Statistical Analysis Plan

Version No.: 2.0

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy

Name of Study Treatment: Natalizumab

Protocol No.: 101EP201/NCT03283371

Study Phase: Phase II

STATISTICAL ANALYSIS PLAN

Product Studied: Natalizumab (BG00002)

Protocol Number(s): 101EP201

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects with Drug-Resistant Focal Epilepsy

Date of Protocol: 30 May 2018, Final Version 2

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This document has been reviewed and approved by:

[redacted]	[redacted]	2/12/2020
SMT Statistician (Printed Name)	Signature	Date
[redacted]	[redacted]	2/12/2020
Program Statistician (Printed Name)	Signature	Date
[redacted]	[redacted]	14 Feb 2020
Study Medical Lead (Printed Name)		Date

VERSON HISTORY

Version No.	Version Date	
Version 1.0	26-November-2018	Statistical Analysis Plan Final v1.0

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LIST OF ABBREVIATIONS

ADA	Antidrug antibody
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
AUC_{tau}	area under the serum concentration-time curve for a dosing interval
BMI	Body mass index
CI	confidence interval
C_{max}	maximum serum concentration
CNS	central nervous system
eCRF	electronic Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ET	Early Termination
[redacted]	[redacted]
ICH	International Council for Harmonisation
IERC	independent epilepsy review committee
ITT	intent-to-treat
IV	Intravenous(ly)
IXRS	Interactive Response Technology
JCV	John Cunningham virus
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PP	Per-protocol
Q4W	Every 4 weeks
[redacted]	[redacted]
REML	Restricted maximum likelihood
RNA	ribonucleic acid
RNS	Responsive neurostimulation
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]
US	United States

USUBJID	Unique subject identifier
VNS	Vagus nerve stimulation
WBC	white blood cell
WHO	World Health Organization

1 Introduction

The purpose of this SAP is to provide details of the statistical analyses as outlined in the study protocol. This SAP is written based on the following documentation in consideration of ICH guidance:

Document	Date	Version
Protocol	30 May 2018	2.0
eCRF	24 Jan 2019	3.0

2 Study Overview

2.1 Study Objectives and Endpoints

2.1.1 Primary Efficacy Objective

The primary objective of the study is to determine if adjunctive treatment with natalizumab 300 mg IV infusion Q4W reduces the frequency of seizures in adult subjects with drug-resistant focal epilepsy.

2.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in log-transformed seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment.

2.1.3 Secondary Efficacy Objectives

The secondary objectives of this study are designed to assess the effects of natalizumab versus placebo in drug-resistant focal epilepsy on additional measures of seizure frequency.

2.1.4 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- Proportion of responders defined as subjects with a ≥50% reduction from baseline in seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment.
- Proportion of subjects free from seizures during Weeks 8 to 24 of treatment.
- Percentage of seizure-free days gained, standardized over 28 days, during Weeks 8 to 24 of treatment compared with baseline.
- Proportion of subjects with inadequate treatment response during Weeks 8 to 24, defined as either of the following:
  - Modification of AEDs after Week 12 of the placebo-controlled phase due to lack of improvement or ongoing seizures.
  - Discontinuation of study treatment after the 8-week active run-in period due to lack of efficacy.

2.1.5 Exploratory Efficacy Objectives

[redacted]

2.1.6 Exploratory Efficacy Endpoints

[redacted]

2.1.7 PK Objective

PK objective of this study is to evaluate the PK of natalizumab in subjects with focal epilepsy.

2.1.8 PK Endpoints

The PK endpoints are as follows:

- C_{max} at steady state.
- AUC_{tau} at steady state.

2.1.9 Safety Objectives

Safety objectives of this study are to assess the safety and tolerability of natalizumab in subjects with drug-resistant focal epilepsy. Safety and tolerability assessments include AEs/SAEs data, clinical laboratory data, and electronic eC-SSRS/C-SSRS.

2.2 Study Design

This is a 6-month randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of natalizumab as adjunctive therapy in the treatment of adult subjects with drug-resistant focal epilepsy.

All subjects will complete a 6-week prospective baseline period without study treatment to establish a baseline seizure frequency. After completing screening assessments and fulfilling the criteria for study entry, eligible subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio, and each subject will receive 1 dose of study treatment at Week 0 with dosing Q4W for 24 weeks, according to 1 of the following 2 regimens: 300 mg IV natalizumab infused over 1 hour or placebo IV. The randomization will be stratified, as much as possible, based on the presence or absence of structural etiology for focal epilepsy and based on the presence or absence of a high seizure frequency (≥24 seizures) during the 6-week prospective baseline period. Structural etiology for focal epilepsy is defined as abnormalities visible on structural neuroimaging where the electroclinical assessment together with the imaging findings lead to a reasonable inference that the imaging abnormality is the likely cause of the subject's seizures [Scheffer 2017]; this assessment will be adjudicated by an IERC.

There will be no dose titration of natalizumab. The initial 8 weeks of the placebo-controlled phase will constitute an active run-in period permitting natalizumab to achieve approximately 75% of steady state in subjects without anti-natalizumab antibodies, based on prior studies in MS.

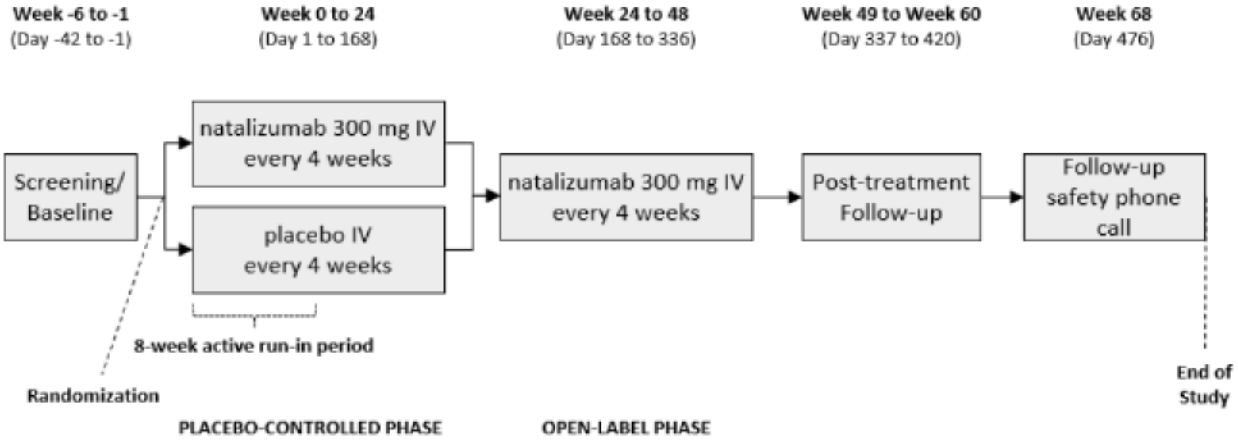
At the end of the placebo-controlled phase, subjects will continue into a 24-week, open-label safety and efficacy phase in which all subjects will receive natalizumab 300 mg IV infusion Q4W for 24 weeks.

A post-treatment follow-up visit and a Follow-Up Safety Phone Call will occur 16 weeks and 24 weeks, respectively, after the last dose of study treatment.

Approximately 70 subjects are expected to be enrolled, randomized, and dosed (~35 subjects in each treatment group) at approximately 44 sites in the US. The study will aim to include approximately 28 subjects with a structural etiology for focal epilepsy and approximately 28 subjects with a high seizure frequency, which are not mutually exclusive.

See Figure 1 for a schematic of the study design.

Figure 1: Study Design Schematic



2.3 Study Duration for Subjects

The total duration of study participation will be up to approximately 74 weeks for subjects completing the placebo-controlled, open-label, and follow-up phases. This comprises: a 6-week prospective baseline period; a 24-week double-blind placebo-controlled phase consisting of an 8-week active run-in period and a 16-week efficacy period; a 24-week open-label phase; a 12-week post-treatment follow-up period; and a Follow-Up Safety Phone Call (24 weeks after the last dose of study treatment).

The end of study date for a subject may be the last study visit, last protocol-specified assessment, or date of AE resolution if the subject has ongoing AEs requiring follow-up.

2.4 End of Study

The end of study is last subject, last phone call for final collection of data. The end of the placebo-controlled phase will be after the assessments are taken at Week 24, before study treatment administration for the open-label phase.

2.5 Sample Size Considerations

Twenty-nine subjects per treatment arm will provide 80% power to detect a treatment difference of -0.375 between natalizumab and placebo in the natural log-transformed seizure frequency, standardized over 28 days, at a 2-sided significance level of 0.050, assuming a common standard deviation of the log-transformed frequency of 0.5. For example, if the placebo group has a 20% reduction from baseline in seizure frequency and the active group has a 45% reduction from baseline in seizure frequency, the sample size would provide 80% power to detect this difference. A total of approximately 70 subjects will be randomized to allow for a discontinuation rate up to 15%.

3 Definitions

3.1 Dates and Points of Reference

In general, data that are summarized by visit; ET visits or unscheduled visits will be assigned to an appropriate scheduled visit by using the windowing scheme shown in Table 2. If the date of the ET visit falls between the lower bound and upper bound dates for an analysis visit, it will be assigned to that visit. However, if a prior visit is mapped to the same analysis visit, then the ET visit will be remapped to the next analysis visit. The visit window mapping will not be applied to the end of study visit Week 60 or Follow-up visit for ET subjects.

The date of the first infusion will be the reference point (Day 1). Relative days after Day 1 are calculated as (assessment date - Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date - Day 1 date). The day prior to Day 1 is Day -1.

Table 2: Visit Window Mapping

Phase - Study Visit	Analysis Visit	Target Day	Visit Window	
			Vital signs, laboratory assessment, eC-SSRS/C-SSRS	[redacted]
Screening - Screening	Week -6	-42	≤ -1	≤ -1
PCP - Baseline	Baseline	≤1	≤1	≤1
PCP - Visit 2	Week 4	28	2-41	--
PCP - Visit 3	Week 8	56	42-69	--
PCP - Visit 4	Week 12	84	70-97	2-97
PCP - Visit 5	Week 16	112	98-125	--
PCP - Visit 6	Week 20	140	126-153	--
PCP - Visit 7	Week 24	168	154-181	98-181
OLP - Visit 8	Week 28	196	182-209	--
OLP - Visit 9	Week 32	224	210-237	--
OLP - Visit 10	Week 36	252	238-265	182-265
OLP - Visit 11	Week 40	280	266-293	--
OLP - Visit 12	Week 44	308	294-321	--
OLP - Visit 13	Week 48	336	322-349	266-349

Abbreviations: PCP=Placebo-Controlled Phase; OLP=Open-Label Phase

If more than one observation is within the same window, data closest to the target regularly scheduled visit will be used in the summary statistics and analyses. If more than one observation falls in the same distance from the target regularly scheduled visit day, the last observation will be used in the summary statistics and analyses.

The seizure calculation window for a visit will start on the date of previous visit and end on the date immediately before the current visit date. If an infusion is missed, the seizure frequency will be calculated based on the projected visit date (i.e., 28 days from the date of previous visit). If the subject withdrew from the study prematurely, the seizure frequency after the last infusion will be calculated from last infusion until the date of the ET visit or 28 days after last infusion, whichever is earlier. The calculated frequency will be assigned to the next scheduled visit had ET not occurred. In the post-treatment period, the number of seizures will be counted for every 28 days and the calculated seizure frequency will be assigned to weeks in a 4-week interval.

Study Periods

Baseline period is defined as the period from screening visit to the day prior to first infusion of study treatment (i.e., placebo and natalizumab).

The end-of-treatment day is defined as 27 days after last infusion in the study or the day prior to ET visit, whichever is earlier. Treatment period is defined as the period from first dosing date to the end-of-treatment day, inclusive. Within treatment period, placebo-controlled phase is defined as the period from first infusion in the study until prior to infusion at the Week 24 visit, while open-label phase is defined as the period from infusion at the Week 24 visit to the end-of-treatment day.

Post-treatment period is defined as the period from 28 days after last infusion date or ET visit, whichever is earlier, to end-of-study visit (Week 60 visit for completers and Follow-up visit for early withdrawal subjects).

Baseline definition

- Study baseline: The baseline assessments in general will be defined as the closest non-missing value prior to/on the date of the first infusion of study treatment except for that of the seizure data. Study baseline for seizure data will be derived using the standardized calculation for baseline period seizure diary data, as described in Section 3.3.1.
- Open-label phase baseline: Open-label phase baseline in general except for that of the seizure data is defined as the closest non-missing value prior to/on the date of the first infusion of natalizumab in the study. Open-label phase baseline for seizure frequency is defined as the 28-day standardized seizure frequency assigned to the visit of the first natalizumab infusion in the study.

3.2 Treatment Group

Unless otherwise specified, data will be summarized using the following labels for treatment group in the placebo-controlled phase analysis, in the order presented:

- Placebo
- Natalizumab 300 mg,

and using the following labels for treatment group in the open-label phase analysis, in the order presented:

- Placebo to Natalizumab 300 mg
- Natalizumab 300 mg to Natalizumab 300 mg

The randomized treatment will be based on IXRS randomization code. The actual received treatment in the placebo-controlled phase will be natalizumab if the subject receive any dose of natalizumab; otherwise, the actual treatment will be placebo. The actual received treatment in the open-label phase will be natalizumab to natalizumab if the subject receive any dose of natalizumab in the placebo-controlled phase; otherwise, the actual treatment will be placebo to natalizumab.

3.3 Key Derived Variables

3.3.1 Calculation of Standardized Seizure Frequency

Both sources of seizure diary data (electronic and paper) will be pooled together for the efficacy analysis. The pooled data will be referred to as seizure diary data in the analysis. Seizures included in efficacy analyses are focal aware seizures (previously termed "simple partial seizures") with motor signs, focal impaired awareness seizures (previously termed "complex partial seizures"), and focal to bilateral tonic-clonic seizures (previously termed "partial onset with secondary generalization"). Focal aware seizures without motor signs will not be included in the calculation of seizure frequency.

For the assessment of seizure frequency, the standardized seizure frequency (number of seizures per 28 days) at each visit will be calculated based on the sum of the seizures reported in the subject seizure diary and the number of days with non-missing seizure frequency data in the seizure calculation window for the corresponding visit (defined in Section 3.1). A report of unknown seizure occurrence will be considered as a missing seizure diary data but in compliance to seizure reporting.

Seizure frequency (number of seizures per 28 days) will be calculated based on both sources of subject seizure diary data (electronic and paper) in the seizure calculation window, as follows:

$$\text{Standardized Seizure Frequency} = \frac{\text{Number of seizures}}{\text{Number of days with non-missing seizure diary}} \times 28$$

Study team will monitor the number of visits with zero counts in the standardized seizure frequency (number of seizures over 28 days). If more than five percent of the visits during the placebo-controlled phase have zeros in the standardized seizure frequency across all the subjects in the ITT population, the following formula will be used to perform the natural log-transformation, $y=\ln(x+0.2)$, where x is the standardized seizure frequency. The final analysis results will be back calculated by adjusting for 0.2 increment. The median standardized seizure frequency will be calculated as *exp* (mean of log standardized seizure frequency) -0.2.

If no more than 5% of the visits during the placebo-controlled phase are observed with zeros in the standardized seizure frequency across all the subjects in the ITT population, $y=\ln(x+0.2)$ will only be used for the visits with zero seizure frequency. The final analysis results will not be adjusted for the small increment of 0.2. This method only applies to the log transformed analysis and will not be employed for the responder analysis.

To maintain the high compliance rate for seizure data postbaseline, if 15% of diary data or more are missing between two infusions (i.e., the diary compliance <85%), the seizure frequency at the following visit will be assigned to missing. If a visit doesn't take place, projected visit date (defined as 28 days from the date of previous visit) will be used to calculate the seizure frequency. Also, seizure data will not be used after modification of AEDs as recorded on the eCRF page of Anti-Epileptic Treatment Compliance.

Sensitivity analyses (details in Section 5.10.2) will be performed to include all the observed seizure data.

3.3.2 Definition of Responder

A responder is defined as a subject with a ≥50% reduction from study baseline in seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment. The overall seizure frequency per 28 days during Weeks 8 to 24 will be calculated similarly as described in Section 3.3.1. Any subjects who have received modification of AEDs during the placebo-controlled phase will be considered as non-responder. Modification of AEDs will be determined based on what is reported on the eCRF page of Anti-Epileptic Treatment Compliance. Focal aware seizures without motor signs will not be included in the calculation of seizure frequency.

3.3.3 Definition of Free from Seizure

A seizure-free subject is defined as a subject who has no (zero) seizures (calculation of seizure frequency described in Section 3.3.1) during Weeks 8 to 24 of treatment. Unless otherwise specified, if subjects have missing seizure diary data, they will not be considered as seizure free.

3.3.4 Definition of Number of Seizure-free Days

The number of seizure-free days will be calculated based on the number of seizure-free days among the days with non-missing seizure diary data in the seizure calculation window for a visit. The number of seizure-free days per 28 days will be calculated as: (number of seizure-free days / number of days with non-missing seizure dairy) × 28 days.

3.3.5 Study Treatment Compliance

The study treatment compliance in the placebo-controlled phase is defined as the percentage of study treatment infusions received over the number of infusions that the subject is expected to have received up to the end of the placebo-controlled phase. The definition of study treatment compliance in the open-label phase is the same.

3.4 Stratification Factors and Subgroup Variables

3.4.1 Stratification Factors

The stratification factors used in the IXRS randomization are listed as follows:

- Seizure frequency category during the 6-week prospective baseline period:
  - ≥24 seizures
  - <24 seizures

- Structural etiology category for focal epilepsy:
  - Presence of structural etiology
  - Absence of structural etiology

3.4.2 Subgroup Variables

The following variables will be used for subgroup analyses:

- Structural etiology category for focal epilepsy (presence, absence)

  The IERC assessment of structural etiology will be used as the true presence of structural etiology.

- Seizure frequency category (high: ≥24; low: <24 seizures)

  Based on seizure diary data in the baseline period, the observed seizure frequency will be standardized to 42 days to account for the 6-week baseline period. The 42-day standardized seizure frequency will be categorized by ≥24 or < 24 seizures as the observed high or low seizure frequency category.

- Duration of epilepsy (in years) from diagnosis to randomization date (<10 and ≥10 years)

  The year of epilepsy diagnosis will be used to calculate the duration of epilepsy, as (year of randomization date - year of epilepsy diagnosis).

The subgroup variables will be determined by the IERC-adjudicated or observed baseline data instead of randomization stratification factors.

3.5 Analysis Populations

The analysis will include the ITT, PP, Safety, PK, and PD populations.

ITT Population

The ITT population is defined as all subjects who were randomized and received any dose of study treatment. Subjects will be analyzed in the treatment group to which they were randomized. All efficacy endpoints will be evaluated based on the ITT population according to the randomized treatment.

All subjects who received any dose of study treatment during the open-label phase will be included in the ITT population for the open-label phase. The data during the open-label phase will be summarized by the actual treatments received in the study.

PP Population

The PP population will include the subset of the ITT population who have completed the placebo-controlled phase (as recorded on the eCRF page 'End of Treatment [Placebo-Controlled Phase]'), have overall diary compliance greater than 90% during the placebo-controlled phase, and have no significant protocol deviations that would be expected to affect efficacy assessments. Subjects will be analyzed based on actual treatment received for the PP population. The PP population will be used for analysis of primary endpoint and selected secondary efficacy endpoints.

The list of significant protocol deviations for exclusion from the PP population includes, but is not limited to:

- Subjects who missed at least 1 infusion during the placebo-controlled phase.
- Subjects who experienced <6 seizures during the baseline period or were seizure free for more than 21 consecutive days during the baseline period and were randomized in the study. Focal aware seizures without motor signs will not be included in the seizure count.
- Subjects who missed more than 6 days of seizure diary data during the baseline period and were randomized in the study.
- Subjects who modified AEDs during the baseline period.
- Subjects who were accidentally unblinded.

The validity of subject inclusion in the PP population will be reviewed and approved prior to the database lock.

Safety Population

The Safety population, comprising all subjects who were randomized and received any dose of study treatment, will be used for the analysis of safety data. Subjects will be analyzed based on actual treatment received for the safety population.

All subjects who received any dose of study treatment during the open-label phase will be included in the safety population for the open-label phase.

PK Population

The PK population is defined as all subjects who received any dose of study treatment and had at least 1 measurable concentration of natalizumab in serum.

The PK population for the open-label phase is defined as all subjects who received any dose of study treatment during the open-label phase and had at least 1 measurable concentration of natalizumab in serum.

Subjects will be analyzed based on actual treatment received for the PK population.

PD Population

The PD population is defined as all subjects who received any dose of study treatment and had at least 1 postbaseline measurement of the parameter being analyzed for PD.

The PD population for the open-label phase is defined as all subjects who received any dose of study treatment and had at least 1 postbaseline measurement of the PD parameters.

Subjects will be analyzed based on actual treatment received for the PD population.

4 List of Planned Study Analyses

4.1 Interim Analysis

A planned interim analysis with optional sample size re-estimation is described in Section 16.7 of the protocol. However, based on actual study recruitment, this potential analysis would have occurred only approximately 6 months prior to the end of the study and after all subjects would have been expected to be enrolled. Therefore, Biogen in collaboration with the study advisory committee and drug-safety monitoring committee decided that a formal interim analysis with sample size re-estimation was not warranted. No stopping decision will be made based on the efficacy data before 24 weeks of treatment.

4.2 Primary Analysis

The primary database lock and readout will occur at the end of the placebo-controlled phase after all study subjects have had the opportunity to complete the Week 24 visit. The primary analysis will include the efficacy and safety of natalizumab as adjunctive therapy in adult subjects with drug-resistant focal epilepsy during the placebo-controlled phase.

4.3 Final Analysis

The final database lock will occur after all subjects have completed the entire study. The analysis will be performed to assess the durability of treatment response, quality of life, mood, and the safety of natalizumab during the open-label phase.

5 Statistical Methods for Planned Analyses

5.1 General Principles

For continuous endpoints, the summary statistics will generally include number of subjects with data (n), mean, standard deviation, median, quartiles, and range. For categorical endpoints, the summary statistics will generally include the number of subjects in the corresponding analysis population, and the number and percentage of subjects in each category. The statistical software, SAS® version 9.4 or above, will be used for all summaries and statistical analyses.

5.2 Missing Data Handling Conventions

No imputation will be performed for completely missing dates of AEs, concomitant medications/therapies, and medical history events. The following rules will be used to impute the partial start dates of AEs and concomitant medications/therapies:

- If only the day is missing and month and year are present,
    - If month and year are the same as the first dose date of study treatment, then assign to the day of the first dose date of study treatment;
    - If month and year are not the same as the month and year of the first dose date of study treatment, then assign to the first day of the month.
- If only the year is present and month and day are missing,

- If year is the same as the year of the first dose date of study treatment, then assign to the month and day of the first dose date of study treatment;
- If year is not the same as the year of the first dose date of study treatment, then assign to January 1st.

The partial end dates will be imputed as follows:

- If only day is missing and month and year are present, then assign to the last day of the month;
- If only year is present and month and day are missing, then assign to December 31st.

For medical history events with partial onset dates, the following rules will be applied:

- If year and month are present, and day is missing, impute the day as the 15th of the month;
- If year is present, and month and day are missing, impute the month and day as June 30th of the year.

5.3 Subject Accountability

The number (and %) of subjects will be presented as follows: those randomized; those dosed; those included in each of the analysis populations; those completing the treatment in the placebo-controlled phase; those who discontinued the treatment in the placebo-controlled phase, along with reasons for discontinuation; those entering the open-label phase; those completing the treatment in the open-label phase; those who discontinued the treatment in the open-label phase, along with reasons for discontinuation; and those withdrawing from the study with the reason for withdrawal.

Listings of those subjects who discontinued treatment during the placebo-controlled phase or the open-label phase and/or withdrew from the study, along with the reasons for discontinuation/withdrawal, will be presented.

5.4 Demographic and Baseline Disease Characteristics

Demographic and study baseline data (demography, medical history, epilepsy history, seizure history, number of prior and concomitant epilepsy drug and non-drug therapies) will be summarized for the ITT population only.

Demography includes age, age group (≤30, 31 to 45, 46 to 60, ≥61 years old), sex, race, study baseline height, study baseline weight and study baseline BMI. Randomization stratification factors to be summarized include: structural etiology for focal epilepsy (presence, absence); category of seizure frequency (≥24 seizures, <24 seizures) during the 6-week prospective baseline period used in IXRS; and the observed/adjudicated values of the two factors.

Medical history will be coded using the latest version of MedDRA (version 22.1 or later if updated) and the number (and %) of subjects with each history will be presented using the preferred term.

Epilepsy history includes age at epilepsy diagnosis, presence or absence of focal epilepsy, presence or absence of multifocal epilepsy, and most likely epilepsy etiology. Relevant results of neuroimaging, neurophysiology, and neuropsychology findings will be presented in the listings.

Seizure history includes the duration of seizure types since onset, calculated as (randomization date - first seizure onset date)/365.25, and the estimated frequency in the last year, which will be summarized by type of seizure and treatment group. The partial onset date will follow the imputation rules for medical history events described in Section 5.2.

Epilepsy treatment history will be tabulated by treatment groups. The number (and %) of subjects taking previous epilepsy treatment as well as prior or ongoing non-drug therapies for epilepsy (VNS, RNS, epilepsy surgery, and ketogenic diet) will be summarized. A listing of Epilepsy treatment history for all subjects will be presented.

Formal statistical analyses will not be done to test for homogeneity between treatment groups. If there are apparent heterogeneities between the groups in any of the subject characteristics that are of clinical importance or could affect the treatment outcome, the impact of the imbalances will be investigated, and adjustments made in the efficacy and safety analyses if appropriate.

5.5 Protocol Deviations

The major/critical protocol deviations will be summarized for the ITT population. A listing of major/critical protocol deviations will be presented.

5.6 Extent of Exposure

Subjects will receive study treatment Q4W in the treatment period.

Study treatment compliance (defined in Section 3.3.5) will be summarized for the Safety population by treatment groups in the placebo-controlled phase. The number of interrupted infusions and total volume administered will also be summarized by treatment group in the placebo-controlled phase.

Study treatment compliance, interrupted infusions, and total volume administered in the open-label phase will be summarized in the same manner as in the placebo-controlled phase.

5.7 Non-AED Concomitant Medication/Therapy

All non-AED concomitant medications will be coded using the WHO medication dictionary (WHODD GLOBAL version B3 March 2019, or later if updated). All concomitant non-drug therapies will be coded using MedDRA (version 22.1 or later if updated). A concomitant therapy in the placebo-controlled phase will be defined as any therapy that was taken on or after the day of the first dose of study treatment in the placebo-controlled phase. A concomitant therapy in the open-label phase will be defined as any therapy that was taken on or after the day of the first dose of study treatment in the open-label phase.

For the placebo-controlled phase, this includes therapies that start prior to the initiation of the first dose of study treatment if their use continues on or after the date of the first dose of study treatment in the placebo-controlled phase. For the open-label phase, this includes therapies start prior to the initiation of the first dose of study treatment if their use continues on or after the date of the first dose of study treatment in the open-label phase. In order to define concomitant for therapies with completely missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates of a therapy are completely missing, that therapy will be considered concomitant in both the placebo-controlled phase and the open-label phase.
- If the start date of a therapy is completely missing and the stop date of that therapy falls on or after the date of the first dose of study treatment in the placebo-controlled phase, that therapy will be considered concomitant in the placebo-controlled phase.
- If the start date of a therapy is completely missing and the stop date of that therapy falls on or after the date of the first dose in the open-label phase, that therapy will be considered concomitant in both the placebo-controlled phase and the open-label phase.
- If the stop date of a therapy is completely missing and the start date of that therapy falls before the date of the first dose in the open-label phase, that therapy will be considered concomitant in both the placebo-controlled phase and the open-label phase.

For a therapy with a partial start or stop date, the imputation will be performed as described in Section 5.2 and the imputed dates will be used to determine whether the therapy is concomitant.

The number (%) of subjects taking non-AED concomitant medications and non-drug therapies will be summarized for the ITT population by treatment groups in the placebo-controlled phase and the open-label phase separately.

5.8 Concomitant Anti-Epileptic Drugs

The number (and %) of subjects taking concomitant AEDs at randomization will be summarized for the ITT population.

Benzodiazepines (including Lorazepam, Clonazepam, Clobazam, Diazepam, Alprazolam, Midazolam, Chlordiazepoxide) that are used as rescue medication for occasional seizure exacerbation will be identified from seizure diary sources (both electronic and paper). The number (and %) of subjects taking any rescue medication will be summarized for the baseline period and placebo-controlled phase in the ITT population. The number of days a benzodiazepine is taken as rescue medication per 28 days during the baseline period and placebo-controlled phase will be summarized descriptively by treatment group.

The number (and %) of subjects who had an AED modification will be tabulated by treatment group and treatment period based on the study visit (i.e., 6-week prospective baseline period, 8-week active run-in period, 16-week efficacy period, the overall placebo-controlled phase). The reason and details of AED modifications will be presented in a listing. Modifications of AEDs during the open-label phase will be tabulated and listed separately.

5.9 Diary Seizure Compliance

Compliance of reporting seizure data via electronic source and the compliance of overall seizure diary data (including both electronic and paper sources) in the placebo-controlled phase will be summarized by visit and overall for each treatment group in the ITT population. The compliance of diary data at each visit is defined by the number of days with non-missing diary entry, including the documentation of seizures, the confirmation of no seizure on the day, and report of 'unknown' seizure occurrence, divided by the number of study days between two visits. The electronic diary seizure compliance and the overall diary compliance of each subject will be listed by visit.

Compliance of reporting seizure data via electronic diary and the compliance of overall diary data will also be summarized for the open-label phase.

5.10 Primary Endpoint

5.10.1 General Analysis Methods for Efficacy Endpoints

The following statistical methods will be used to analyze the efficacy endpoints in the placebo-controlled phase:

- The primary method for analyzing the continuous efficacy endpoints assessed at ≥1 visit postbaseline will use an MMRM under the missing at random framework based on the REML method for estimation. All postbaseline visits during the placebo-controlled phase will be used in the MMRM. For change from baseline of an endpoint, an MMRM will include the following: treatment; visit; treatment-by-visit interaction; IXRS randomization strata of seizure frequency category (high: ≥24, low: <24 seizures during baseline period); IXRS randomization strata of structural etiology (presence, absence); and baseline value of the endpoint on analysis as fixed-effect covariates. An unstructured variance-covariance matrix will be used in the model. If there is a convergence problem for the unstructured covariance matrix, appropriate covariance matrix structures, such as compound symmetry and auto-regressive (1), will be explored, and the one with the least Akaike information criteria will be employed in the primary analysis. Denominator degrees of freedom for the F-test for fixed effects will be estimated using Kenward-Roger approximation.
- ANCOVA models will be used as the primary method to analyze the continuous endpoints with 1 postbaseline assessment (for example, [redacted]), including treatment, IXRS randomization stratification factors of seizure frequency category and structural etiology, and baseline value as fixed effects.
- Logistic regressions will be used as the standard method for binary efficacy endpoints, with covariates including treatment, IXRS randomization stratification factors of seizure frequency category and structural etiology, and log-transformed study baseline seizure frequency per 28 days.

5.10.2 Primary Endpoint

The primary efficacy endpoint of change from study baseline of log-transformed seizure frequency (number of seizures per 28 days), as defined in Section 3.3.1, will be summarized using descriptive statistics by treatment group and visit (including 28-day standardized seizure frequency during Weeks 8 to 24). The primary method for analyzing the change from study baseline of log-transformed seizure frequency is the MMRM model as described in Section 5.10.1. The average effect over Weeks 8 to 24 of each treatment group, as well as the treatment difference, will be displayed with a 95% CI and p-value. The effect of each treatment group, as well as the treatment difference will be summarized by visit. The results after the back transform will be displayed.

In addition, the seizure frequency per 28 days at the original scale will be summarized descriptively by treatment group and visit (including 28-day standardized seizure frequency during Weeks 8 to 24). The

least square mean of change from baseline in log-transformed seizure frequency obtained from the MMRM model and the associated 95% CI will be plotted separately by visit and treatment groups.

Following sensitivity analyses will be performed:

- The same analysis as the primary analysis in the ITT population including observed seizure frequency at all visits regardless whether compliance is ≥85% or not.
- The same analysis as the primary analysis will be repeated for the PP population as a sensitivity analysis.
- The same analysis as the primary analysis in the ITT population using stratification factors based on observed or adjudicated data instead of the ones used in IXRS for randomization stratification.
- Multiple imputation of missing daily seizure occurrence will also be performed. The ANCOVA model will be used in analyzing the change from study baseline of log-transformed seizure frequency (number of seizures per 28 days) over Weeks 8 to 24 of treatment and the imputations will be performed on the daily seizure data. Seizure frequency over Weeks 8 to 24 will be calculated based on the imputed daily seizure data. Multiple imputations will be performed using PROC MI in SAS. Fully conditional specification logistic regression method will be used to impute the missing postbaseline daily seizure data during the placebo-controlled phase. The treatment variable will be coded so that the natalizumab group is the first in the sort order. When the multiple imputation procedure is performed by treatment, the imputation will be done on the natalizumab subjects first.

  Prior to the PROC MI step the dataset will be sorted by descending treatment code and then ascending USUBJID. The imputation will include the treatment, the log-transformed study baseline seizure frequency (number of seizures per 28 days), and stratification factors as well as all available postbaseline seizure diary data during the placebo-controlled phase and the study day from the date of randomization in the model. A set of 100 complete imputed data sets will be generated with 10 burn-in iterations and the relative efficiency parameter will be checked.

  The following pseudo SAS code and seed 1748463 will be used to perform the multiple imputation.

  ```
  proc mi data= in_data seed=x nimpute=100  out=imp_data;
  class  <treatment> <stratification factors> <daily diary frequency>;
  var  <treatment> <stratification factors> <logbase> <study day of diary> <daily diary frequency>;
  fcs NBITER=10 logistic(<daily seizure frequency> = <treatment> <stratification factors> <logbase> <study day of diary>);
  run;
  ```

  The average effect over Weeks 8 to 24 of each treatment group, the treatment difference as well as p-value from the primary analysis model will be obtained using PROC MIANALYZE. The results after the back transform will be displayed.

Subgroup analysis (as defined in Section 3.4.2) will be performed for the primary endpoint using the MMRM as described in Section 5.10.1.

5.10.3 Secondary Endpoints

Proportion of Responders

A responder is as defined in Section 3.3.2. This analysis includes all randomized subjects in the ITT population who have at least 1 postbaseline seizure assessment after Week 8. Subjects who withdraw from treatment or require modifications of AEDs prior to Week 24 (completion of the placebo-controlled phase) or death related to epilepsy will be considered as non-responders in the responder analysis. The proportion of responders will be analyzed using a logistic regression model, as described in Section 5.10.1. The odds ratio from the logistic regression model will be displayed with 95% CI and p-value and the responder rate will be summarized by treatment groups.

Sensitivity analyses will be performed to evaluate the proportion of responders with ≥25% reduction and ≥75% reduction from study baseline.

These analyses will be repeated for the PP population.

Proportion of Subjects Free from Seizures

The proportion of subjects free from seizures during Weeks 8 to 24 of treatment will be summarized descriptively with proportion and 95% exact binomial CI by treatment group for the ITT population who have at least 1 postbaseline seizure assessment after Week 8. The difference of the proportion between natalizumab and placebo group and the 95% Miettinen-Nurminen CI of the difference will be presented. Subjects who withdrew from treatment, required modification of AEDs prior to Week 24 (completion of the placebo-controlled phase), or had any missing diary data during Weeks 8 to 24 of treatment will not be considered as free from seizures in this analysis.

A sensitivity analysis will be performed based on the reported seizure data assuming that no seizure occurs when the diary is missing. If the subject had no seizure reported between Week 8 visit and Week 24 visit and didn't discontinue the study due to lack of efficacy, the subject will be considered seizure free.

These analyses will be repeated for the PP population.

Percentage of Seizure-Free Days Gained, Standardized Over 28 Days, During Weeks 8 to 24 of Treatment Compared with Study Baseline

An MMRM, as described in Section 5.10.1, will be used to analyze the change from study baseline of log-transformed seizure-free days per 28 days (defined in Section 3.3.1). The average effect over Weeks 8 to 24 of each treatment group and the effect by visit, as well as the treatment difference, will be displayed with a 95% CI and p-value.

These analyses will be repeated for the PP population.

Proportion of Subjects with Inadequate Treatment Response During Weeks 8 to 24

The proportion of subjects with protocol-defined inadequate treatment response after Week 8 visit and prior to Week 24 visit will be analyzed using a logistic regression model, as described in Section 5.10.1.

If there are fewer than 5 events, the IXRS randomization stratification factors will be dropped out of the logistic model. Protocol-defined inadequate treatment response includes subjects who withdraw from treatment due to lack of efficacy, require modifications of AEDs prior to Week 24 (completion of the placebo-controlled phase), or die in a manner related to Epilepsy. The odds ratio from the logistic regression will be displayed with 95% CI and p-value. The proportion of subjects with protocol-defined inadequate treatment response will be tabulated by treatment groups and visit.

Time to inadequate treatment response will be analyzed using the Cox proportional hazards model. Independent variables to be included in the model are treatment and IXRS randomization stratification factors. Kaplan-Meier Curve by treatment groups will also be presented. Time to inadequate treatment response is defined as the time from the first infusion of study treatment to the first reported date of protocol-defined inadequate treatment response.

Subjects who do not have a protocol-defined inadequate treatment response during the placebo-controlled phase will be censored. The censor date is the time of the last study contact (last scheduled/unscheduled visit) during the placebo-controlled phase.

These analyses will be repeated for the PP population.

5.10.4 Exploratory Efficacy Endpoints During the Placebo-controlled Phase

[redacted]

[redacted]

5.10.5 Efficacy Analyses during Open-Label Phase

The formal analysis of open-label phase data will be performed at the final analysis at the end of study.

Summary statistics will be presented for seizure frequency data by visit (including 28-day standardized seizure frequency during Weeks 32 to 48) and treatment group during the open-label phase as described below:

- Change from study baseline in log-transformed seizure frequency
- Percent change from study baseline in seizure frequency at original scale
- Change from open-label baseline in log-transformed seizure frequency
- Percent change from open-label baseline in log-transformed seizure frequency

The durability of treatment response to natalizumab in the open-label phase will be assessed by the proportion of subjects who continue to respond to natalizumab in the open-label phase among the responders in the placebo-controlled phase (defined in Section 3.3.2). A responder in the open-label phase is defined as a subject with a ≥50% reduction from study baseline in seizure frequency (number of seizures per 28 days) during Weeks 32 to 48 of treatment. Sensitivity analyses will be performed to

evaluate the durability of treatment response by defining responders as 1) subjects with ≥25% reduction and 2) subjects with ≥75% reduction from study baseline, for both the placebo-controlled phase and open-label phase.

[redacted]

[redacted]

[redacted]

5.11 Safety Endpoints

No formal statistical testing will be performed on the safety data. Safety assessment will be presented separately for the placebo-controlled phase and the open-label phase based on the date of sample collection. The baseline used in safety assessments for placebo-controlled phase and open-label phase will primarily be the study baseline and open-label phase baseline, respectively, unless otherwise specified. The safety assessments for the open-label phase will not be performed in the primary readout, but will be performed in the final analysis at the end of study.

5.11.1 Adverse Events

AEs will be presented separately for the placebo-controlled phase and the open-label phase based on the start date of the event. AEs will be coded using the MedDRA (version 22.1 or later if updated).

Treatment-emergent AEs are defined as the events having onset on/after the date of the first infusion in each phase, or a sign, symptom, or diagnosis that worsens since the event was previously reported. If a subject is not enrolled into the open-label phase of the study or never receives open-label infusion of natalizumab during the open-label phase, all treatment-emergent AEs will be considered as occurring during the placebo-controlled phase of the study.

In order to define treatment-emergent AEs in each phase with completely missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates for a particular event are completely missing, then that event is considered treatment emergent.

- If the start date for a particular event is completely missing and the stop date occurs after the start date/time of the study first dose, then that event is considered treatment emergent.

In order to define the study period for AEs with completely missing start or stop dates, the following additional criteria will be used:

- If both the start and stop dates for a particular event are completely missing, then that event is considered as an event in the placebo-controlled phase.
- If the start date for a particular event is completely missing and the stop date occurs after the start date of the study first dose, then that event is considered as an event in the placebo-controlled phase.
- If the stop date for a particular event is completely missing and the start date occurs on/after the start date of the first dose in the placebo-controlled phase and before the date of the first infusion in the open-label phase, then that event is considered as an event in the placebo-controlled phase.
- If the stop date for a particular event is completely missing and the start date occurs on/after the start date of the first dose in the open-label phase, then that event is considered as an event in the open-label phase.

For AEs with a partial start date, the imputation rule will be performed as described in Section 5.2 and the imputed dates will be used to determine whether the event is treatment-emergent and the study period to which it belongs. If treatment-emergence and study period cannot be determined, the event will be assumed to be a treatment-emergent during the placebo-controlled phase.

A summary of the incidence of treatment-emergent AEs will be provided by treatment group overall , by severity, by relationship to study treatment, by seriousness, and by treatment discontinuation or study withdrawal.

The incidence of treatment-emergent AEs will also be tabulated overall and by treatment group, severity, and relationship to study treatment. The tabular summaries will include incidence by system organ class and by preferred term. AEs and SAEs resulting in study withdrawal will be summarized by treatment group.

Treatment-emergent AEs will be summarized separately by treatment group and overall as follows:

- By preferred term
- By primary system organ class
- By primary system organ class and preferred term
- By severity, primary system organ class and preferred term
- By relationship to study treatment, primary system organ class, and preferred term
- By primary system organ class and preferred term for serious adverse events.

A listing of the following will be presented:

- Serious adverse events
- AEs leading to discontinuation of study treatment
- AEs leading to withdrawal from study

- Deaths

The incidence of treatment-emergent adverse events occurring in at least 5% in any treatment group will be presented by preferred term, and by system organ class and preferred term.

For the analysis of incidence by severity, the occurrence of the AE with the greatest severity will be used, and a subject will be counted only once and only in the event category of the maximum severity. For the analysis of incidence by relationship to study treatment, the occurrence of the AE with the strongest relationship to study treatment will be used and a subject will be counted only once and only in the category of the strongest relationship to study treatment for each event.

In addition, AEs of special interest will be identified by a pre-specified list of coded terms. For each AE of special interest, the number (and %) of subjects with said event will be summarized by preferred term. The AEs of special interest may include but are not limited to the following:

- PML
- Infusion site reactions
- Opportunistic infections
- Drug-induced liver injury
- Hypersensitivity reactions

5.11.2 Clinical Laboratory Results

The following laboratory assessments will be performed to evaluate the safety of the study treatment:

- Hematology: complete blood count with differential and platelet count, and ANC
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium
- Serology: hepatitis B and C serologies
- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal)
- Serum and urine pregnancy tests

The laboratory data will focus on analysis of data from baseline to postbaseline. In the placebo-controlled phase, laboratory data will be summarized using shift tables where appropriate. Subject hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory or as "unknown" if no result is available.

In the placebo-controlled phase, shifts from baseline to high/low status for hematology and blood chemistry parameters will be presented. In each summary, the denominator for the percentage is the number of subjects at risk for the shift. The number at risk for shift to low is the number of subjects whose baseline value was not low and who had at least one postbaseline value. The number at risk for shift to high is the number of subjects whose baseline value was not high and who had at least one postbaseline value. Subjects will be counted only once for each parameter and each type of shift

regardless of how many postdosing assessments had that type of shift. Subjects with shift to low or high will be listed by laboratory parameter and shift type.

Summary statistics for actual values and changes from baseline during the placebo-controlled phase will also be summarized by treatment groups and overall by visit.

Laboratory data will also be listed for each subject.

A summary of the number and percentages of subjects meeting the laboratory abnormality criteria during the placebo-controlled phase listed below will be provided:

- ALT > 3x ULN
- ALT > 5x ULN
- AST > 3x ULN
- AST > 5x ULN
- AST or ALT > 3x ULN
- AST or ALT > 5x ULN
- Total Bilirubin > 2x ULN
- ALP >1.5x ULN
- AST or ALT > 3x ULN and Total Bilirubin > 2x ULN

These analyses will be repeated for the open-label phase.

5.11.3 Anti-John Cunningham Virus Antibodies

Serum anti-JCV antibody results, including index values, will be summarized by treatment group and overall by visits for the placebo-controlled phase and the open-label phase. Serum anti-JCV antibody results, including index values, will also be listed for each subject.

5.11.4 Vital Signs

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities.

For the placebo-controlled phase, the number of subjects evaluated and the number and percentage of subjects with clinically relevant postbaseline abnormalities will be presented by treatment group. The criteria for clinically relevant postbaseline abnormalities are shown in the following table. Summary statistics for actual values and change from baseline will also be presented.

The same analysis will be performed for the open-label phase.

Table 3: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C and an increase from predose of at least 1°C
Heart rate	>120 beat per minute and an increase from predose of more than 20 beats per minute. <50 beats per minute and a decrease from predose of more than 20 beats per minute.
Systolic Blood Pressure	>180 mmHg and an increase from predose of more than 40mmHg. <90 mmHg and a decrease from predose of more than 30 mmHg.
Diastolic Blood Pressure	>105 mmHg and an increase from predose of more than 30 mmHg. <50 mmHg and a decrease from predose of more than 20 mmHg.
Respiratory rate	≥20 breaths per minute with a predose rate of < 20 breaths per minute ≤10 breaths per minute with a predose rate of > 10 breaths per minute

5.11.5 eC-SSRS/C-SSRS

Summary statistics for the eC-SSRS/C-SSRS at each visit will be presented by treatment group and study period using observed data. The baseline value will be based on the closest non-missing recency score prior to first dose of study drug.

The number of subjects evaluated and the number and percentage of subjects with any positive report at postbaseline visits will be presented by treatment group. A positive report is defined as a "yes" response on ideation items 4 and/or 5, or a "yes" response to any behavior item (except non-suicidal self-injury). eC-SSRS/C-SSRS assessments will also be presented in separate shift tables (the shift from baseline to the maximum postbaseline value) for the placebo-controlled phase and the open-label phase.

eC-SSRS/C-SSRS assessment results for each subject at each visit will be listed by treatment group using observed data. Both lifetime and recency scores during the baseline period will be listed.

[redacted]

[redacted]

5.15 Immunogenicity (Anti-Natalizumab Antibodies)

Anti-natalizumab antibodies in serum will be collected at timepoints outlined in the schedule of activities (Appendix A) and analyzed at the primary readout with data in the placebo-controlled phase and at the end of the study with data in the overall treatment period. Results including percentage of subjects who develop ADAs will be summarized by treatment groups at each scheduled timepoint.

The percentage of subjects who develop ADAs will be determined and summarized by treatment group in the placebo-controlled phase and overall treatment period by timepoint. The overall percentage of subjects who are ADA positive at any time will also be summarized by treatment group in the placebo-controlled phase and in the overall treatment period.

The analysis population for immunogenicity will be defined as all subjects in the safety population who have at least 1 postdose sample evaluated for immunogenicity.

- For immunogenicity, the baseline value is defined as the latest immunogenicity data collected at any time prior to the first dose of study treatment. If no immunogenicity data are collected prior to the first dose, the baseline value is missing and will be imputed as ADA negative for immunogenicity analyses.
- Subjects with at least one confirmed postbaseline positive ADA result will be considered ADA positive if their baseline result is negative.
- Subjects for whom none of the postbaseline samples were positive for ADAs will be considered negative regardless of their baseline result.
- For subjects who are confirmed positive at baseline and have at least one postbaseline sample with a ≥4-fold increase in titer will be considered ADA positive. Subjects who are positive at baseline with subsequent postbaseline samples titers that are within 2-fold will be considered ADA negative.
- In addition, for subjects who are considered ADA positive with final immunogenicity data, the following may be evaluated:
    - Persistence of the ADA response: positive result detected at the last postbaseline sampling time point, or two or more time points during treatment where the first and last positive samples are separated by a period ≥112 days, irrespective of any negative samples in between.
    - Transient ADA response: positive result detected at only one postbaseline sampling time point (excluding last time point) or at two or more time points during treatment where the first and last positive samples are separated by a period <112 days, irrespective of any negative samples in between.

The impact on efficacy may be evaluated by summarizing the primary endpoint and one secondary endpoint (proportion of responders with ≥50% reduction) by antibody status (positive or negative, persistent/transient) in the ITT population with at least 1 postdose immunogenicity sample. In addition, to determine the relationship (if any) of ADAs on safety, incidence of AEs, SAEs, and events of particular interest will be presented by antibody status (positive or negative, persistent/transient) as well as by timing of the events.

6 Changes from Protocol Specified Analyses

The protocol-planned interim futility analysis will not be performed, as the timing of this potential analysis would occur only approximately 6 months prior to the end of the study and after all subjects are expected to be enrolled. The decision was made by Biogen in collaboration with the study advisory committee and drug-safety monitoring committee.

7 Summary of Changes from the Previous Version of the SAP

Section No.	Details and Rationale for Change
Section 3	Definitions such as study periods and baseline used throughout the SAP were moved to this section. Details of the PP population exclusion criteria were added.
Section 4.1	The interim analysis for futility specified in the protocol will not be performed. No stopping decision will be made based on the efficacy data before 24 weeks of treatment.
Section 5.2	Added imputation rules for partial dates of AE and concomitant medications/therapies.
Section 5.8	Added analysis for rescue medication
Section 5.10	Added subgroup analysis.
Section 5.10.2	The sensitivity analysis using a time-varying indicator for AED modification in the MMRM model was removed due to very small number of subjects with AED modifications.
Section 5.10.3	Replaced logistic regression for the binary endpoint of seizure free or not by the descriptive summary due to the rare event nature of this endpoint.
[redacted]	[redacted]
	[redacted]

8 References

Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521. Epub 2017/03/08.

APPENDIX A

Table 4: Schedule of Activities for Study 101EP201

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	Screening	Placebo-Controlled Phase							Open-Label Phase						Post-Treatment Follow-Up	
Study Days	Day -42 +1 day[5]	Day 1 +5 days[5]	Day 28 ±5 days	Day 56 ±5 days	Day 84 ±5 days	Day 112 ±5 days	Day 140 ±5 days	Day 168 ±5 days		Day 196 ±5 days	Day 224 ±5 days	Day 252 ±5 days	Day 280 ±5 days	Day 308 ±5 days	Day 336 ±5 days	Day 420 ±5 days	Day 476 ±5 days
Informed Consent	X																
Review Inclusion and Exclusion Criteria	X	X															
Demographics and Medical History Including Seizure and Antiepileptic Medication History[6]	X																
Physical and Neurological Examination[7]	X							X							X	X	
Vital Signs[8]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
MRI brain scan[9]	X																
Pregnancy Test[10]	X	X															
Randomization		X															

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	**Screening**	**Placebo-Controlled Phase**							**Open-Label Phase**						**Post-Treatment Follow-Up**	
Study Days	**Day -42 +1 day[5]**	**Day 1 +5 days[5]**	**Day 28 ±5 days**	**Day 56 ±5 days**	**Day 84 ±5 days**	**Day 112 ±5 days**	**Day 140 ±5 days**	**Day 168 ±5 days**	**Day 196 ±5 days**	**Day 224 ±5 days**	**Day 252 ±5 days**	**Day 280 ±5 days**	**Day 308 ±5 days**	**Day 336 ±5 days**	**Day 420 ±5 days**	**Day 476 ±5 days**
Study Treatment Administration[11]		X	X	X	X	X	X		X	X	X	X	X	X		
Distribute Seizure Diary[12]	X															
Review Seizure Diary[13]		X	X	X	X	X	X	X		X	X	X	X	X	X	
Hematology and Blood Chemistry[13, 14]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X				X			X		
Blood Sample for Hepatitis B and C Serologies	X															
Blood Sample for Anti-Natalizumab Antibodies[13]		X			X			X						X		
Blood Sample for Anti-JCV Antibody Index	X							X						X		
Blood Sample for Flow Cytometry Including α4 Saturation[13]		X	X		X			X		X		X		X		

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	Screening	Placebo-Controlled Phase							Open-Label Phase						Post-Treatment Follow-Up	
Study Days	Day -42 +1 day[5]	Day 1 +5 days[5]	Day 28 ±5 days	Day 56 ±5 days	Day 84 ±5 days	Day 112 ±5 days	Day 140 ±5 days	Day 168 ±5 days	Day 196 ±5 days	Day 224 ±5 days	Day 252 ±5 days	Day 280 ±5 days	Day 308 ±5 days	Day 336 ±5 days	Day 420 ±5 days	Day 476 ±5 days
[redacted]																
Blood Samples for PK[13]		X[16]	X	X	X	X	X[16]	X		X	X	X	X	X[16]	X		
[redacted]																
eC-SSRS/C-SSRS[18]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
AEs and SAEs[19]		X														
Concomitant Therapies/Procedures		X														
Assessment of new neurological symptoms[20]																X

Abbreviations: AE = adverse event; CNS = central nervous system; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; ET = Early Termination; IERC = independent epilepsy review committee; JCV = John Cunningham virus;

[redacted]; MRI = magnetic resonance imaging; PK = pharmacokinetics; PML = progressive multifocal leukoencephalopathy; [redacted] RNA = ribonucleic acid; SAE = serious adverse event; [redacted]; WBC = white blood cell.

[1] All study assessments at Week 24 must be performed prior to study treatment administration as part of the placebo-controlled phase. Study treatment administration at Week 24 will be the start of the open-label phase.

[2] Subjects who terminate the study early should have an Early Termination Visit 4 weeks after their last dose of study treatment.

[3] Subjects who terminate the study early should have a Follow-up Visit 16 weeks after their last dose of study treatment.

[4] Subjects who terminate the study early should have a Follow-Up Safety Phone Call 24 weeks after their last dose of study treatment.

[5] Day -42 is the day of signing the informed consent. Day 1 is the day of eligibility determination and randomization and must be at least 42 days after initiating seizure diary collection. Additional days of diary entry may be completed if required for visit scheduling; however, eligibility criteria apply to diary data completed in the 42 days immediately prior to Day 1. The study day windows allow for completion of other study activities, if necessary.

[6] Medical history should include an assessment of prior substance abuse.

[7] Includes height and weight measurements. Height should only be measured at the Screening Visit (Week -6). Height and weight measurements that are performed as standard of care do not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in subject's CRF.

[8] Vital signs collected at each of the specified timepoints include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Vital signs collected as part of the subject's standard of care on the same day as a study visit do not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in the subject's CRF. Vital signs at Week 0 through Week 44 must be performed prior to study treatment administration.

[9] MRI scan of the brain is required within 48 months prior to screening to assist in the electroclinical assessment of a structural etiology for focal epilepsy. MRI done as part of the subject's standard of care and that falls within 48 months prior to screening does not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in the subject's CRF. If MRI is not performed within this time frame and the subject meets other inclusion and exclusion criteria, MRI scan of the brain should be performed during the screening period and results should be reviewed by the IERC prior to Visit 1 in order to adjudicate the presence or absence of a structural etiology for focal epilepsy. 3T MRI scanning is preferred wherever possible. Subjects without an MRI of the brain within 48 months prior to screening and with an absolute contraindication to MRI will be considered on a case-by-case basis.

[10] Required only for women of childbearing potential. A serum pregnancy test should be performed at the Screening Visit (Week -6), and a urine pregnancy test should be performed at Week 0 prior to randomization. The urine pregnancy testing will be performed locally prior to randomization. Follow-up pregnancy testing throughout the study will be done at the discretion of the Investigator or as required by local law.

[11] Subjects must be observed for 1 hour after completion of infusion.

[12] Subjects (or their caregivers) must record their seizure type and frequency daily from Screening Visit (Week -6) through End of Study Visit (Week 60), or for subjects who terminate the study early through the Follow-up Visit 16 weeks after their last dose of study treatment. Subjects must bring their seizure diary with them to each study visit.

[13] Blood samples should be collected prior to study treatment administration at Week 0 through Week 44. The time of collection, along with the start and stop times for the study treatment infusion, must be recorded in the subject's source data and on the subject's CRF.

[14] WBC (other than absolute neutrophil count) data will be reviewed by an Independent Safety Monitor.

[redacted]

[16] Both predose and postdose blood samples are to be collected for PK at Week 0, Week 20, and Week 44. The postdose sample must be collected within 1 hour after completion of study treatment infusion. The time of collection, along with the start and stop times for the study treatment infusion, must be recorded in the subject's source data and on the subject's CRF.

[redacted]

[18] The "baseline/screening" eC-SSRS/C-SSRS must be completed at the Screening Visit (Week -6); at all other visits, the "since last visit" eC-SSRS/C-SSRS must be used.

[19] SAE reporting for PML or new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days) must continue from the End of Study Visit (Week 60) through the Follow-Up Safety Phone Call. Otherwise, after the End of Study Visit or Follow-up Visit for ET subjects, SAEs should be reported only if the Investigator considers the SAE to be related to study treatment.

[20] Subjects should be contacted by phone 24 weeks after the last dose of study treatment to discuss if there has been any new development of any new neurological symptoms. PML or new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days) must be immediately reported as an SAE.