228]
Week 36	253	[250, 256]
Week 40	281	[278, 284]
Week 44	309	[306, 312]
Week 48	337	[334, 340]

12 Appendix C: Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an assessment that evaluates suicidal ideation and behavior. Measurements are collected with the C-SSRS Baseline version at screening visit, and the C-SSRS Since last visit version is used instead at all other study visits until the EOS visit, including the unscheduled visits if applicable.

There are 11 common "Yes/No" questions at screening and post-screening visits. Five questions on *suicidal ideation* and five questions on *suicidal behavior* are re-ordered and follow increasing severity order respectively as shown in Table 12; another question on *self-injurious behavior without suicidal intent* is listed separately. In particular, only participants who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any participants who answered "No" to question 2, an answer "No" will also be assumed to question 3, 4, and 5. An additional "Yes/No" question is used to record if participant had committed suicide in post-screening visits.

Table 12 C-SSRS re-ordered questions

Suicidal Ideation	
Question 1	Wish to be dead
Question 2	Non-specific active suicidal thoughts
Question 3	Active suicidal ideation with any methods (not plan) without intent to act
Question 4	Active suicidal ideation with some intent to act, without specific plan
Question 5	Active suicidal ideation with specific plan and intent
Suicidal Behavior	
Question 6	Preparatory acts or behavior
Question 7	Aborted attempt
Question 8	Interrupted attempt
Question 9	Actual attempt

Question 10	Suicidal behavior
Question 11 (post-screening visits only)	Suicide
Self-Injurious Behavior without Suicidal Intent	
Question 12	Self-injurious behavior without suicidal intent

A participant is considered to have *suicidal ideation* at the period of interest if a "Yes" is answered to any of the five suicidal ideation questions (Question 1-5). A participant is considered to have *suicidal behavior* at the period of interest if a "Yes" is answered to any of the five suicidal behavior questions (Question 6-10) at screening visit or a "Yes" is answered to any of the six suicidal behavior questions (Question 6-11) at post-screening visits.

A participant's *Suicidal Ideation Score* is defined as the maximal suicidal ideation question number (maximal of 1-5) with an answer "Yes" per visit. The score is defined as 0 if the participant answered "No" to all 5 Suicidal Ideation questions at that visit.

A participant is considered to have treatment-emergent suicidal ideation if the participant had either new or worsening suicidal ideation. A participant is considered to have new suicidal ideation if the participant's Suicidal Ideation Score increased at any post-screening visit compared to a score 0 at screening visit. A participant is considered to have worsening suicidal ideation if the participant's Suicidal Ideation Score increased at any post-screening visit compared to a positive score at screening visit.

A participant is considered to have treatment-emergent suicidal behavior if the participant answered "Yes" to any suicidal behavior questions at any post-screening visit while answered "No" to all suicidal behavior questions at the screening visit.