COVER PAGE

Official Title:	A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration
NCT Number:	NCT03689972
Document Date:	SAP Part 1 version 2.0: 05 May 2021 SAP Part 2 version 2.0: 30 Aug 2023

Statistical Analysis Plan

Version No.: Final Version 2

Study Title: A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment

Name of Study Treatment: Natalizumab (BG00002)

Protocol No.: 101MS329

Study Phase: Phase 3b

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STATISTICAL ANALYSIS PLAN

Product Studied: Natalizumab (BG00002)

Protocol Number(s): 101MS329

A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment

Date of Protocol: 08 July 2020, Final Version 3

Date of Statistical Analysis Plan: 04 May 2021

This document has been reviewed and approved by:		
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Study Medical Lead (Printed Name)	Signature	Date

1 VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Final version 1.0	06-Jun-2019	Finalized version 1
Final version 2.0	04-May-2021	Finalized version 2. To add amendment to include additional analyses to evaluate impact of COVID-19, and to clarify/amend some planned analyses, such as the definition of per-protocol (PP) population.

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
CI	confidence interval
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
EDSS	Expanded Disability Status Scale
EID	extended interval dosing
EOS	end of study
[redacted]	[redacted]
Gd	gadolinium
ICF	informed consent form
INEC	Independent Neurology Evaluation Committee
IRT	interactive response technology
IV	intravenous(ly)
[redacted]	[redacted]
KM	Kaplan-Meier
MMRM	mixed model of repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
PBMC	peripheral blood mononuclear cell
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
[redacted]	[redacted]
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
[redacted]	[redacted]
SID	standard interval dosing
[redacted]	[redacted]
[redacted]	[redacted]
US	United States
SDV	Source data verification

2 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment, with the goal of estimating the difference between SID and EID, with high precision and a narrow 95% confidence interval (CI), to support the treatment decision based on individualized benefit/risk assessments.

The primary endpoint that relates to this objective is the number of new or newly enlarging T2 hyperintense lesions at Week 72.

2.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To evaluate additional relapse-based clinical efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
- To evaluate disability worsening of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
- To evaluate additional MRI-lesion efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
- To evaluate the safety of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months in relation to continued SID treatment.

The secondary endpoints are:

- Time to first relapse (relapses will be adjudicated by an Independent Neurology Evaluation Committee [INEC])
- Annualized relapse rate at Week 72
- Time to Expanded Disability Status Scale (EDSS) worsening (confirmed after at least 24 weeks)
- Number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48
- Number of new gadolinium (Gd)-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72
- Safety assessments of AEs and serious adverse events (SAEs)

[redacted]

[redacted]

3 STUDY DESIGN

3.1 Study Overview

This is a prospective, randomized, interventional, controlled, open-label, rater-blinded, Phase 3b study in subjects with RRMS who have been receiving natalizumab SID for at least 12 months without relapses in the last 12 months. All MRI scans will be read at a central facility with raters blinded to subject assignment. Approximately 480 subjects are expected to be enrolled at approximately 100 sites in North America, Europe, and Australia. Subjects will be randomly assigned to continue to receive natalizumab in 1 of the following 2 arms:

- SID: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion every 4 weeks (28 -2/+5 days).
- EID: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion every 6 weeks (42 -2/+5 days).

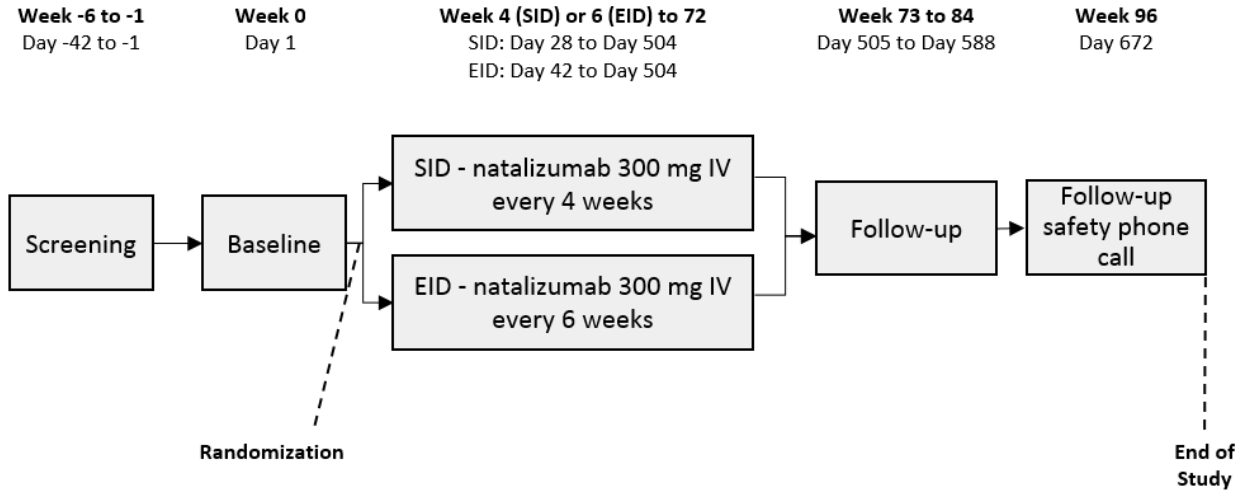
Randomization will be stratified by country/region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia), body weight (≤ 80 kg versus > 80 kg), and duration of natalizumab exposure (≤ 3 years versus > 3 years). Subjects will receive open-label natalizumab at their assigned frequency throughout the 72 weeks of the study.

See Figure 1 for a schematic of the study design.

The total duration of study participation for each subject will be up to 102 weeks; this consists of a screening period of up to 6 weeks, a treatment period of 72 weeks, and follow-up period of 12 weeks. A follow-up safety phone call will be performed 24 weeks after the last dose of study treatment.

The end of study (EOS) date for a subject may be the last study visit, last follow-up phone conversation, or last protocol-specified assessment, or if the subject has ongoing AEs that are being followed up, then the date may be the date of AE resolution.

Figure 1: Study Design



3.2 Schedule of Events

- See Protocol Section 5.
- Start date of COVID-19 phase

COVID-19 phase refers to the time period during which conduct of this study is impacted by COVID-19 infection or COVID-19 pandemic measures. The start date of the COVID-19 phase for this study is 02 March, 2020.

- COVID-19 pandemic measures

Refer to any action or challenges arising due to COVID-19 that may impact study conduct, including quarantines, site closures, travel limitation, interruptions to the supply chain for the investigational product, or other considerations if site personnel become infected with COVID-19.

4 SAMPLE SIZE JUSTIFICATION

Historical data on MS treatments, including a meta-analysis on the relationship between new or newly enlarging T2 lesions and relapses, suggest little or no clinical relevance of a difference of 0.2 to 0.3 in mean lesion numbers over 72 weeks [Sormani and Bruzzi 2013]. With the planned sample size of N = 200/group, the precision of the estimated mean lesion numbers is sufficient to allow > 80% probability to observe the lower limit of the 95% CI for the ratio of EID to SID in the estimated mean lesion number above 1 if the true mean is 0.5 and 0.3 in the EID and SID group, respectively. If the true mean is 0.6 and 0.3 in the EID and SID group, respectively, the probability will be approximately 90%. In the other direction, the sample size provides a precision that allows approximately 90% probability to

observe the upper limit of the 95% CI to be ≤ 2 if the true mean lesion numbers in both groups are 0.3. Approximately 480 subjects will be enrolled to account for a drop-out rate of approximately 17%.

5 STATISTICAL ANALYSIS METHODS

5.1 General Considerations

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

Country/region will be categorized as following in the analysis, including the demographics, the covariate in statistical models and subgroup analysis:

- North America (includes USA and Canada)
- United Kingdom
- Europe and Israel (includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain)
- Australia

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first randomized treatment infusion. Change from baseline will be defined as post-baseline value minus baseline value.

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 underdispersion will be used.

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

The statistical software, SAS® will be used for all summaries and analyses.

5.2 Treatment Period Definitions

Treatment period: treatment period is defined as from the date of the first study infusion to the date of the last study infusion (Week 72) or the date of ET visit.

Study period: Study period is defined as from the date of the first study infusion to a subject's last study visit, last follow-up phone conversation, or last protocol-specified assessment, or if the subject has ongoing AEs that are being followed up, to the date of AE resolution.

5.3 Analysis Population

- Modified Intent-to-treat (mITT) population:

  The modified intent-to-treat population is defined as all randomized subjects who receive at least 1 dose of study treatment and have at least 1 postbaseline result from below clinical efficacy assessments:

  - MRI Efficacy Assessments (not include locally read MRIs)
  - Relapses (clinical relapses are assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours; see protocol section 7.3 for further details)
  - Neurological examination and EDSS
  - [redacted]
  - [redacted]
  - [redacted]

  Subjects will be analyzed in the groups to which they are randomized for mITT population.

- Per-protocol (PP) population:

  The per-protocol (PP) population is defined as the subset of the mITT population and also

  - Have no significant of following protocol deviations that would be expected to affect efficacy assessments:
    - Subject was enrolled without meeting one or more inclusion or met any exclusion criteria
    - Subject receives rescue medication without meeting protocol-defined rescue criteria
  - Subjects with <=3 total number of missed doses or doses received outside of the protocol defined dosing visit windows.

  The primary and secondary endpoints will be evaluated on the per protocol population. Subjects will be analyzed in the groups to which they are randomized.

- Safety population:

  The safety population is defined as all randomized subjects who receive at least 1 dose of study treatment. Subjects will be analyzed based on the treatment they receive.

- [redacted]

  [redacted]

- [redacted]

[redacted]

Subjects will be analyzed based on randomized treatment for mITT population and per-protocol population, while subject will be analyzed based on actual treatment received for safety population, [redacted]. If a subject is randomized to EID arm but half or more number of doses the subject receives are actually given every four weeks, then the actual treatment for this subject is SID, and vice versa.

5.4 Background Characteristics

The summaries in this section will be based on the mITT population.

5.4.1 Accounting of Subject

Disposition of subjects will be summarized and the summary data will include number of subjects randomized and dosed, number of subjects who completed the treatment (week 72 visit), number of subjects who completed week 84 visit, number of subjects who completed the study including week 96 safety phone call follow-up, and number of subjects who discontinued treatment and/or withdrew from study. For subjects 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.

Number of subjects in each analysis population will be summarized. Number of subjects dosed will be summarized by country/region. In addition, number of subjects who completed the treatment/study will be summarized by country/region.

The number of subjects whose visits are impacted by the pandemic, including missing or out-of-window study treatment will be summarized, according to information recorded in the study protocol deviation listing. Due to COVID-19 pandemic measures, there may be challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV). The number of subjects who have any pending SDV data and the number of study visits without SDV performed will be presented.

5.4.2 Demographics and Baseline Characteristics

The demographic data including age (years), age category (<40 and ≥ 40), sex, ethnicity, race, Country/region, height, weight, and body mass index (BMI) will be summarized by treatment groups.

Body weight at baseline will also be categorized and presented using the following two groupings: <40 kg, 40 to 59 kg, 60 to 79 kg, 80 to 89 kg, and ≥ 90 kg, and ≤ 80 kg, > 80 kg.

Baseline disease characteristics will also be summarized by treatment groups, using descriptive statistics. These include years since disease (MS) onset, years since diagnosis, number of relapses during the one year prior to first dose of Tysabri, score of last EDSS assessment prior to first dose of Tysabri and baseline EDSS scores. In addition, summary statistics for following baseline MRI assessments will also be presented.

- T2 hyperintense lesion volume
- Gd-enhancing lesion number and volume
- T1 hypointense volume
- Normalized brain volume

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Number and percentage of subjects with previous MS treatments other than Tysabri will be summarized by medications and treatment groups. Prior MS treatments other than Tysabri will also be listed.

In addition, Tysabri treatment history will also be summarized. These include total number of doses of Tysabri the subjects have ever received prior to enrollment, total duration of Tysabri the subjects have received prior to enrollment, number of doses of Tysabri the subjects have received in the last 12 months prior to enrollment, and number and percentage of subjects missed any doses of Tysabri in the last 3 months of treatment prior to the screening visit. Details of Tysabri treatment history will be listed for each subject.

5.4.3 Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary. All concomitant non-drug therapies will be coded using the MedDRA dictionary. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first infusion of study drug. This includes therapies that start prior to the initiation of the first infusion if their use continues on or after the date of first infusion. 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 infusion, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first infusion 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 infusion 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 infusion, that therapy will be considered as concomitant.

The number and percentage of subjects taking concomitant medication and non-drug therapies will be summarized by treatment groups. Non-drug therapies will be presented by treatment groups. Concomitant medications and non-drug therapies will be listed.

The most frequent concomitant medications, defined as those taken by at least 10% of subjects in any group, will also be summarized by treatment groups. In addition, number and percentage of subjects taking (switching to) rescue treatment will also be summarized.

5.4.4 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 (presented by treatment groups). Listings will be generated for the major and minor protocol deviations, respectively. All protocol deviations related to COVID-19 pandemic measures will be provided in a listing with all available details.

5.4.5 Study Drug Exposure and Study Drug Compliance

Study drug compliance will be summarized for each treatment group. Overall compliance, which is the percentage of drug infusion actually received over total planned infusions for 72 weeks, will be summarized regardless of treatment completion for all subjects. Study drug compliance percentage up to the last dose of randomized treatment received will be defined as the number of infusions actually received divided by the number of infusions that the subject is expected to receive during the study period.

The total number of infusions actually received and the number of infusions missed at the protocol defined dosing visit window will be summarized by treatment groups. Time on study, time on randomized treatment and time exposed to study treatment will separately be summarized. Time on study is defined to start on the date of the first study infusion and will continue until the last date on study. The last date on study will be taken as the last visit / evaluation from all available data for the subject. Time on randomized treatment is based on number of days from the date of the first study infusion to the date of the last study infusion before the rescue treatment and will be summarized using descriptive statistics and will be categorized into 24 week intervals and summarized by treatment groups. Time exposed to study treatment is based on number of days from the date of the first study infusion to the 28 days after the date of the last study infusion before the rescue treatment. Time on study excluding time on rescue treatment and time on study after the last dose will also be presented. In addition, average duration between two study infusions before rescue treatment will be presented by treatment groups.

In this study, some subjects with study treatment administration are impacted by COVID-19 infection or COVID-19 pandemic measures. Therefore, drug non-compliance due to COVID-19 will be presented by treatment arm, including the missed and out-of-window doses.

5.5 Efficacy Analysis

All efficacy analyses will be performed on the mITT population. In addition, the primary and secondary endpoints will also be performed on the per-protocol population. The efficacy analysis will be presented by treatment groups (per randomization).

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 1. If there are 2 or more assessments available in the same analysis window for a subject, 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. MRI data collected at unscheduled visit for safety monitoring won't be included in the efficacy analysis.

Table 1 Visit Windows for Efficacy Endpoints

Analysis visit	Target visit day	Analysis visit window
Baseline	1	Most recent non-missing pre-dose value<=1
Week 12	85	[2,127]
Week 24	169	[128,211]
Week 36	253	[212,295]
Week 48	337	[296,379]
Week 60	421	[380,463]
Week 72	505	[464,547]
Week 84	589	>=548

5.5.1 Primary Efficacy Endpoint

5.5.1.1 Primary Analysis

The primary endpoint, the number of new or newly enlarging T2 hyperintense lesions at Week 72, will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years

versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia) as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value. The treatment will be considered different if the lower limit of the 95% CI is above 1. As a secondary inference, the possibility of a 2-fold increase in the mean lesion number in the EID group as compared with the SID group will be considered ruled out if the upper limit of 95% CI is no greater than 2. However, if the total number of observed new/newly enlarging T2 lesion at Week 72 is less than 15, then the negative binomial regression model won't be conducted, and only descriptive summary statistics at Week 72 will be presented. Otherwise, if negative binomial regression model doesn't work, poisson regression model will be conducted instead, and if poisson regression model doesn't work, either, then only descriptive summary statistics at Week 72 will be presented. This rule will be applicable to the analysis of new/newly enlarging T2 lesion number at Week 24 and Week 48 as well as the analysis of other MRI parameters.

The study plans to make every effort to retain subjects in the study and to continue follow-up in the cases of the initiation of rescue treatment, switching to different dosing frequency, and treatment discontinuation due to AEs, lack of efficacy, or for other reasons. This will allow continuing assessments of subjects' MS disease activity. Efforts will also be made to obtain details of withdrawals in the generic categories of "lost to follow-up" or "other" whenever possible. Classification of the withdrawals in these nonspecific categories into "possibly efficacy related", "possibly safety related", or "no information" will be made based on all available information by independent Sponsor personnel who are blinded to treatment regimen and will be documented prior to database lock.

The proposed primary estimand will be based on a treatment policy strategy, in which the study is intended to estimate the difference of a potential treatment decision of switching subjects from SID to EID compared with keeping subjects on SID over the next 72 weeks in a realistic clinical setting, where switching to a different dosing regimen or different medication may occur depending on disease activity. Therefore, the primary analysis will utilize all measurements regardless of whether subjects remain on randomized treatment. For subjects who withdraw from the study for reasons related to efficacy or an AE or who have a "possibly related" withdrawal, as described above, the missing values will be imputed by the worst observed value of the subjects on study treatment at the given timepoint. For withdrawals classified as "no information", the missing values will be treated as missing at random and will be addressed using multiple imputation. The number and proportion of subjects with intercurrent events and the time to intercurrent event will also be tabulated by randomized groups.

The secondary estimand will be based on a hypothetical strategy, in which the difference in the efficacy of EID versus SID at the 72 weeks following randomization if no intercurrent events occurred will be the target of estimation. The analysis for this estimand will treat the data obtained post-intercurrent event as missing values. For treatment discontinuation or switching due to efficacy as well as withdrawal that is due to efficacy or is "possibly efficacy related", the missing values will be imputed by the worst observed values of the subjects on study treatment at the given timepoint. For intercurrent events due to other reasons, the resulting missing values will be addressed using multiple imputation.

Multiple Imputation

Multiple imputation using fully conditional specification logistic regression method will be performed to impute intercurrent events due to other reasons. The treatment group variable will be coded so that the EID group is the first in the sort order. When the multiple imputation (MI) procedure is performed by treatment, the imputation will be done on the EID subjects first.

Prior to the Proc MI step the dataset will be sorted by treatment code and ascending unique subject identifier (USUBJID). The imputation will include the treatment, baseline volume of T2 hyperintense lesions, and stratification factors (country/region, body weight (≤ 80 kg versus > 80 kg) and duration of natalizumab exposure (≤ 3 years versus > 3 years)) as well as the number of new or newly enlarging T2 hyperintense lesions at each time point up to week 72 and the study visit in the model. A set of 100 complete imputed data sets will be generated with 100 burn-in iterations and the relative efficiency (RE) parameter will be checked.

The pseudo SAS code can be found in Appendix I and seed 87922 will be used to perform the multiple imputation.

To handle the missing MRI data, the reason for the occurrence of the first intercurrent event should be determined first. If the first intercurrent event is receiving rescue treatment, including switching from EID to SID or taking non-natalizumab rescue treatment, then the reason will be 'possibly efficacy related'. If the first intercurrent event is early termination from randomized treatment (EOT) or early withdrawal from study (EOS), then medical team will review the data of each EOT/EOS subject, including EOT/EOS, adverse event, lab, MRI, EDSS, concomitant medication and relapse, and adjudicate the reason, which takes a value from 'possibly efficacy related', 'possibly safety related', 'no information' or 'no information/not related'. Therefore, missing MRI data due to COVID-19 can be still handled with the procedure as prespecified above. Additionally, the MRI data (except the collection date) won't need SDV because they are collected from a central vendor, and the chance that the pending SDV collection date will affect the primary analysis is minimal. Therefore, as a supportive analysis, we will only present the pending SDV MRI collection date by treatment arm.

5.5.1.2 Sensitivity analysis

All the sensitivity analyses will be conducted for the mITT population and will be performed for both estimands, respectively.

5.5.1.2.1. Tipping point analysis

Tipping point analysis will be performed to assess the robustness of the primary analysis to deviation from the missing-at-random assumption.

The tipping-point analysis is a progressive stress-testing to assess how severe departures from missing-at-random must be in order to overturn the conclusion of the primary analysis [Yan et al. 2009]. For this study, subjects are assumed to have more N/NE T2 lesions after early withdrawal from study due to other reasons compared to subjects who remain on study.

The missing data are first imputed by the standard multiple imputation (assuming missing at random). To reflect the worse performance after early withdrawal, pre-specified shift parameters, the imputed values for subjects on SID and EID will be multiplied by a factor delta, δc and δt, respectively. The

adjusted multiple imputed datasets will then be analyzed by a negative binomial model and the results will be combined using the Rubin's rule for inference. A range of δ_c and δ_t will be applied by including -log(δ_c) and -log(δ_t) as offset in the negative binomial regression model for the missing data imputed by the multiple imputation.

The ratio of mean lesion numbers of EID versus SID (EID/SID) with a 95% CI and associated p-value will be calculated for each combination of δ_c and δ_t. The tipping region is defined as the combinations of δ_c and δ_t such that if the upper limit of the 95% CI is above 2. δ_c and δ_t will range between 1 and 5 in increments of 0.5 for the number of new or newly enlarging T2 hyperintense lesions at 72 weeks. For a given comparison, if a tipping point was observed with analysis at 0.5 increments, the δ values will be further refined down to 0.25 increments for the relevant interval. For example, if a tipping point is identified when increasing δ_t from 1 to 1.5, the matrix will be expanded to include also the value δ_t = 1.25.

The tipping region of yielding the lower limit of the 95% CI below 1 will also be presented, respectively.

The scientific plausibility of the tipping region will be evaluated. If implausible departures from the missing-at-random assumption (large δ) are needed in order to change the results from statistically significant to insignificant, the results of the primary analysis are considered to be robust to departure from the missing-at-random assumption.

5.5.1.2.2. Adjusting for baseline volume of T2 hyperintense lesions

Baseline volume of T2 hyperintense lesions will be added to the negative binomial regression model of primary analysis specified in section 4.5.1.1 as a sensitivity analysis for the primary endpoint.

5.5.1.3 Supplementary analysis

5.5.1.3.1. Assuming all missing values as missing at random

The primary analysis will be repeated by imputing all missing values by treating all as missing at random using multiple imputation. Both primary estimand and secondary estimand will be estimated in this supplementary analysis. The multiple imputation model specified in the primary analysis will be employed.

5.5.1.3.2. Per-protocol analysis

The per-protocol analysis will repeat the primary analysis as specified in Section 4.5.1.1 based on the per-protocol population.

5.5.1.3.3. Proportion of subjects with no new or newly enlarging T2 hyperintense lesions over week 72

The proportion of subjects with no new or newly enlarging T2 hyperintense lesions over week 72 will be analyzed using logistic regression models with the same covariates as those described above. Data will be censored at the time the subject starts rescue treatment or withdraw from study treatment. Responder for this analysis is defined as subjects who complete study treatment until week 72 and have no new or newly enlarging T2 hyperintense lesions prior to week 72. Non responder includes subjects

with new or newly enlarging T2 hyperintense lesions reported prior to week 72 and subjects who discontinue randomized treatment and switch due to efficacy as well as withdraw due to efficacy or is "possibly efficacy related" prior to week 72. Subjects who discontinue treatment or switch due to non-efficacy reasons prior to week 72 and have no new or newly enlarging T2 hyperintense lesions reported prior to the intercurrent event will be excluded from this analysis.

As a sensitivity analysis, subjects who discontinue treatment or switch due to non-efficacy related reasons prior to week 72 and have no new or newly enlarging T2 hyperintense lesions reported prior to the intercurrent event will be included as responders.

5.5.2 Secondary Efficacy Endpoint

5.5.2.1 Time to First Relapse

Only INEC-confirmed protocol-defined relapses prior to Week 72 will be included in the analysis for this endpoint. Relapses that occur after subjects have received rescue treatment including reverting to natalizumab SID as a rescue treatment or switching to another disease-modifying therapy prior to Week 72 will be excluded from the analyses of time to first relapse, and the subject's time in the study will be censored at the time the subject starts rescue treatment. If a subject withdraws from the study prior to Week 72 and the subject did not experience relapse as adjudicated by INEC prior to withdrawal, he or she will be censored on the last day they were in the study if the reason for withdrawal is not related to lack of efficacy. For withdrawals due to lack of efficacy, the withdrawal time will be considered as event time. The start date for time to first relapse or censoring is defined as the date of first randomized infusion.

The proportion of relapsed subjects will be estimated using the Kaplan-Meier (KM) product limit method and be presented as KM curves over time. The comparison of treatment groups will be based on Cox regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years) and region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain]) as covariates. The hazard ratio of relapse of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value.

5.5.2.2 Annualized Relapse Rate

Only INEC-confirmed protocol-defined relapses prior to Week 72 will be included in the analysis for this endpoint. Relapses that occur after subjects receive rescue treatments will be excluded from the analyses of relapse rate, and the subject's time on study will be censored at the time the rescue treatment is started.

The relapse rate for each treatment group will be calculated as the total number of relapses experienced in the group divided by the total number of patient-years on study at the time of the last randomized treatment infusion (week 72) or at the time of censoring for the group. This is the unadjusted relapse rate.

In addition, the relapse rate for an individual subject will be calculated as the number of relapses for that subject divided by the duration of the subject on study in years at the time of the last randomized treatment infusion (week 72) or at the time of censoring. Based on these individual relapse rates, the mean and median for each treatment group will be presented. This is called the subject relapse rate.

The annualized relapse rate at Week 72 will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region as covariates. The logarithmic transformation of the number of years in the study at the time of the last randomized treatment infusion (week 72) or at the time of censoring will be included in the model as the "offset" parameter. The ratio of mean annualized relapse rate of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value.

5.5.2.3 EDSS Worsening

Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score ≥ 1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 that is confirmed after at least 24 weeks. The EDSS worsening is defined as confirmed when this minimum EDSS change is present on the next study visit.

EDSS worsening will not be confirmed at a visit where a relapse is also occurring. A subject is considered to be having a relapse for at least 29 days after the start date of an INEC-confirmed objective relapse. If a subject meets the defined criteria of EDSS worsening and is also having a relapse, the subject will be required to meet the defined minimum criteria at the subsequent visit. If subjects had a tentative EDSS worsening prior to the start of rescue MS medication, the EDSS evaluation after rescue MS medication will be used to confirm EDSS worsening. If subjects had a tentative EDSS worsening at Week 72, the EDSS evaluation at Week 84 will be used to confirm the tentative worsening.

Death due to MS will be counted as confirmed EDSS worsening. If the subject was in the midst of a tentative EDSS worsening at the time of death (e.g. the EDSS evaluation prior to death is a tentative worsening), the EDSS worsening date will be the date of the start of the worsening. If the subject had a confirmed EDSS worsening prior to death, the EDSS worsening date is the start date of the tentative worsening. Otherwise, the EDSS worsening date will be the date of death.

EDSS worsening can be confirmed at the early (premature) study withdrawal visit, according to the rules above, as long as the early withdrawal visit is not also a relapse assessment visit.

Subjects who do not have a confirmed EDSS worsening based on the above rules will be censored. The censor date will be the date of the last EDSS assessment in the study, or the last EDSS assessment prior to the rescue treatment, unless the subject has a tentative EDSS worsening at this assessment. For subjects with a tentative EDSS worsening at the last study visit, (or the last EDSS prior to rescue treatment that was not confirmed) the censor date will be the date of the EDSS assessment prior to the last EDSS. The start date for calculation of day to confirm EDSS worsening or censor will be date of first infusion, and if date of first infusion is incomplete, date of randomization will be used.

Subjects who withdraw from the study after the baseline visit but prior to the first clinical evaluation scheduled visit will be censored at baseline. The start date is defined as the date of dose of natalizumab during the study.

Time to first confirmed EDSS worsening will be analyzed using KM estimates and Cox regression models similar to the method described above for time to first relapse.

5.5.2.4 Secondary MRI Endpoints

The number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 and the number of new Gd-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72 will be analyzed using the same approach as that for the primary endpoint.

Missing values of secondary MRI endpoints will be imputed following the same approach for the primary analysis based on hypothetical strategy.

5.5.2.5 Sensitivity/Supplementary analysis

Per-protocol analyses will be performed as supplementary analyses for secondary efficacy endpoints.

5.5.3 Subgroup Analysis

Subgroup analyses of the primary and key secondary endpoints will be conducted, as defined below, to evaluate the consistency of findings across populations.

- Baseline EDSS (EDSS score ≤ 2.0 versus EDSS score > 2.0)
- Age at baseline (age < 40 years versus age ≥ 40 years)
- Duration of natalizumab exposure (≤ 3 years versus > 3 years) at baseline
- Sex
- Country/region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)
- Baseline weight (40 to 59 kg, 60 to 79 kg, 80 to 89 kg, and ≥ 90 kg)
- [redacted]

In addition, subgroup analysis of the primary and key secondary endpoints will be evaluated in subgroups defined by prior disease activity, and the number and type of therapies prior to natalizumab [redacted] at baseline and Weeks 24.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.6 Safety Analysis

All Safety analyses will be performed on the Safety population.

All adverse events (AEs) and serious adverse events (SAEs), clinical laboratory abnormalities, vital sign measurements, physical examination findings, body weight and Columbia Suicide Severity Rating Scale (C-SSRS), will be evaluated for safety. Safety data collected by follow-up safety phone call visit (week 96 or earlier for early termination subjects) will be summarized using descriptive statistics by treatment groups. 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 visit and unscheduled visit will be mapped to an appropriate analysis visit using a windowing scheme (Tables 4-9 in APPENDIX II).

5.6.1 Clinical Adverse Events

Any AE experienced by the subject after the first infusion in this study (Day 1/Baseline visit) until the follow-up safety phone call is to be recorded in the eCRF, regardless of the severity of the event or its relationship to study treatment. Any SAE experienced by the subject between the time of the signing of the ICF and the follow-up safety phone call visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment.

Unless otherwise specified, only treatment-emergent adverse events will be presented in the summary tables. Treatment-emergent is defined as having onset date on or after the first randomized infusion date and prior to the 84 days after the last randomized infusion date.

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

The overall summary table of AEs will present the number of subjects with the following events for each treatment group. A subject is counted only once in each category.

- Any AE;
- AE with severity as “moderate” or “severe”;
- AE with severity as “severe”;
- Natalizumab related AE;

- Any SAE;
- Natalizumab related SAE;
- AE leading to discontinuation of study treatment; and
- AE leading to withdrawal from study.
- AE of special interest

The incidence of AEs will be also presented for each treatment group. They will be summarized by the following,

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

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

- a subject will be counted only once within each PT, and PTs will be ordered by decreasing incidence in the column of overall group, which combines all subjects in the study;
- a subject will be counted only once within each primary SOC, and primary SOCs will be ordered by decreasing incidence in the column of overall group;
- a subject will be counted only once within each primary SOC/PT, and PTs will be ordered by decreasing incidence within each primary SOC in the column of overall group.
- a subject 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 incidence within each primary SOC in the column of overall group.
- a subject will be counted only once within each primary SOC/PT, and the AE with the strongest relationship to study treatment will be used. PTs will be ordered by decreasing incidence within each primary SOC in the column of overall group.

The incidence of SAEs, incidence of AEs that led to withdrawal from study, and incidence of AEs that led to discontinuation of study drug will be also summarized by treatment groups with the use of primary SOCs/PTs. The data will be processed as what is done for incidence of AEs. Listing of AEs, SAEs, AEs that led to study treatment discontinuation and AEs that led to study withdrawal, regardless of treatment emergent or not, will be presented. Listing of death will be provided if applicable.

The incidence of adverse events of special interest will also be presented. These adverse event of special interest categories are defined mainly based on Standardized MedDRA Queries (SMQs), SOCs, and/or PTs. The AEs of special interest categories may include but are not limited to the following:

- PML progressive multifocal leukoencephalopathy (all events occur before the end of the study)
- Infusion reaction
- Opportunistic infections
- Drug induced liver injury
- Hypersensitivity reactions

In some AE/SAE listings, complete AE start and end dates are needed to calculate the relative study days of AE start and end. Therefore, any partial date will be imputed for these listings. Specifically, the partial AE start date will be imputed as the earliest possible date on or after the first infusion based on the partial information, and the partial AE end date will be imputed as the latest possible date on or before the follow-up safety phone call visit.

5.6.2 Clinical Laboratory Data

The following clinical laboratory parameters are assessed as stated in the protocol Section 5 and Section 14.2:

- Blood hematology: complete blood count with differential and platelet count, and absolute neutrophil count.
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyl-transferase (GGT), glucose, calcium, phosphorus, bicarbonate, chloride, sodium and potassium.

All the laboratory tables and listings, unless otherwise specified, will be presented by treatment groups.

5.6.3 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 treatment groups and visit. Number of evaluable subjects, mean, standard deviation, median, min and max 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 4-5 in APPENDIX II). 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 subject, 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 subject, 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 subject, then the record with the later time will be used for the by visit analysis.

5.6.4 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 subject'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 subjects shift to low (or high) divide by number of subjects at risk followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of subjects 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 subjects with any post-baseline PCS laboratory abnormalities will be summarized by treatment groups for the parameters provided in Table 2.

Subject listings will also be presented for all subjects with any PCS laboratory abnormalities. In these listings, each subject'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 2 Criteria to Determine Clinically Relevant Abnormalities in blood 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.

Listing of the liver function test parameters by treatment groups will be provided.

5.6.5 Vital Sign Measurements

Vital signs collected in this study include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate and body weight. All measurements are collected at all study visits until the EOS visit except body weight, which is only collected at screening visit and then every 24 weeks from baseline visit to EOS visit. All measurements are collected at unscheduled visits if applicable. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities from Day 1/Baseline to the EOS visit, based on the following criteria in Table 3.

Table 3 Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C and an increase from pre-dose of at least 1°C
Heart rate	> 120 beat per minute and an increase from pre-dose of more than 20 beats per minute. < 50 beats per minute and a decrease from pre-dose of more than 20 beats per minute.
Systolic Blood Pressure	> 180 mmHg and an increase from pre-dose of more than 40mmHg. < 90 mmHg and a decrease from pre-dose of more than 30 mmHg.
Diastolic Blood Pressure	> 105 mmHg and an increase from pre-dose of more than 30 mmHg. < 50 mmHg and a decrease from pre-dose 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 subjects with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of subjects with an abnormality divided by number of subjects evaluated followed by corresponding percentages. Number evaluated is the number of subjects 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 treatment groups and visit. The line of mean vital sign over time by treatment groups may be graphed.

A subject listing will be presented for subjects with any post-baseline clinically relevant abnormalities in vital signs. In this listing, each subject's complete vital sign values from screening visit to EOS visit will be listed with abnormalities labeled.

For vital sign visit summaries, the analysis visit will be defined by visit window (Tables 6-7 in APPENDIX II). For the same parameter for a subject, 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.

5.6.6 Physical and Neurological Examination

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

5.6.7 Columbia Suicide Severity Rating Scale (C-SSRS)

Please refer to appendix IV for the structure of this scale, and how to use it to assess suicidal ideation and behavior.

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

- Descriptive summary of subjects who answered "Yes" to any question 1-12 as well as subjects 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 subjects who were dosed and had assessment at screening visit; the denominator for post-baseline summary is the number of subjects who were dosed and had at least one assessment at the post-screening visits for each question.
- Descriptive summary of subjects who had treatment-emergent suicidal ideation, subjects who had new suicidal ideation as well as subjects who had worsening suicidal ideation. The denominator is the number of dosed subjects with suicidal ideation assessment at both screening visit and at least one post-screening visit.
- Descriptive summary of subjects who had treatment-emergent suicidal behavior. The denominator is the number of subjects who answered "No" to all suicidal behavior questions at screening visit and had suicidal behavior assessment at least one post-screening visit.

Listing of subjects having treatment-emergent suicidal ideation will be provided. Subjects who had new suicidal ideation and subjects 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 subject. Listing of subjects having treatment-emergent suicidal behavior will also be provided.

[redacted]

[redacted]

[redacted]

6 INTERIM ANALYSIS

An interim futility analysis, based on the number of new or newly enlarging T2 hyperintense lesions at 24 weeks, will be conducted when 50% of subjects have at least 6 months of randomized treatment.

The interim data will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI. The study may be stopped for futility if the lower limit of the 95% CI is > 2 and a 2-fold increase in mean lesion numbers in the EID group can be concluded with 97.5% confidence.

7 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

7.1 COVID-19 Related Analyses

In 2020 there is a worldwide outbreak of respiratory disease named as “Coronavirus Disease 2019” (COVID-19). It has been recognized that this COVID-19 public health emergency may impact the conduct of clinical trials of medical products and the challenges caused by the COVID-19 pandemic may lead to difficulties in meeting protocol-specified procedures including administering the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing (FDA 2020 and EMA 2020).

For this study 101MS329, most subjects have visits impacted by COVID-19 pandemic. The missing MRI data can be imputed and handled with the procedure prespecified, and therefore, no extra inferential analysis of the primary endpoint will be added. But some summary analyses due to COVID-19 are considered, including summary of study subjects with early termination from randomized treatment, early withdrawal from study, protocol deviation, missed or out-of-window dose due to COVID-19 as well as AE and non-drug concomitant treatment related to COVID-19.

There were also challenges to conduct on-site monitoring visits and thereof result in some study data pending source data verification (SDV) because of COVID-19. The incomplete SDV on dosing information, EOT/EOS data, as well as key efficacy assessments and AE/SAE due to the pandemic will be summarized by visit.

8 SUMMARY OF CHANGES FROM THE PREVIOUS VERSION OF THE SAP

8.1 Changes in Planned Analysis Methods

A few changes are made to the planned analysis methods to best suit the characteristics of the data to be analyzed, as well as to focus on the most relevant analyses addressing the trial objectives and scientific questions of interest. These changes include the following.

- The definition of actual treatment arm is added for the analysis of safety/[redacted]
- The definition of the per-protocol population is updated by changing the total number of missed dose/out-of-window dose that are allowed from 1 to 3.
- [redacted]
- [redacted]
- The definition of AE of special interest (AESI) is also updated by replacing 'Injection site reactions' with 'Infusion reaction'.
- [redacted]

8.2 COVID-19 Related Analyses

As discussed in Section 7, additional analyses are added in the SAP to assess impact of the COVID-19 pandemic.

9 APPENDIX I: PSEUDO SAS CODE FOR MULTIPLE IMPUATION

Following pseudo SAS code will be used for multiple imputation:

```
proc mi data= in_data seed=x nimpute=100  out=imp_data;
        class   treatment region wtgrp expogrp visit NNET2cnt;
        var  treatment region wtgrp expogrp visit NNET2cnt T2volbl;
        fcs NBITER=100 logistic(NNET2cnt = treatment region wtgrp expogrp T2volbl visit);
run;
```

where, treatment: Planned treatment for the trial; region : Country/region; wtgrp: Baseline body weight (≤ 80 kg versus > 80 kg); expogrp: Duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years); visit: Study visit; NNET2cnt: Number of new or newly enlarging T2 hyperintense lesions from previous visit.

Note that variable or parameter names may change prior to database lock.

10 APPENDIX II: VISIT WINDOW MAPPING

For data that are summarized by visit and 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. Analysis visit windows are defined in Table 4- 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 subject, 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 72 and for EOS visit can be up to Week 84.

Table 4: Visit Windows for Blood Hematology

Analysis visit	Target visit day	Analysis visit window for SID Group	Analysis visit window for EID group
Baseline/Day 1	1	≤ 1	≤ 1
Week 24	169	[2,253]	[2,253]
Week 48	337	[254, 421]	[254, 421]
Week 72	505	[422,547]	[422,547]
Week 84	589	≥ 548	≥ 548

Table 5: Visit Windows for Blood Chemistry

Analysis visit	Target visit day	Analysis visit window for SID Group	Analysis visit window for EID group
Baseline/Day 1	1	≤ 1	≤ 1
Week 84	589	≥2	≥2

Table 6: Visit Windows for Vital Signs Measurements

Analysis visit	Target visit day	Analysis visit window visit for SID Group	Analysis visit window for EID group
Baseline/Day 1	1	≤ 1	≤ 1
Week 4	29	[2,43]	NA
Week 6	43	NA	[2,64]
Week 8	57	[44,71]	NA
Week 12	85	[72,99]	[65,106]
Week 18	127	NA	[107,148]

Analysis visit	Target visit day	Analysis visit window visit for SID Group	Analysis visit window for EID group
Week 16	113	[100,127]	NA
Week 20	141	[128,155]	NA
Week 24	169	[156,183]	[149,190]
Week 28	197	[184,211]	NA
Week 30	211	NA	[191,232]
Week 32	225	[212,239]	NA
Week 36	253	[240,267]	[233,274]
Week 40	281	[268,295]	NA
Week 42	295	NA	[275,316]
Week 44	309	[296,323]	NA
Week 48	337	[324,351]	[317,358]
Week 52	365	[352,379]	NA
Week 54	379	NA	[359,400]
Week 56	393	[380,407]	NA
Week 60	421	[408,435]	[401,442]
Week 64	449	[436,463]	NA
Week 66	463	NA	[443,484]
Week 68	477	[464,491]	NA
Week 72	505	[492,547]	[485,547]
Week 84	589	≥ 548	≥ 548

Table 7: Visit Windows for Body Weight

Analysis visit	Target visit day	Analysis visit window for SID Group	Analysis visit window for EID Group
Baseline/Day 1	1	≤ 1	≤ 1
Week 24	169	[2,253]	[2,253]

Analysis visit	Target visit day	Analysis visit window for SID Group	Analysis visit window for EID Group
Week 48	337	[254,421]	[254,421]
Week 72	505	[422,547]	[422,547]
Week 84	589	≥ 548	≥ 548

[redacted]

[redacted]

[redacted]

[redacted]

12 APPENDIX IV: COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia Suicide Severity Rating Scale (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 4; another question on *self-injurious behavior without suicidal intent* is listed separately. In particular, only subjects who answered "Yes" to question 2 will proceed to question 3, 4 and 5. Thus, for any subjects 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 subject had committed suicide in post-screening visits.

Table 11 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 subject 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 subject 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 subject'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 subject answered "No" to all 5 Suicidal Ideation questions at that visit.

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

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

13 REFERENCE

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Email:	Access to a valid email account
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Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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STATISTICAL ANALYSIS PLAN
NOVA PART 2

Version No.: 2.0

Date: 30 Aug 2023

Author: [redacted]

Study Title: A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6 Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects with Relapsing Remitting Multiple Sclerosis Switching From Treatment With 4 Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration

Name of Study Treatment: natalizumab (Tysabri®; BG00002)

Protocol No.: 101MS329

Study Phase: 3b

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This document has been reviewed and approved by:		
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SMT Statistician	Signature	Date
[redacted]	DocuSigned by: [redacted]	30-Aug-2023
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SMT Medical Director	Signature	Date
[redacted]	DocuSigned by: [redacted]	30-Aug-2023
[redacted]	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	23 March 2023	*Not Applicable*
2.0	30 August 2023	Updated to clarify details of the analysis performed.

TABLE OF CONTENTS

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
CI	confidence interval
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
EDSS	Expanded Disability Status Scale
EID	extended interval dosing
EOS	end of study
[redacted]	[redacted]
Gd	gadolinium
ICF	informed consent form
INEC	Independent Neurology Evaluation Committee
IV	intravenous(ly)
JCV	John Cunningham virus
KM	Kaplan-Meier
mITT	modified intent to treatment
MCMC	Markov chain Monte Carlo
MMRM	mixed model of repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PBVC	percentage of brain volume change
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPQ	patient preference questionnaire
[redacted]	[redacted]
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SID	standard interval dosing
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe in detail the planned statistical analyses to be performed upon completion of the two-period open-label crossover extension study (NOVA Part 2). All references to the protocol refer to Version 4.0, dated 20 August 2020 and Protocol Clarification Letter dated 25 October 2022. A detailed description of the planned TFLs is provided in the accompanying TFL shell document.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR.

2. Study Overview

2.1. Part 2 Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate subject preference for SC versus IV route of natalizumab administration.	• Proportion of subjects indicating a preference for natalizumab SC administration at the end of Part 2
Secondary Objectives	**Secondary Endpoints**
To evaluate treatment satisfaction with SC versus IV route of administration.	• Total score on Treatment Satisfaction Questionnaire for Medication (TSQM)
To evaluate drug preparation and administration time between SC and IV routes of natalizumab administration.	• Mean time for drug preparation and administration.
To evaluate the safety and immunogenicity of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • The proportion of subjects with treatment emergent AEs • The proportion of subjects who develop anti-natalizumab antibodies

To evaluate the efficacy of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • Number of new or newly enlarging T2 hyperintense lesions • Time to first relapse • Annualized relapse rate • Change in EDSS score • Number of new Gd-enhancing lesions • Number of new T1 hypointense lesions • PBVC and change in cortical and thalamic brain region volume
To characterize PK and PD of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • C_{trough} • Trough α4 integrin saturation on MNC, monocytes, lymphocytes, B cell (CD19), T cells (CD4, CD8), and dendritic cells. In addition, [redacted] biomarkers may include soluble VCAM- 1.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	

2.2. Part 2 Study Design

Part 2 is a 108-week OLE for approximately 158 subjects at approximately 45 sites in Canada, the United Kingdom, Europe, Israel, and Australia who complete their randomized treatment in Part 1, provide consent, and are eligible to participate immediately following completion of the 72-week treatment period.

Subjects who did not participate in Part 1 but provide consent and satisfy the inclusion-exclusion and eligibility requirements of Part 1, including treatment with natalizumab SID for at least 12 months without relapses in the last 12 months, may also be enrolled in Part 2 as new subjects to ensure adequate sample size for the Part 2 analysis.

Subjects enrolled in Part 2 will receive natalizumab 300 mg by IV infusion once every 6 weeks (42 ± 7 days) for a period of 36 weeks (run-in phase) and be randomized to an additional 48 weeks of crossover treatment comprising 24 weeks EID SC Q6W and 24 weeks EID IV Q6W (crossover phase). All MRI scans will be read at a central facility by blinded raters.

Subjects will be randomized in a 1:1 ratio, stratified by their treatment assignment in Part 1 (SID, EID, new subjects) to receive SC/IV or IV/SC before the first dose of crossover treatment in Part 2 of the study.

At the completion of their 48-week crossover treatment phase, subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion with the route of administration being the subject's choice, proceed to the 12-week follow-up period, and receive a follow-up safety phone call 12 weeks later (i.e., 24 weeks after the last dose of study treatment) before completing the study.

The design of the study is presented in Figure 1. The week numbers below correspond to the NOVA Part 1 baseline. Randomization into the crossover period of the study takes place at Week 108 for continuing Part 1 subjects and after the 36-week run-in period for new subjects in Part 2. The mapping of analysis visits in Part 2 is presented in Section 3.1.2.

Figure 1: Study Design

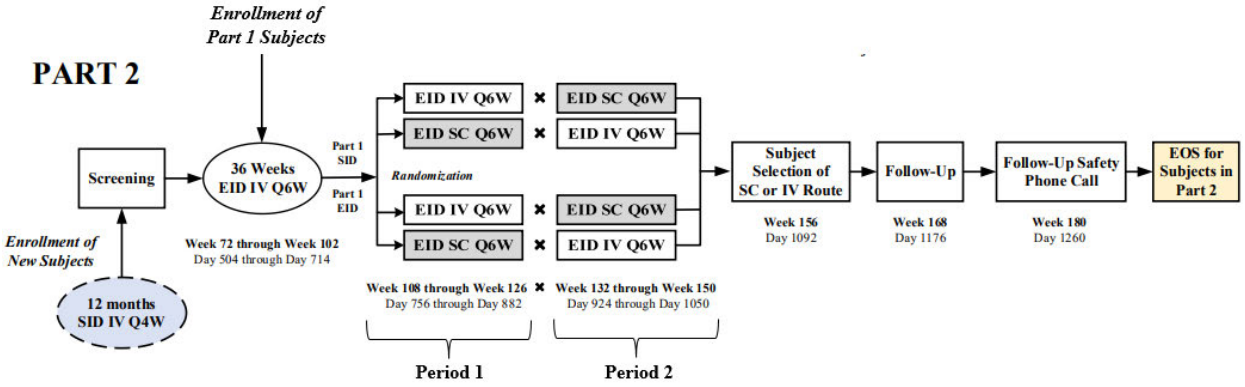

Figure 2: Nominal Visit Mapping

Phase	IV run-in		Period 1				Period 2				Last dose[a]	EOS	Safety follow-up
Part 1	Week 72	102	108	114	120	126	132	138	144	150	156	168	180
Part 2	Week 1	30	36	42	48	54	60	66	72	78	84	96	108
Part 2 crossover			Week 1[b]	6	12	18	24	30	36	42	48	60	72

[a] Last dose is subject's choice. [b] Randomization visit.

2.3. Part 2 Study Duration for Subjects

The total duration of study participation in Part 2 for these subjects will be approximately 108 weeks. This comprises EID IV treatment for 36 weeks; a randomized EID SC vs. EID IV crossover treatment phase of 48 weeks; a follow-up period of 12 weeks; and a follow-up safety phone call 12 weeks after the follow-up period (i.e., 24 weeks after the last dose of study treatment). The EOS date for subjects participating in Part 2 may be the last study visit, the follow-up safety phone call, or last protocol-specified assessment; if the subject has ongoing AEs that are being followed, then the date may be the date of AE resolution.

2.4. Sample Size Considerations

Historical data on MS treatments, including a meta-analysis on the relationship between new or newly enlarging T2 lesions and relapses, suggest little or no clinical relevance of a difference of 0.2 to 0.3 in mean lesion numbers over 72 weeks [Sormani and Bruzzi 2013]. With the planned sample size of N = 200/group in Part 1, the precision of the estimated mean lesion numbers is sufficient to allow > 80% probability to observe the lower limit of the 95% CI for the ratio of EID to SID in the estimated mean lesion number above 1 if the true mean is 0.5 and 0.3 in the

EID and SID group, respectively. If the true mean is 0.6 and 0.3 in the EID and SID group, respectively, the probability will be approximately 90%. In the other direction, the sample size provides a precision that allows approximately 90% probability to observe the upper limit of the 95% CI to be ≤ 2 if the true mean lesion numbers in both groups are 0.3. Approximately 480 subjects will be enrolled in Part 1 to account for a drop-out rate of approximately 17%.

For Part 2, in the absence of EID SC natalizumab data, it is assumed that the proportion of subjects who would prefer SC natalizumab is 75%, with a 7.5% margin of error; therefore, a sample size of 130 subjects for the 95% CIs to be within 67.5% and 82.5%. Approximately 160 subjects are needed to allow for 20% of subjects who do not provide an evaluable preference assessment (calculated by nQuery Advisor Version 7).

3. Definitions

3.1. Dates and Points of Reference

3.1.1. Definition of Baseline

The randomization visit for the crossover phase of the study takes place after the 36-week run-in period at Week 108 for Part 1 subjects and Week 36 for new subjects in Part 2. Unless stated otherwise, baseline data is defined as the data collected prior to the time and/or on the date of the first randomized dose which is usually the same day as baseline visit for the crossover phase. If there is more than one value on/before the date of first randomized dose, the non-missing value closest to and prior to first dose will be used as the baseline value.

3.1.2. Visit Mapping in Part 2

As the NOVA Part 2 OLE will be treated as independent study, the analysis visits will be remapped based on the Part 2 randomization date as follows (Table 1).

Table 1 Visit Mapping in Part 2

Raw Visit Label	SDTM Visit Label	Analysis Visit Label
Screening OLE	Screening – Part 2	Screening
Baseline-week 72	Week 1 – Part 2	Run-in period – visit 1
Week 78	Week 6 – Part 2	Run-in period – visit 2
Week 84	Week 12 – Part 2	Run-in period – visit 3
Week 90	Week 18 – Part 2	Run-in period – visit 4
Week 96	Week 24 – Part 2	Run-in period – visit 5
Week 102	Week 30 – Part 2	Run-in period – visit 6
Week 108	Week 36 – Part 2	Baseline *
Week 114	Week 42 – Part 2	Week 6
Week 120	Week 48 – Part 2	Week 12
Week 126	Week 54 – Part 2	Week 18
Week 132	Week 60 – Part 2	Week 24
Week 138	Week 66 – Part 2	Week 30
Week 144	Week 72 – Part 2	Week 36
Week 150	Week 78 – Part 2	Week 42
Week 156	Week 84 – Part 2	Week 48
Week 168	Week 96 – Part 2	Week 60 – End of Study
Week 180	Week 108 – Part 2	Week 72 – Safety Follow-up

* Randomization visit.

3.2. Study Treatment in Part 2

All subjects enrolled in Part 2 will receive natalizumab as a 300 mg IV infusion Q6W (42 [2/+5] days) for a period of 36 weeks. Subjects will then be randomized in a 1:1 ratio, stratified by Part 1 treatment group (SID, EID, new subjects) to receive natalizumab 300 mg SC Q6W for 24 weeks followed by 300 mg IV Q6W for 24 weeks or the 48-week crossover in reverse treatment sequence order.

3.3. Study Treatment Periods in Part 2

Period 1 is defined as the first 24 weeks of the crossover phase.

Period 2 is defined as the second 24 weeks of the crossover phase.

3.4. Key Derived Variables

3.4.1. Baseline Weight of Crossover Study

Weight for all subjects at baseline of the crossover phase will be taken as the last value closest to and prior to (including on) the date of first dose in Period 1.

3.4.2. Baseline Duration of Exposure to Tysabri of Crossover Study

Data of first dose of Tysabri will be taken from the CRF for newly enrolled subjects and drawn from Part 1 data for continuing subjects.

Duration of exposure to Tysabri at baseline of the crossover phase will be calculated as follows:

(Date of Randomization in Period 1 – Tysabri Start Date +1) / 365.25

Subjects will be grouped by duration of exposure (≤ 3 years versus > 3 years).

3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

The study randomization stratification factor and corresponding categories is listed as follows.

- Treatment assignment in Part 1 (SID, EID, new subjects)

3.5.2. Subgroup Variables

Subgroup analyses may be performed for selected endpoints to evaluate the consistency of findings across populations. Subgroups may be defined by prior disease activity, and the number and type of therapies prior to natalizumab as well as quartiles of the trough PK concentrations, α-integrin saturation levels and sVCAM-1 at baseline and after 24 weeks of treatment.

Other subgroups may include, but are not limited to:

- Baseline weight (≤ 80 kg, and > 80 kg)
- Baseline weight (40 to 59 kg, 60 to 79 kg, 80 to 89 kg, and ≥ 90 kg)
- Duration of natalizumab exposure (≤ 3 years versus > 3 years) at baseline
- [redacted]
- Anti-drug antibody status (positive versus negative)
- Baseline EDSS (EDSS score ≤ 2.0 versus EDSS score > 2.0)
- Country/region (Canada, United Kingdom, Europe, and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)
- Age at baseline (age < 40 years versus age ≥ 40 years)
- Sex

3.6. Analysis Populations

3.6.1. Safety population

The safety population is defined as all randomized subjects who receive at least one dose of study treatment during the crossover phase of Part 2. Subjects in the safety population will be analyzed according to the actual treatment received.

Any safety analyses performed on data collected during the run-in phase (prior to randomization into the crossover phase) will be presented separately for all enrolled subjects in Part 2 of NOVA.

3.6.2. Modified intent to treat population

The protocol-defined mITT population is defined as all randomized subjects who receive at least one dose of SC natalizumab after randomization in Part 2 and who completed at least the first question in the PPQ on one occasion.

The primary endpoint will be evaluated on the mITT population. Subjects will be analyzed by randomized treatment sequence and overall.

3.6.3. Full analysis set

The full analysis set is defined as all randomized subjects who receive at least one dose of study treatment during at least one study period and have at least one baseline assessment from the below clinical efficacy assessments:

- MRI Efficacy Assessments (not including locally read MRIs)
- Relapses (clinical relapses are assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours; see protocol section 7.3 for further details)
- Neurological examination and EDSS
- PPQ, TSQM, [redacted]

The secondary and [redacted] efficacy endpoints will be evaluated on the full analysis set.

3.6.4. Per-protocol population

The per-protocol population is defined as the subset of the full analysis set who

- Did not have a significant protocol deviation that would be expected to affect efficacy assessments, which may include but is not limited to,
    - Subject was enrolled without meeting one or more inclusion or met any exclusion criteria
- Subjects with ≤ 3 total number of missed doses or doses received out of the protocol-defined dosing visit windows.

3.6.5. Immunogenicity population

In Part 2, the analysis population will include all subjects who receive at least one dose of SC or IV natalizumab and have at least one assessment for anti-drug antibody during the crossover phase of Part 2.

Subjects will be analyzed according to actual treatment received.

[redacted]

3.6.7. PK population

In Part 2, the PK population is defined as all subjects who receive at least one dose of SC or IV natalizumab and have at least one assessment for the concentration of natalizumab in serum during the crossover phase of Part 2.

Subjects will be analyzed according to actual treatment received.

3.6.8. PD population

In Part 2, the PD population is defined as all subjects who receive at least one dose of SC or IV natalizumab and have at least one assessment of the PD parameter during the crossover phase of Part 2. PD parameters may include trough α4 integrin saturation on MNC, monocytes, lymphocytes, B cell (CD19), T cells (CD4, CD8), and dendritic cells.

In addition, [redacted] biomarkers may include soluble VCAM- 1.

Subjects will be analyzed according to actual treatment received.

4. List of Planned Study Analyses

No formal interim analysis is planned. After the last subject has completed the last dosing visit, data will be cleaned, and pages signed up to and including the last dosing visit and data will be reviewed.

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 subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum and maximum. For categorical variables, this will generally include number of subjects randomized or dosed, number with data, and the percent of those with data in each category.

Country/region will be categorized as follows:

- Canada
- United Kingdom
- Europe and Israel (includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain)
- Australia

Unless otherwise specified, baseline value is defined as the most recent non-missing measurement collected prior to the first randomized dose. Change from baseline will be defined as post-baseline value minus baseline value.

If a sample result is received as an inexact value, e.g., >2.35, then the numerical value excluding the non-numerical character will be taken for analysis purposes.

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 underdispersion will be used.

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

The statistical software, SAS® 9.4 or higher will be used for all summaries and analyses.

5.2. Subject Accountability

Subject disposition will be summarized by randomized treatment sequence and overall. Summary data will include the number of subjects enrolled into Part 2, dosed during the run-in phase, randomized into the crossover phase of the study, dosed during Period 1, dosed during Period 2, and dosed during Periods 1 and 2. The number of subjects who discontinued treatment and/or withdrew from study, and the reasons for discontinuation and/or withdrawal will be summarized and listed.

Number of subjects dosed will be summarized by country/region and time on study after randomization will also be summarized and listed by randomized treatment sequence and overall.

Time on randomized treatment and time exposed to study treatment will be summarized by route of administration and listed.

Subjects impacted by the COVID-19 pandemic will be summarized. The number of subjects who discontinued treatment and/or withdrew from the study due to COVID-19 will be summarized and listed. COVID-19 adverse events and concomitant non-drug treatments related to COVID-19 will be summarized. Protocol deviations, including the impact of and reasons for protocol deviations due to COVID-19 will be summarized.

5.3. Demographic and Baseline Characteristics

Demographic data and baseline characteristics collected at the Part 1 screening visit will be imported for the continuing subjects rolling over from the Part 1 and summarized alongside data collected at the Part 2 screening visit for newly enrolled subjects. A footnote will be provided on relevant tables to ensure clarity.

Demographic data collected at screening including age (years), age category (<40 and ≥ 40), sex, ethnicity, race, country/region, height, and childbearing potential will be summarized by randomized treatment sequence (SC/IV or IV/SC).

MS disease characteristics collected at screening including number of relapses during the one year prior to first dose of Tysabri, and score of last EDSS assessment prior to first dose of Tysabri will also be summarized by treatment sequence, using descriptive statistics.

In Part 2, baseline refers to the randomization visit for the crossover phase of the study (Week 108 for continuing Part 1 subjects and Week 36 for newly enrolled subjects) unless specified.

MS baseline characteristics will be derived relative to the date of randomization and will be summarized by treatment sequence, using descriptive statistics, including years since disease (MS) onset, and years since diagnosis.

Weight, body mass index (BMI), and EDSS score at baseline will also be summarized, where baseline is the last assessment prior to randomization. Body weight at baseline will also be categorized and presented using the following two groupings: <40 kg, 40 to 59 kg, 60 to 79 kg, 80 to 89 kg, and ≥ 90 kg, and ≤ 80 kg, > 80 kg.

In addition, summary statistics for following baseline MRI assessments (where baseline is the last assessment prior to randomization) will also be presented.

- T2 hyperintense lesion volume
- Gd-enhancing lesion number and volume
- T1 hypointense volume
- Normalized brain volume

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v25.1 or higher). The number (%) of subjects with history (including both ongoing and not ongoing medical conditions) will be summarized by system organ class and preferred term. A listing of medical history will be generated.

Number and percentage of subjects with previous MS treatments other than Tysabri will be summarized by medications and treatment sequence. Prior MS treatments other than Tysabri will also be listed.

In addition, Tysabri treatment history will also be summarized. These include total number of doses of Tysabri the subjects have ever received prior to enrollment, total duration of Tysabri the subjects have received prior to enrollment, number of doses of Tysabri the subjects have received in the last 12 months prior to enrollment, and number and percentage of subjects missed any doses of Tysabri in the last 3 months of treatment prior to the screening visit. Details of Tysabri treatment history will be listed for each subject.

Medical history, prior MS treatment and Tysabri treatment history were only collected at the screening visit of Part 1 for the continuing subjects who rolled over into Part 2 of the NOVA study. Therefore, medical history, prior MS treatments, and Tysabri treatment history collected at the Part 1 screening visit will be imported for continuing subjects and summarized alongside data collected at the Part 2 screening visit for newly enrolled subjects. A footnote will be provided on relevant tables to ensure clarity.

5.4. 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 by treatment sequence and route of administration. Protocol deviation will be assigned to the most recent route of administration received before the deviation date. All protocol deviations will be listed.

All protocol deviations related to COVID-19 pandemic measures will be provided in a listing with all available details.

5.5. Concomitant Medications and Non-Drug Therapies

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary September 2022 version or higher. All concomitant non-drug therapies will be coded using the MedDRA dictionary v25.1 or higher. A concomitant medication/therapy will be defined as any therapy that was taken on or after the day of the first dose of study drug after randomization in Period 1 of the crossover phase. This includes therapies that start prior to the initiation of the first dose if their use continues on or after the date of first dose. 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 dose, that therapy will be considered concomitant.
- if the start date of a therapy is prior to the date of the first dose 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 dose 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 dose, that therapy will be considered as concomitant.

Concomitant medications and non-drug therapies will be assigned to the most recent route of administration received before the start date of the medication or non-drug therapy. Missing or partial start dates will be handled in the same manner as for determining concomitance.

The number and percentage of subjects taking concomitant medication and non-drug therapies will be summarized by treatment sequence and route of administration. Non-drug therapies will be presented by treatment sequence and route of administration. Medications taken prior to first dose in Period 1, concomitant medications and non-drug therapies will be listed.

The most frequent concomitant medications, defined as those taken by at least 10% of subjects in any group, will also be summarized by treatment sequence and route of administration.

5.6. Study Treatment Exposure

Study treatment exposure will be summarized by route of administration.

Time on randomized treatment in weeks is calculated as (the date of last dose of the period - the date of first dose of the specific treatment period + 1)/7.

Time exposed to each route of administration during the crossover phase in weeks is calculated as (the date of last dose of the period + 42 - the date of first dose of the specific period + 1)/7.

5.7. Study Treatment Compliance

A summary of doses received over time by visit and treatment sequence will be provided.

Study treatment compliance will be summarized for each route of administration (IV or SC). The number of doses received by IV or SC, and percentage compliance will be presented.

Compliance (%) is calculated as number of actual doses / number of planned doses * 100 per route of administration. Planned doses are calculated based on the number of doses a subject is scheduled to receive, based on their time on study.

5.8. Efficacy Endpoints

5.8.1. General Consideration for Efficacy Endpoints

The primary endpoint will be evaluated on the mITT population. The mITT population may also be used for selected secondary [redacted] efficacy endpoints.

All secondary [redacted] efficacy endpoints will be evaluated on the full analysis set (FAS). The number of subjects included in statistical analyses will be those with baseline data and data from at least one treatment period.

Subjects will be analyzed according to randomized route of administration.

5.8.2. Handling of Missing Data

Missing data will be not imputed for the primary endpoint. Multiple imputation may be conducted for selected secondary [redacted] endpoints as part of ad hoc sensitivity analyses if appropriate.

For continuous or count endpoints, multiple imputation will be performed on the actual values using the Markov chain Monte Carlo (MCMC) method. The imputation model will include treatment sequence (IV/SC, SC/IV), the endpoint values at each visit (baseline, week 24, week 48), stratification factor (new subject, SID, EID), baseline body weight, baseline Tysabri exposure (≤ 3 years versus > 3 years). The imputed complete datasets can then be used to calculate the change from/relative to baseline for each period.

Prior to imputation, the dataset will be sorted by ascending unique subject identifier (USUBJID). All categorical variables be coded in numerical form in the imputation model. A set of 100 complete imputed datasets will be generated with 100 burn-in iterations and the relative efficiency (RE) will be checked. The seed used for imputation is 87922.

5.8.3. Lesion Count Data

If the total number of lesions across the two arms are less than 15 for each visit, then the negative binomial regression model will not be conducted for that parameter, and only descriptive summary statistics will be presented.

Otherwise, if negative binomial regression model does not work, Poisson regression model will be conducted, and if Poisson regression model does not work, then only descriptive summary statistics will be presented. This rule will be applicable to the analysis of all lesion parameters.

5.8.4. Primary Efficacy Endpoint

5.8.4.1. Proportion of subjects indicating a preference for natalizumab SC administration at the end of Part 2

The primary endpoint in Part 2 of the study is the proportion of subjects indicating a preference for natalizumab SC administration at the end of Part 2. The mITT population will be used for analyses of the primary endpoint.

For each subject, the first answer in the PPQ will be used to derive the primary endpoint of Part 2 'All things considered which method of administration did you prefer? (IV, SC, No preference)'.

The proportion of subjects preferring SC natalizumab at the end of Part 2 will be estimated, and the 95% CI will be calculated using the exact Binomial method.

Summary statistics will be provided for the preferred route of administration, strength of preference and two main reasons for preference at each visit (Week 30, Week 42 relative to the randomization visit). Summary statistics will be presented by treatment sequence and overall.

Subjects' choice of last dose on the study (IV or SC) will be summarized by treatment sequence and overall.

5.8.5. Secondary Efficacy Endpoints

5.8.5.1. Treatment Satisfaction Questionnaire for Medication (TSQM)

Summary statistics for total TSQM score, each sub score, and the change in each from baseline to Week 24 and Week 48 will be presented by treatment sequence and visit.

Change from baseline in total TSQM score for each route of administration after 24 weeks will also be calculated relative to the beginning of the treatment period and analyzed using a linear mixed effect model including route of administration (IV, SC), treatment period, and treatment sequence as fixed effects and subject as random effect, adjusting for baseline body weight (continuous variable), baseline duration of natalizumab exposure (≤ 3 years versus > 3 years), stratification factor (SID, EID, new subjects), and baseline total TSQM score.

Estimates for each route of administration, as well as the difference between IV and SC routes after 24 weeks of treatment will be presented, along with 95% CI and p-value.

5.8.5.2. Mean time for drug preparation and administration between SC and IV routes of administration

Mean time for preparation of IV treatment will be summarized. Mean drug administration time will be summarized for both IV and SC treatments. Data is collected for the preparation and administration of each route of administration at each visit and will be pooled before summarizing. Preparation time, administration time, and total administration time (preparation time + administration time) will be calculated and presented by route of administration.

Number of new or newly enlarging T2 hyperintense lesions

The number of new or newly enlarging T2 hyperintense lesions will be summarized over time by treatment sequence and visit. The number of new or newly enlarging T2 hyperintense lesions from Baseline to Week 24, Week 24 to Week 48, and Baseline to Week 48 (calculated cumulatively over time) will be presented.

The number of new or newly enlarging T2 hyperintense lesions after 24 weeks of treatment relative to the beginning of the period will also be summarized and analyzed using a negative binomial generalized linear model. The model will include route of administration (IV or SC), treatment period, and treatment sequence, as fixed effects, and subject as random effect, adjusting for baseline body weight (continuous variable), baseline duration of natalizumab exposure (≤ 3 years versus > 3 years), stratification factor (SID, EID, new subjects), and baseline number of lesions.

The ratio of mean lesion numbers of SC versus IV will be derived from the model with a 95% CI and associated p-value.

However, if the total number of observed new/newly enlarging T2 lesion is less than 15 across both arms for each visit, then the negative binomial regression model will not be conducted, and only descriptive summary statistics will be presented.

Otherwise, if negative binomial regression model does not work, Poisson regression model will be conducted, and if Poisson regression model does not work, then only descriptive summary statistics will be presented. This rule will also be applicable to the analysis of other MRI parameters.

5.8.5.3. Proportion of subjects with no new or newly enlarging T2 hyperintense lesions over 48 weeks

The proportion of subjects with no new or newly enlarging T2 hyperintense lesions over 48 weeks will be summarized by treatment sequence and overall. Data will be censored at the time of withdrawal from study treatment.

Responders for this analysis are defined as subjects who complete study treatment until Week 48 and have no new or newly enlarging T2 hyperintense lesions prior to Week 48. Non responders include subjects with new or newly enlarging T2 hyperintense lesions reported prior to Week 48 and subjects who discontinue randomized treatment due to lack of efficacy prior to Week 48. Subjects who discontinue treatment due to non-efficacy reasons prior to Week 48 and have no new or newly enlarging T2 hyperintense lesions reported prior to the intercurrent event will be excluded from this summary.

5.8.5.4. Time to first relapse

Given the nature of crossover study design, the proposed protocol-specified analytical approach does not account for the correlation of within subject effect. In Part 2, the start date for time to first relapse or censoring will be defined as the start date of the first randomized dose. If a subject withdraws from the study prior to the end the crossover phase and did not experience a relapse reported prior to withdrawal, the subject will be censored on the last day in the crossover phase.

The proportion of relapsed subjects will be estimated using the KM product limit method and be presented as KM curves over time by treatment sequence. The hazard ratio of SC/IV versus IV/SC will be estimated from the Cox model with terms for treatment sequence, baseline body weight (continuous), baseline duration of Tysabri exposure (≤ 3 years versus > 3 years), and stratification factor (SID, EID, new subjects).

Analysis will only be performed if a number of events sufficient to obtain a reliable estimate are observed.

5.8.5.5. Annualized relapse rate

During each period of the crossover design in Part 2, all relapses reported prior to the end of each period will be included in the analysis for this endpoint.

The relapse rate for each route will be calculated as the total number of relapses experienced for the administration route divided by the total number of subject-years on study at the end of each period for the route of administration. This is the unadjusted relapse rate.

In addition, the relapse rate for an individual subject will be calculated as the number of relapses for that subject in each period divided by the duration of the subject on study in years at the end of each period. Based on these individual relapse rates, the mean and median for each route will be presented. This is called the subject relapse rate.

The annualized relapse rate at the end of each period will be analyzed using a negative binomial regression model, with route of administration, treatment sequence, treatment period, and

stratification factor (SID, EID, new subjects) as the classification variables and with baseline body weight (continuous), and duration of natalizumab exposure (≤ 3 years versus > 3 years) as covariates. The logarithmic transformation of the number of years in the study at the time end of each period will be included in the model as the "offset" parameter. The ratio of mean annualized relapse rate of SC versus IV will be derived from the model with a 95% CI and associated p-value. If negative binomial regression model does not converge, a Poisson regression model with the same classification variable and covariates will be used instead. If Poisson regression model doesn't work, then only descriptive summary statistics will be presented.

Annualized relapse rate will only be calculated if a number of events sufficient to obtain a reliable estimate are observed.

5.8.5.6. Change in EDSS score

EDSS score and change from baseline will be summarized over time by treatment sequence and visit. Change from baseline will also be calculated after 24 weeks relative to the beginning of the period and analyzed by route of administration in the same manner as described in section 5.8.5.1 for the TSQM total score.

Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score >=1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 (observed at the Week 24 visit), that is confirmed after at least 24 weeks (at the Week 48 visit).

The number of subjects with confirmed EDSS worsening will be presented by treatment sequence. The proportion of subjects free of confirmed EDSS worsening at Week 48 will be estimated based on the Kaplan-Meier product limit method.

Confirmed EDSS improvement is defined as a decrease of at least 1.0 point from a baseline EDSS score of >=2.0 (observed at the Week 24 visit) that is confirmed after at least 24 weeks (at the Week 48 visit). The number of subjects with confirmed EDSS improvement will be presented in the same manner as described for confirmed EDSS worsening.

Worsening or improvement observed at Week 48 only could not be confirmed without follow-up data.

5.8.5.7. Number of new Gd-enhancing lesions

The number of new Gd-enhancing lesions over time will be summarized by treatment sequence and visit. The number of new or newly enlarging T2 hyperintense lesions from Baseline to Week 24, Week 24 to Week 48, and Baseline to Week 48 (calculated cumulatively over time) will be presented.

The number of lesions observed after 24 weeks of treatment relative to the beginning of the treatment period will be summarized and analyzed by route of administration in the same manner as described in section 0 for new or newly enlarging T2 hyperintense lesions.

5.8.5.8. Number of new T1 hypointense lesions

The number of new T1 hypointense lesions over time will be summarized by treatment sequence and visit. The number of new T1 hypointense lesions from Baseline to Week 24, Week 24 to Week 48, and Baseline to Week 48 (calculated cumulatively over time) will be presented. The number of lesions observed after 24 weeks of treatment relative to the beginning of the treatment period will be summarized and analyzed by route of administration in the same manner as described in section 0 for new or newly enlarging T2 hyperintense lesions.

5.8.5.9. PBVC

Summary statistics for normalized brain volume will be presented by treatment sequence and visit. Change from baseline and percentage change from baseline in brain volume over time will be presented by treatment sequence and visit.

Percentage change from baseline in normalized brain volume will also be calculated after 24 weeks of treatment relative to the beginning of the treatment period and analyzed using a linear mixed effect model. The model will include route of administration, treatment period, and treatment sequence as fixed effects and subject as random effect, adjusting for baseline body weight (continuous variable), baseline duration of natalizumab exposure (≤ 3 years versus > 3 years), stratification factor (SID, EID, new subjects), and baseline normalized brain volume.

Estimates for each route of administration, as well as the mean difference between IV and SC groups after 24 weeks of treatment, will be presented, along with 95% CI and p-value.

5.8.5.10. Cortical brain region grey matter volume

Summary statistics for normalized cortical grey matter volume and change from baseline in cortical grey matter volume over time will be presented by treatment sequence and visit.

Change from baseline in cortical grey matter volume will also be calculated after 24 weeks of treatment relative to the beginning of the treatment period and analyzed using a linear mixed effect model. The model will include route of administration, treatment period, and treatment sequence as fixed effects and subject as random effect, adjusting for crossover baseline body weight (continuous variable), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), baseline stratification factor (SID, EID, new subjects), and baseline normalized cortical grey matter volume.

Estimates for each route of administration, as well as the mean difference between IV and SC groups after 24 weeks of treatment, will be presented, along with 95% CI and p-value.

5.8.5.11. Thalamic brain region volume

Summary statistics for normalized thalamic volume and change from baseline in thalamic volume over time will be presented by treatment sequence and visit.

Change from baseline in thalamic volume after 24 weeks relative to the beginning of the period will be analyzed for each route of administration in the same manner as described in section 5.8.5.10 for the cortical grey matter volume.

[redacted]

[redacted]

5.10. Immunogenicity Endpoints

The immunogenicity population will be used for immunogenicity analysis. Immunogenicity data will be mapped to an appropriate analysis visit using the windowing scheme described in Appendix I.

5.10.1. Anti-Natalizumab Antibodies Analysis

Serum samples to test for anti-natalizumab antibodies will be collected immediately prior to dosing, at baseline of the crossover phase, and at weeks 12, 24, 36, and 48 relative to randomization.

The percentage of subjects who develop antibodies will be determined and summarized over time by treatment sequence (at baseline, Week 12, Week 24, Week 36, and Week 48 relative to randomization) and by route of administration (at beginning of period, and after 6, 12, 18, and 24 weeks relative to the beginning of the period).

- The baseline value is defined as the latest immunogenicity data collected at any time prior to the first dose of the crossover phase. If no immunogenicity data are collected prior to the first dose, the baseline value will be designated 'Missing' in summary tables.

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

- Subjects with no positive post-treatment samples for anti-natalizumab antibodies will be considered negative regardless of their baseline result.
- Subjects with at least one confirmed post-treatment positive result will be considered positive for anti-natalizumab antibodies if their baseline result is negative.
- In addition, for subjects that are considered anti-natalizumab antibody positive, the following may be evaluated:
  - Persistent anti-natalizumab antibody response:

    More than one positive time point that are ≥112 days apart

    or

    One or more positive time point, but < 112 days of evaluable data post first positive time point.
  - Transient anti-natalizumab antibody response:

    A single positive time point, followed by ≥112 days results which are all negative.

    or

    Two positive data points with <112 days apart, with later negative samples that are ≥112 days apart from the first positive result.

An impact on efficacy and safety may be conducted by considering antibody status [positive (transient and persistent) or negative].

A listing will be generated for subjects determined to be persistent positive including confirmed progression status, on study relapse status (both INEC confirmed and any reported) and the following by visit data, anti-natalizumab antibody result, and EDSS.

A separate listing will be generated for subjects determined to be persistent positive and who had a hypersensitivity event.

[redacted]

5.12. Pharmacokinetic Endpoints

The PK population will be used for pharmacokinetics analysis. Concentration data taken from early termination visits will be assigned to the next scheduled visit within the same route of administration.

Serum trough natalizumab concentration (C_{trough}) will be summarized using descriptive summary statistics (number of subjects with data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, maximum, geometric mean, and CV%)). Summary statistics will be presented at 6-weekly intervals for each scheduled visit from baseline of the crossover period up to pre-dose at Week 48 for each treatment sequence. Summary statistics will also be presented at 6-weekly intervals (at beginning of period, and after 6, 12, 18, and 24 weeks relative to the beginning of the period), for each route of administration. Concentrations below the limit of quantification (BLQ) will be treated as zero for summary statistics and shown as BLQ in data listings.

Plots of arithmetic mean concentration by visit will be provided for all time points. All above analyses will be summarized by treatment sequence and by route of administration.

Population PK and PK/PD analysis may be performed when data supports and deemed necessary.

5.13. Pharmacodynamic Endpoints

The PD population will be used for pharmacodynamic analysis. Post-baseline measurements will be mapped to an appropriate analysis visit using the windowing scheme described in Appendix I.

The PD properties of natalizumab will be evaluated using the following assessments that include, but may be not limited to, the following:

- trough α4 integrin saturation on MNC, monocytes, lymphocytes, B cell (CD19), T cells (CD4, CD8), and dendritic cells.

In addition, [redacted] biomarkers may include soluble VCAM- 1.

Measurements taken at Baseline/Day1, Week 6, Week 12, Week 18, Week 24, Week 36 and Week 48, and the changes from baseline over time will be summarized by treatment sequence and visit. Mean values will also be plotted over time for each parameter. Parameters with non-normal distributions may be analyzed in logarithmic scale.

For statistical analyses, change from baseline will be obtained within each period separately, where the baseline of each period is defined as the last assessment before the first dose administration during that period.

Change from baseline relative to the first dose of the period will be analyzed over the 24-week treatment period by route of administration. Data from both treatment periods will be used. Change from baseline will be analyzed using a linear mixed model to estimate the mean difference between routes of administration (IV vs SC) at each time point. Visit, route, treatment period, and sequence will be treated as class variables. Visit, route, treatment period, sequence, and the interaction term for route and visit will be included in the model as fixed effect and subject as random effect. The model will also be adjusted for crossover baseline body weight (continuous), duration of natalizumab exposure (≤ 3 years or < 3 years), and stratification factor (SID, EID, new subjects).

The LS means of each route as well as the estimated differences between each route of administration (IV vs SC) will be presented, along with 95% CI and p-value at each visit.

Where a MMRM model is used, an unstructured covariance (UN) matrix will be used to model the within-subject variability. Model convergence will be checked. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm will be used to provide initial values of the covariance parameters. In the event that none of the above methods yield convergence, a structured covariance such as heterogeneous Toeplitz (TOEPH) structure will be used.

5.14. Safety Endpoints

All safety analyses will be performed on the safety population.

Clinical laboratory data (including any abnormalities), vital sign measurements, physical examination findings, neurological examination findings, and body weight, will be evaluated for safety up to the end of study visit (Week 60 or earlier for early termination subjects).

Adverse events (AEs), and serious adverse events (SAEs) will continue to be evaluated up to the follow up safety phone call at Week 72 relative to the randomization visit (Week 180 relative to the start of Part 1).

Unless otherwise specified, no formal statistical testing will be performed on the safety data.

Safety data collected at ET visits and unscheduled visits will be mapped to an appropriate analysis visit using a windowing scheme described in Appendix I.

Additional safety analyses may be performed as needed after reviewing data from all subjects .

Data from subjects who experienced an SAE, an AESI, withdrew from the study or discontinued from study treatment due to a TEAE, life-threatening event, hepatic injury events, malignancies, or pregnancy related outcomes will be provided as required for the purposes of reporting subject narratives. Additional subject narratives may be provided as needed after reviewing the safety data.

Listings will be presented by randomized sequence and will indicate the most recent route of administration received before the assessment where appropriate.

5.14.1. Clinical Adverse Events

Any AE experienced by the subject from the time of signing of the ICF through the follow-up safety phone call is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. Any SAE experienced by the subject between the time of the signing of the ICF and the follow-up safety phone call visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment.

5.14.1.1. Treatment-emergent adverse events

Treatment-emergent is defined as having an onset date on or after the first randomized dose, up to and including 84 days after the last dose date (or up to and including 168 days after the last dose date for PML events).

Adverse events with onset date 85 days or later after last dose, will be presented separately.

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

Adverse events will be assigned to the most recent route of administration received before the start date of the adverse event. Missing or partial start dates will be handled in the same manner as for determining treatment emergence.

The overall summary table of AEs will present the number of subjects with the following events for each treatment sequence and route of administration. A subject is counted only once in each category.

- Any AE;
- AE with severity as “moderate” or “severe”;
- AE with severity as “severe”;
- Natalizumab related AE;
- Any SAE;
- Natalizumab related SAE;
- AE leading to discontinuation of study treatment; and
- AE leading to withdrawal from study.
- AE of special interest
- Other events of interest
- Deaths

The incidence of AEs will be also presented for each treatment sequence and route of administration. They will be summarized by the following,

- preferred term (PT);
- primary system organ class (SOC);
- primary system organ class (SOC) and preferred term (PT);

- severity, primary SOC and PT; and
- relationship to study treatment, primary SOC and PT.

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

- a subject will be counted only once within each PT, and PTs will be ordered by decreasing incidence in the column of overall group, which combines all subjects in the study;
- a subject will be counted only once within each primary SOC, and primary SOCs will be ordered by decreasing incidence in the column of overall group;
- a subject will be counted only once within each primary SOC/PT, and PTs will be ordered by decreasing incidence within each primary SOC in the column of overall group.
- a subject 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 incidence within each primary SOC in the column of overall group.
- a subject will be counted only once within each primary SOC/PT, and the AE with the strongest relationship to study treatment will be used. PTs will be ordered by decreasing incidence within each primary SOC in the column of overall group.

The incidence of SAEs, incidence of AEs that led to withdrawal from study, and incidence of AEs that led to discontinuation of study drug will be also summarized by treatment groups and by route of administration with the use of primary SOCs/PTs. The data will be processed as what is done for incidence of AEs. Listing of AEs, SAEs, AEs that led to study treatment discontinuation and AEs that led to study withdrawal, regardless of treatment emergent or not, will be presented. Listing of death will be provided if applicable.

The incidence of adverse events of special interest and other events of interest will also be presented. These adverse event of special interest categories are defined mainly based on Standardized MedDRA Queries (SMQs), SOCs, and/or PTs.

The AEs of special interest categories include but are not limited to the following:

- PML progressive multifocal leukoencephalopathy (all events occur before the end of the study)
- Serious herpes infections
- Malignancies
- Immunogenicity of Tysabri SC

Other events of interest include but are not limited to the following:

- Infusion and injection reactions (defined as any event occurring within 2 hours of the start of infusion or injection)
- Infusion and injection site reactions (defined as any PT occurring under the higher-level terms (HLT) of 'Injection site reactions' or 'Infusion site reactions')
- Injection site reactions upon switching to SC (defined as any PT under the HLT of 'Injection site reactions' occurring on or after the first dose of SC but prior to the second dose of SC.
- Injection site pain
- Opportunistic infections (excluding PML)
- Hepatic injury
- Drug induced liver injury
- Hypersensitivity reactions

In some AE/SAE listings, complete AE start and end dates are needed to calculate the relative study days of AE start and end. Therefore, any partial date will be imputed for these listings. Specifically, the partial AE start date will be imputed as the earliest possible date on or after the first dose based on the partial information, and the partial AE end date will be imputed as the latest possible date on or before the follow-up safety phone call visit.

5.14.1.1. Events occurring during the run-in period

AEs occurring during the run-in period are defined as any event occurring on or after the time of informed consent and prior to time of first dose after randomization (at Week 108 for continuing Part 1 subjects and Week 36 for newly enrolled subjects). AEs occurring during the run-in period will be presented for the following groups, 'discontinued during run-in period/or who were randomized but who did not receive a dose after randomization', 'IV/SC after randomization', and 'SC/IV after randomization', for all enrolled subjects. Tabulations for AEs and SAEs as well as listings for each will be provided.

5.14.1.2. Events ongoing at the end of Part 1

Of 497 participants who entered Part 1, 68 participants rolled over into Part 2 before or at Week 84 and were not included in the safety population for the 101MS329 Part 1 CSR Addendum dated 07JUL2022 as their safety data (for completed AEs before rollover) were already included in the 101MS329 Final (Part 1) CSR dated 12APR2021. Ongoing AEs at the time of rollover will be summarized as part of the Part 2 safety analysis and will be identified as events beginning prior to the date of informed consent in Part 2. AEs will be presented by the treatment received during Part 1 (SID or EID). Tabulations for AEs and SAEs as well as listings for each will be provided.

5.14.2. Clinical Laboratory Data

The following clinical laboratory parameters are assessed as stated in the protocol Section 5 and Section 14.2:

- Blood hematology: complete blood count with differential and platelet count, and absolute neutrophil count
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma-glutamyl-transferase (GGT), glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium

Laboratory tables and listings, unless otherwise specified, will be presented over time by treatment sequence and will indicate the most recent route of administration received before the assessment where appropriate.

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 treatment sequence and visit. Number of evaluable subjects, mean, standard deviation, median, min and max 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 (Appendix I). 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 subject, 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 subject, 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 subject, then the record with the later time will be used for the by visit analysis.

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 subject'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 subjects shift to low (or high) divide by number of subjects at risk followed by corresponding percentages. Number at risk for shifting to low (or high) is the number of subjects 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 subjects with any post-baseline PCS laboratory abnormalities will be summarized by treatment sequence and route of administration for the parameters provided in Table 2. Post-baseline PCS laboratory abnormalities will be assigned to the most recent route of administration received before the sample date.

Subject listings will also be presented for all subjects with any PCS laboratory abnormalities. In these listings, each subject'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 2 Criteria to Determine Clinically Relevant Abnormalities in blood 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.

Listing of the liver function test parameters will be provided.

5.14.3. 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 6-weekly study visits until the EOS visit. All measurements are collected at unscheduled visits if applicable. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities from Day 1/baseline of the crossover phase up to the EOS visit, based on the following criteria in Table 3.

Table 3 Criteria to Determine Clinically Relevant Abnormalities in Vital Sign

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C and an increase from pre-dose of at least 1°C
Heart rate	> 120 beat per minute and an increase from pre-dose of more than 20 beats per minute. < 50 beats per minute and a decrease from pre-dose of more than 20 beats per minute.
Systolic Blood Pressure	> 180 mmHg and an increase from pre-dose of more than 40mmHg. < 90 mmHg and a decrease from pre-dose of more than 30 mmHg.
Diastolic Blood Pressure	> 105 mmHg and an increase from pre-dose of more than 30 mmHg. < 50 mmHg and a decrease from pre-dose 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 subjects with any clinically relevant post-baseline abnormalities will be provided. In the summary table, entries are numbers of subjects with an abnormality divided by number of subjects evaluated followed by corresponding percentages. Number evaluated is the number of subjects 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 treatment sequence and visit. The line of mean vital sign over time by treatment sequence may be graphed.

Subjects with any post-baseline clinically relevant abnormalities in vital signs will be tabulated by treatment sequence and route of administration and listed. Clinically relevant abnormalities in vital signs will be assigned to the most recent route of administration received before the date of assessment.

In the listing, each subject's complete vital sign values from screening visit to EOS visit will be listed with abnormalities labeled. A separate listing of adverse events will also be provided for subjects with any post-baseline clinically relevant abnormalities in vital signs.

For vital sign visit summaries, the analysis visit will be defined by visit window (Tables 4-10 in APPENDIX II). For the same parameter for a subject, 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.

5.14.1. Body Weight

Body weight, collected at the screening visit, baseline of the crossover phase, Week 24, and Week 48 will be summarized by treatment sequence over time.

5.14.2. Physical and Neurological Examination

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

5.14.3. Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS was not assessed during the crossover phase of Part 2 of the study.

C-SSRS was collected at Week 84 relative to the start of Part 1 for rollover subjects only and recorded in the Part 2 database. Analysis of Week 84 data will be performed alongside C-SSRS data from all other visits in Part 1 as a separate analysis.

6. Changes from Protocol-Specified Analyses

This SAP supersedes the statistical considerations identified in the protocol; analyses specified in the SAP reflect an approach that accounts for the Part 2 crossover study design. The full analysis set was defined to address secondary [redacted] endpoints.

1. The per-protocol set was defined to provide supportive analyses of selected efficacy endpoints as needed.
2. Considerations have been made for data pertaining to subjects rolling over into Part 2 from Part 1.
3. Considerations have been made for data related to the 36-week run-in period prior to randomization into the crossover phase.
4. Time to event analyses will be presented over time by treatment sequence rather than route of administration as the protocol-specified analysis does not account for the correlation of the within subject effect.

7. Summary of Changes from the Previous Version of the SAP

Section	Change and rationale
3.1.1. Definition of Baseline	The definition of baseline of the crossover phase was clarified.
5.1. General Principles	Text added to reflect data handling performed: 'If a sample result is received as an inexact value, e.g., >2.35, then the numerical value excluding the non-numerical character will be taken for analysis purposes.'
5.2. Subject Accountability	Text edited for clarity as last dose is subject's choice (rather than randomized): time exposed to ~~randomized~~ **study** treatment
5.8.5.4. Time to first relapse	Text added to reflect the actual data observed: 'Analysis will only be performed if a number of events sufficient to obtain a reliable estimate are observed.'
5.8.5.5. Annualized relapse rate	Text added to reflect the actual data observed: 'Annualized relapse rate will only be calculated if a number of events sufficient to obtain a reliable estimate are observed.'
5.8.5.6. Change in EDSS score	Definitions and description of analyses performed were added as follows: 'Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score >=1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 (observed at the Week 24 visit), that is confirmed after at least 24 weeks (at the Week 48 visit). The number of subjects with confirmed EDSS worsening will be presented by treatment sequence. The proportion of subjects free of confirmed EDSS worsening at Week 48 will be estimated based on the Kaplan-Meier product limit method. Confirmed EDSS improvement is defined as a decrease of at least 1.0 point from a baseline EDSS score of >=2.0 (observed at the Week 24 visit) that is confirmed after at least 24 weeks (at the Week 48 visit). The number of subjects with confirmed EDSS improvement will be presented in the same manner as described for confirmed EDSS worsening. Worsening or improvement observed at Week 48 only could not be confirmed without follow-up data.'

5.10. Immunogenicity Endpoints	Text edited to reflect data handling performed: Immunogenicity data ~~taken from the early termination visit~~ will be ~~assigned~~ **mapped** to ~~the next scheduled visit~~ **an appropriate analysis visit using the windowing scheme described in Appendix I**.
[redacted]	[redacted]
5.13. Pharmacodynamic Endpoints	Text edited to reflect data handling performed: ~~Measurements taken from early termination visits~~ Post-baseline measurements will be ~~assigned~~ **mapped** to ~~the next scheduled~~ **an appropriate analysis** visit ~~within the same treatment period~~ **using the windowing scheme described in Appendix I**.
5.14.1.1. Treatment-emergent adverse events	Text edited for clarity: Treatment-emergent is defined as having an onset date on or after the first randomized dose ~~in Period 1~~, up to **and including** 84 days after the last ~~randomized~~ dose date. **(or up to and including 168 days after the last dose date for PML events)**.
5.14.1.1. Treatment-emergent adverse events	Text added to reflect data presented: 'Adverse events with onset date 85 days or later after last dose, will be presented separately.'
5.14.1.1. Treatment-emergent adverse events	Adverse event of special interest was clarified: • Immunogenicity of Tysabri **SC**
APPENDIX I - VISIT WINDOW MAPPING	Table 5: Visit Windows for Brain MRI Text added for clarity: 'MRI data collected at scheduled visits will not be mapped. ET data will be mapped to the next scheduled visit.'
APPENDIX I - VISIT WINDOW MAPPING	Subtitle edited for clarity: Table 6: Visit Windows for **TSQM, PROs,** EDSS and Neurological Examination
APPENDIX I - VISIT WINDOW MAPPING	Visit window mapping included to reflect data handling performed: Table 11: Visit Windows for Pharmacodynamic Measurements

8. References

Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics. 2010 Jan;11(1):1-17.

Senn, S, Cross-over Trials in Clinical Trial Research, Second Edition, 2002, John Wiley & Sons, Ltd.

Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. Lancet Neurol. 2013;12(7):669-76.

APPENDIX I - VISIT WINDOW MAPPING

For data that are summarized by visit and 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. Analysis visit windows are defined in Table 4 - Table 10 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 subject, 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 60.

Table 4: Visit Windows for Patient Preference Questionnaire

Analysis visit	Target visit day	Analysis visit window
Week 30	211	[1,253]
Week 42	295	≥ 254

Table 5: Visit Windows for Brain MRI

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 scheduled visits will not be mapped. ET data will be mapped to the next scheduled visit. MRI data collected at unscheduled visit for safety monitoring won't be included in the efficacy analysis.

Table 6: Visit Windows for TSQM, PROs, EDSS and Neurological Examination

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 Blood Hematology

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 24	169	[2,253]
Week 48	337	[254, 379]
Week 60/End of Study	421	≥ 380

Table 8: Visit Windows for Blood Chemistry

Analysis visit	Target visit day	Analysis visit window
Run-in visit 3	-168	≤ 1
Week 60/End of Study	421	≥ 2

Table 9: Visit Windows for Vital Signs Measurements

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 6	43	[2, 64]
Week 12	85	[65, 106]
Week 18	127	[107, 148]
Week 24	169	[149, 190]
Week 30	211	[191, 232]
Week 36	253	[233, 274]
Week 42	295	[275, 316]
Week 48	337	[317, 379]

Analysis visit	Target visit day	Analysis visit window
Week 60/End of Study	421	≥ 380

Table 10: 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 11: Visit Windows for Pharmacodynamic Measurements

Analysis visit	Target visit day	Analysis visit window
Baseline/Day 1	1	≤ 1
Week 6	43	[2, 64]
Week 12	85	[65, 106]
Week 18	127	[107, 148]
Week 24	169	[149, 190]
Week 30	211	[191, 232]
Week 36	253	[233, 274]
Week 42	295	[275, 316]
Week 48	337	≥ 317

[redacted]

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Electronic Record and Signature Disclosure: Accepted: 30 August 2023 | 16:16 ID: 5f31330d-601a-4b83-8f3a-2ceacf0b24a0		

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Editor Delivery Events	**Status**	**Timestamp**
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Witness Events	**Signature**	**Timestamp**
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Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	30 August 2023 | 15:48
Certified Delivered	Security Checked	30 August 2023 | 16:16
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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
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