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Polpharma Biologics S.A.

STATISTICAL ANALYSIS PLAN

PROTOCOL PB006-03-01

Antelope: Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri® in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

Protocol code:	PB006-03-01
SAP Version:	Final 1.1
SAP Date:	28 April 2021
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DOCUMENT HISTORY

VERSION HISTORY

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Final 1.0	01APR2021
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REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
1.1	7.4	Wording in the PP population definition changed to allow patients with just one out of three non-Week 24 post-BL MRI assessments to be selected in the population	Missing intermediate MRI assessment have no impact on the primary endpoint of the study, as the new lesions that could have been identified at these assessment will then be discovered at the Week 24 MRI.

APPROVAL SIGNATURES

STUDY TITLE:
Antelope: Efficacy and Safety of the Biosimilar Natalizumab PB006 in Comparison to Tysabri® in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

PROTOCOL NUMBER: PB006-03-01

PROTOCOL VERSION: V4.0, 15 JULY 2020

SAP Version 1.1, 28-APR-2021

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1. LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ARN	acute retinal necrosis
AST	aspartate aminotransferase
BMI	Body Mass Index
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EU	European Union
FAS	Full Analysis Set (Population)
GCN	granule cell neuronopathy
GdE	gadolinium-enhancing
INN	International Nonproprietary Name
IV	intravenous
JCV	John Cunningham virus
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
PML	progressive multifocal leukoencephalopathy
PP	Per Protocol (Population)
PT	Preferred Term
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting plans for the protocol PB006-03-01 Version 4.0 dated 15 July 2020 (and Russia specific Version 1.1, dated 10 July 2019) and for the electronic case report form (eCRF) Version 39 dated 06 August 2019.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate and compare the cumulative number of new active lesions over 24 weeks.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to:

- Evaluate and compare the cumulative number of new active lesions over 48 weeks
- Evaluate and compare the cumulative number of new gadolinium-enhancing (GdE) T1-weighted lesions over 24 and 48 weeks
- Evaluate and compare the number of patients without new GdE T1-weighted lesions over 24 and 48 weeks
- Evaluate and compare the cumulative number of new/enlarging T2-weighted lesions over 24 and 48 weeks
- Evaluate and compare the number of patients without new/enlarging T2-weighted lesions over 24 and 48 weeks
- Evaluate and compare the number of persistent lesions after 24 and 48 weeks treatment with PB006 or Tysabri
- Evaluate and compare the annualized relapse rates and changes in EDSS after 24 and 48 weeks
- Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs) after 24 and 48 weeks
- Evaluate and compare the immunogenic profile (incidence rate of anti-drug [natalizumab] antibodies [ADA] and persistent antibodies) after 24 and 48 weeks and after switching
- Evaluate and compare the immunogenic profile (incidence rate of neutralizing antibodies) after 24 and 48 weeks and after switching
- Evaluate and compare natalizumab trough concentration (Ctrough) over time
- Evaluate and compare the safety profile (physical examination, vital sign measurements, and clinical laboratory tests) over 24 and 48 weeks

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

This is a Phase 3 multicenter, double-blind, active-controlled, randomized, parallel-group study to assess the equivalence in efficacy and similarity in safety of biosimilar PB006 compared to Tysabri

in patients with relapsing-remitting multiple sclerosis (RRMS).

After obtaining informed consent, screening investigations will begin. Screening will consist of the following 2 parts:

1. Samples for anti-John Cunningham virus (JCV) antibodies and samples for biobanking (blood and urine) will be taken. When JCV test results come back:

a) JCV index >1.5: The patient will be considered a screen failure.

b) JCV index ≤1.5: Proceed with part 2.

2. For patients with JCV index ≤1.5, the Investigator or designee will set up a second visit for all other screening procedures that will be completed for each patient prior to randomization for study treatment (see Appendix I: Time and Events Schedule).

Patient eligibility will be determined by the inclusion and exclusion criteria on screening evaluations listed in Protocol Sections 5.1 and 5.2.

All eligible patients will be randomly assigned to one of two treatment groups in a 1:1 ratio, to receive intravenous (IV) infusions every 4 weeks of either PB006 or Tysabri at a dose of 300 mg starting at Visit 1 (week 0) through Visit 12 (week 44), for a total of 12 infusions. The End-of-Study Visit (Visit 13, week 48) will be performed 4 weeks after the last infusion. The evaluations for patients who withdraw prematurely will be the same as for the End-of-Study Visit.

Physicians should monitor patients who received at least 1 dose of study drug (including prematurely withdrawn patients) for approximately 6 months after discontinuing natalizumab, and patients should be instructed to contact the study site any time in case they experience new signals or symptoms suggestive for progressive multifocal leukoencephalopathy (PML). A PML Follow-Up Visit is performed 24 weeks (± 2 weeks) after the last study drug infusion or earlier in case of new symptoms suggestive for PML. If PML diagnosis is confirmed, no additional PML Follow-Up Visit will be scheduled.

Magnetic resonance imaging (MRI) will be performed at Screening; prior to treatment at visit 1 (week 0); at weeks 8, 16, 20, 24, 48; at any unscheduled visit in case of a suspected PML; and at a PML Follow-Up Visit if PML is suspected. Serum samples for anti-drug (natalizumab) antibody (ADA) formation and blood samples for natalizumab C_{trough} analyses will be collected prior to treatment at Visit 1 (week 0) and at weeks 8, 16, 24, 32, and 48. Blood samples for anti-JCV antibody testing and samples for biobanking (blood and urine) will be collected at Screening, week 24, and week 48. (In Russia, JCV samples will be taken at week 8 as well.) Blood and urine samples for safety laboratory assessments will be collected at Screening, prior to treatment at Visit 1 (week 0), and every 8 weeks through the End-of-Study Visit, at unscheduled visits in case of a relapse, and at unscheduled visits if PML is suspected.

The primary endpoint will be the radiologic response as measured by the cumulative number of new active lesions over a 24-week treatment period, starting with the first infusion at week 0 to week 24. Secondary endpoints evaluated for the primary analysis after 24 weeks and for the final

analysis after 48 weeks include radiologic response criteria, clinical response as defined by the frequency of relapses, changes in EDSS, safety (AEs, physical examination, vital sign measurements, and clinical laboratory tests), natalizumab blood concentration, and immunogenicity (ADA).

In order to evaluate and compare the immunogenic profile between patients treated with Tysabri only and those switching from Tysabri to PB006 at Week 24 and in accordance with FDA requirements, the 130 patients in the Tysabri group will be re-randomized at Week 24 (through a re-randomization step). Out of these 130 patients, approximately 34 (to account for potential dropouts to reach an approximate minimum of 30) random patients will be randomized (switched) to PB006. After re-randomization, the patient groups will be: Tysabri group (n=up to 96); Tysabri switch to PB006 group (n=34); and PB006 group (n=up to 130).

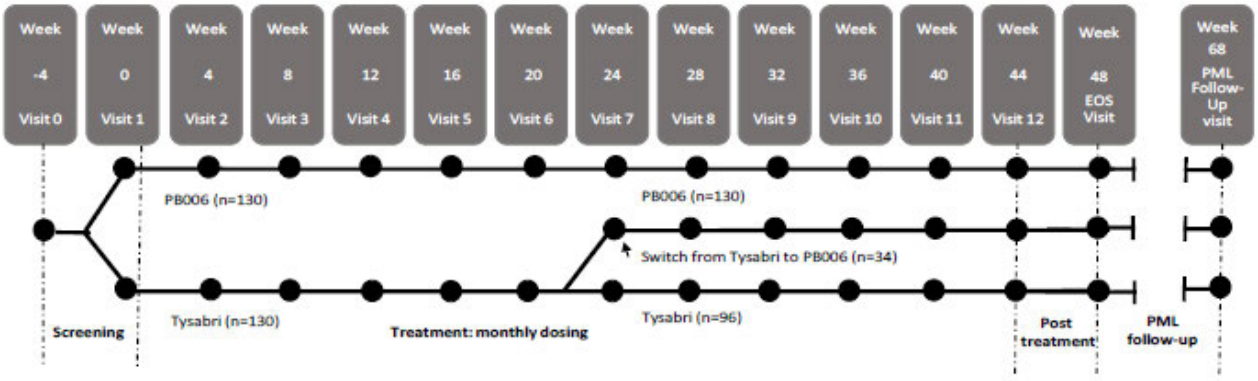
No stratification factors will be considered for the re-randomization for switch.

The following AEs will be considered as AEs of special interest (AESI): PML, JCV granule cell neuronopathy (GCN), opportunistic infections, liver injury, hypersensitivity, encephalitis, meningitis, and acute retinal necrosis (ARN) (Protocol Section 8.10.7).

Treatment assignments will be blinded to the Investigator/neurologist, study personnel, and the patients.

The overall study flowchart is presented in Figure 1.

Figure 1: Overall Study Flow Chart



4.2 STUDY TREATMENT

Test drug - Biosimilar - PB006

The test drug, PB006, a natalizumab biosimilar, is a concentrate for solution for IV infusion. PB006

is provided in an alternative formulation to Tysabri, based on well-established excipients and containing the same concentration of natalizumab as the reference (comparator) product. The detailed composition is: 20 mg/mL natalizumab, 10 mM L-histidine/L-histidine hydrochloride, 150 mM sodium chloride, 0.02% (w/v) polysorbate 80, pH 5.7.

Comparator drug - Tysabri

Tysabri (International Nonproprietary Name [INN]: natalizumab), European Union (EU)-sourced, is a concentrate for solution for IV infusion. The detailed composition is: 20 mg/mL natalizumab, 10 mM sodium phosphate, 140 mM sodium chloride, 0.02% (w/v) polysorbate 80, pH 6.1.

4.3 DATA AND SAFETY MONITORING BOARD (DSMB)

Details on the responsibilities, activities, and deliverables of the external DSMB are detailed in a separate charter.

5. SAMPLE SIZE AND POWER CALCULATION

A total of 230 evaluable patients (115 in each group), i.e., patients who complete the 24-week treatment period without major protocol deviations and for whom sufficient post-baseline MRI data are available, are required to achieve 90% power for the equivalence assessment with respect to the cumulative number of new active lesions over 24 weeks of treatment assuming a common standard deviation of 4.0 lesions and no difference between both groups. To account for potential dropouts and non-evaluable patients of up to 10%, approximately of 260 patients will be randomized.

The sample size calculation is based on data published by Miller et al., 2003, which showed a mean number of cumulative new active lesions of 1.0 (±2.6) in the pooled natalizumab groups (3 mg/kg and 6 mg/kg) versus 9.7 (±27.4) in the placebo group in patients with either relapsing-remitting or secondary progressive multiple sclerosis (MS). An equivalence margin for the mean difference of 2.1 lesions was chosen to ensure that 50% of the treatment effect based on the lower bound of the 95% confidence interval of the pooled effect size estimated in Miller et al., 2003 will be preserved.

6. ANALYSIS ENDPOINTS

The primary endpoint is the cumulative number of new active lesions over 24 weeks.

The secondary endpoints are the:

- Cumulative number of new active lesions over 48 weeks
- Cumulative number of new GdE T1-weighted lesions over 24 and 48 weeks
- Number of patients without new GdE T1-weighted lesions over 24 and 48 weeks
- Cumulative number of new/enlarging T2-weighted lesions over 24 and 48 weeks
- Number of patients without new/enlarging T2-weighted lesions over 24 and 48 weeks

- Number of persistent lesions after 24 and 48 weeks
- Annualized relapse rate after 24 and 48 weeks
- Change from baseline in EDSS after 24 and 48 weeks
- Number of local and systemic AEs and SAEs after 24 and 48 weeks
- Incidence rate of ADA and persistent antibodies after 24 and 48 weeks
- Incidence rate of neutralizing antibodies after 24 and 48 weeks and after switching
- Natalizumab trough concentration (C_{trough}) over time
- Safety profile (physical examination, and change from baseline in vital sign measurements and clinical laboratory tests) over 24 and 48 weeks

7. ANALYSIS POPULATIONS

7.1 SAFETY POPULATION

Patients participating in this study who receive at least one (complete or partial) infusion of the study drug will be included in the Safety Population (SAF). Patients in this group will be analyzed as treated.

7.2 SAFETY-SWITCH POPULATION

Patients who are included in the Safety Population and receive at least one infusion of the study drug after the time point of re-randomization, independent of whether they switch or not, will be included in the Safety-Switch (SSW) Population. Patients in this group will be analyzed as treated after re-randomization, also considering treatment before re-randomization.

7.3 FULL ANALYSIS SET

The Full Analysis Set (FAS) Population will include all patients who were randomized and have received at least one (complete or partial) infusion of the study drug. Patients will be analyzed according to the treatment group to which they were randomized.

7.4 PER-PROTOCOL POPULATION

Only patients participating in this study who complete the 24-week treatment period without major protocol deviations that may influence the analysis of the primary endpoint and for whom sufficient post-baseline MRI data are available (including baseline, Week 24 and at least one out of the three other scheduled MRI visits) will be included in the Per-Protocol (PP) Population. The final decision on the PP Population will be made in the blinded data review meeting before database lock for the week 24 primary analysis.

In addition, a pre-COVID PP population defined as all PP patients, including those who were excluded from PP only due to major deviations related to COVID-19 will be created.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed and data appendices will be created using the SAS system

version 9.4 or higher.

Data collected in this study will be presented in subject data listings and summary tables.

Descriptive statistics (number of patients with non-missing values, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. All raw data will be presented to the original number of decimal places. Means and medians will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data.

Frequency distributions (counts and percentages) will be presented for categorical variables. If not specified otherwise, the number of observations with non-missing values will be the denominator for percentage calculation. Further details on the handling of missing observations are given in Section 8.3.

Safety laboratory results reported as below or above limits of quantification, e.g. “<x.x”, “<=x.x”, “>x.x” or “>=x.x”, will be summarized in the tables using the reported limit of quantification. The listings will show the result as reported.

Where required, the duration in year and months will be calculated as:

Duration [year] = (<end date> - <start date>)/365.25

Duration [month] = (<end date> - <start date>)/30.5

All data collected will be presented in the data listings.

8.2 Definition of Baseline, Study Visits, Visit Windows and Handling of Switch patients in the Analysis

8.2.1 Baseline and Study Visits

Generally, the last assessment before the first administration of study treatment will be considered as the baseline observation; usually this will be the Visit 1/Week 0 observation. If no pre-dose value for Week 0 is available, the latest available previous observation will be used as the baseline observation.

Other than baseline observations, data will be summarized per scheduled visit. No re-mapping of analysis visits will be performed based on the actual timing of assessments. Unscheduled post-baseline observations will be included in “worst case” summaries.

The End-of-Study Visit analysis will combine data from Week 48 Visits and Early Discontinuation Visits, so these analyses will summarize all subjects’ last on-study observations.

8.2.2 Visit Windows

For MRI endpoints that summarize observations across several time points, early discontinuation MRIs will be mapped to the nearest protocol-specified visit with a planned MRI if no MRI data are

available for that visit and if the unscheduled MRI was done within ± 14 days of the planned study day of the visit in relation to first study treatment. If the distance is equal (e.g., days 127, 155), assign to the earlier visit if no such MRI exists, else assign to the later visit.

Early discontinuation MRIs on study days x (Day 1 = treatment start)	Visit assigned
43 to 71	Visit 3 / Week 8
99 to 127	Visit 5 / Week 16
127 to 155	Visit 6 / Week 20
155 to 183	Visit 7 / Week 24
323 to 351	Visit 13 / Week 48

8.2.3 HANDLING OF SWITCH PATIENTS

Approximately 34 patients will be re-randomized to switch from the Tysabri arm to PB006 at week 24. So this switch is not expected to affect the course, result and analysis up to the week 24 analysis including the primary analysis. To reflect both, the initial two-arm parallel group design, and the fact that some patients switch treatment after 24 weeks, study data will be analyzed in different ways:

1. Irrespective of the switch, only summarizing by the treatment arm of the first 24 weeks. If sensible, such summaries (usually “by visit” or “by/up to time point”) will be continued after week 24 for patients who do not switch, only excluding the “Tysabri to PB006” switch patients (or events occurring after switch, respectively) after week 24. This comprises baseline/demography and efficacy analyses, and allows assessment of all subjects who do not switch treatment over the full study period.
2. To assess comparability between groups of continuing and switching patients, additionally all baseline/demography tables will be repeated, splitting the Tysabri arm to switchers and non-switchers. In the same manner efficacy tables will be repeated, summarizing also separately for the first 24 weeks patients continuing their initially randomized treatment in each arm and patients who switch subsequently at week 24. This approach will also be applied to safety variables that are collected by visit (e.g. safety labs). The safety-switch population will be used for this analysis.
3. Adverse events will be summarized by study periods: up to week 24 (for PB006/Tysabri/Total) and after week 24 (for continued PB006, PB006 after switch from Tysabri, all PB006 after week 24 – cumulating the previous two – , continued Tysabri, Total). Additionally TEAEs (including event rates per patient year) will be summarized by preceding treatment: In these tables, patients who switch will contribute periods under different treatments partially to both groups. Furthermore, adverse events with missing dates may be summarized under multiple periods and preceding treatments. This means that AEs with missing dates will be classified into pre- and post-switch periods and also pre- and post-switch treatments.
4. The week 24 pre-dose assessment will be used as the baseline for further analyses in order to assess the effect of switching.

8.3 HANDLING OF MISSING DATA

Unless specified otherwise, no imputation of missing data will be performed. For analysis of clinical endpoints using FAS population, only available results will be used.

In order to derive values for variables such as time since diagnosis, incomplete MS disease and treatment history dates will be imputed with the middle of the possible period, i.e., the 15th of the month if only year and month are known and July 3rd if only the year is known. No imputation will be done if the date is completely unknown.

AE start dates will not be imputed. In case of an incomplete or missing start date, events will be classified as treatment emergent unless sufficient information is available to conclude that the event started or worsened before the first study treatment.

In order to distinguish prior and concomitant medications, the end date will be compared to the start date of the study medication. Incomplete end dates will not be imputed. Medications will be flagged as prior and concomitant if there is uncertainty (e.g., missing end date, while month and year are equal to study treatment start).

8.4 PATIENT DISPOSITION

Patient disposition (enrollment, screening failures and their reasons, study drug administered) will be tabulated for all screened patients. Study completion, premature discontinuation of study drug, and withdrawals from the study will be summarized by treatment group for the FAS and SSW populations.

Patients who discontinued due to COVID-19 will have their reason for discontinuation classified and summarized as such.

8.5 PROTOCOL DEVIATIONS

Major protocol deviations will be tabulated by treatment group for the FAS and SSW populations.

Major protocol deviations due to COVID-19 will be identified and presented as such.

8.6 PATIENT CHARACTERISTICS

Patient characteristics will be summarized for all four analysis populations.

8.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Demographics (age, sex, race, ethnicity, and child-bearing potential) and baseline characteristics (weight, height, and body mass index [BMI]) will be summarized by treatment group.

BMI will be derived as follows:

BMI [kg/m^2] = weight [kg] / (height [m])^2

Frequencies of the following stratification factor levels at screening will be tabulated as well:

- Absence/presence of GdE lesions (0, >0)
- Presence of T2 lesions (≤15, >15)
- JCV status for safety (negative, positive)

The overall impression of the screening electrocardiogram (normal, abnormal - not clinically significant, abnormal – clinically significant) will be tabulated. Free text specifications of clinically significant abnormal findings will be listed.

8.6.2 Medical History and Current Medical Conditions

Medical history (conditions that ended before the date of screening) and current medical conditions (those that started before and were ongoing at screening) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.0 and tabulated by System Organ Class (SOC) and Preferred Term (PT) and by treatment group.

MS disease history data will be summarized using mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. The following MS variables will be assessed:

- Time since diagnosis (years)
- Time since most recent relapse (months)
- Number of relapses in the year prior to screening – frequencies and sample statistics
- Baseline EDSS

8.6.3 Prior and Concomitant Medication

Use of prior medications (stopped before treatment started) and concomitant medications (ongoing at treatment start or started after first study treatment) will be coded and tabulated by treatment group on the Anatomical Therapeutic Chemical (ATC) 2, ATC 4, and preferred name levels.

The following MS-related treatment history variables will be tabulated:

- Time since last dose of corticosteroid treatment, if any
- Frequency of patients who never received corticosteroid treatment for relapse
- Frequency of patients who received any MS treatment in the past

Other details of previous MS treatments will be listed.

8.6.4 Exposure to Study Treatment

The following variables will be summarized per treatment arm:

- Number of started infusions per patient (as frequencies and continuous measure)
- Percentage of completed infusions (based on all infusions)
- Percentage of permanently stopped infusions (based on all infusions)
- Percentage of interrupted and restarted infusions (based on all infusions)
- Percentage of patients without infusion complications
- Percentage of patients with one or more interrupted or permanently stopped infusions
- Total dose (mg) per patient

8.7 EFFICACY ENDPOINTS AND ANALYSES

The following results of MRI assessments will be provided by the central lab, [redacted]

MOCAT (Category for Assessment)	MOTESTCD (Test Short Name)	MOTEST (Test Name)	Time point(s)
LESION COUNT	T2CNT	T2 Lesion Count	At screening
LESION COUNT	NT2CNT	New/Enlarging T2 Lesion Count	At baseline, w8–w48, early discontinuation.
LESION COUNT	NUNT2CNT	New/Enlarging Unenhancing T2 Lesion Count	At baseline, w8–w48, early discontinuation
LESION COUNT	GADCNT	Gad Enhancing Lesion Count	At screening
LESION COUNT	NGADCNT	New Gad Lesion Count	At baseline, w8 –w48, early discontinuation
LESION COUNT	PRGADCNT	Persistent Gad Lesion Count	At baseline, w8 –w48, early discontinuation
PML ASSESSMENT	PMLRSLT	PML Results	At w16, w20, w24, 28, early discontinuation and unscheduled

Gad: Gadolinium; PML, progressive multifocal leukoencephalopathy; w, week.

All new lesion counts are as collected by [redacted] Lesions identified and counted at each visit are assumed to be new lesions which developed since the previous MRI screening.

MRI Endpoint	Derivation
Cumulative number of new active lesions over 24 weeks	Sum (NUNT2CNT[week8, week16, week20, week24]) + sum(NGADCNT [week8, week16, week20, week24])
Cumulative number of new active lesions over 48 weeks	Sum (NUNT2CNT[week8, week16, week20, week24, week48]) + sum(NGADCNT [week8, week16, week20, week24, week48])
Cumulative number of new GdE T1-weighted lesions over 24 weeks	Sum (NGADCNT [week8, week16, week20, week24])
Cumulative number of new GdE T1-weighted	Sum (NGADCNT [week8, week16, week20, week24, week48])

lesions over 48 weeks	
Cumulative number of new/enlarging T2-weighted lesions over 24 weeks	Sum (NT2CNT [week8, week16, week20, week24])
Cumulative number of new/enlarging T2-weighted lesions over 48 weeks	Sum (NT2CNT [week8, week16, week20, week24, week48])
Number of persistent lesions after 24 weeks	Sum (PRGADCNT [week8, week16, week20, week24])
Number of persistent lesions after 48 weeks	Sum (PRGADCNT [week8, week16, week20, week24, week48])

GdE, gadolinium-enhancing.

Corresponding results up to week 8, up to week 16, and up to week 20 will be derived using a similar approach, restricting the MRIs included in the summary.

8.7.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the cumulative number of new active lesions over 24 weeks.

Equivalence between PB006 and Tysabri will be assessed based on the following set of hypotheses:

H_0: $|\mu_{PB006} - \mu_{Tysabri}| > 2.1$ vs. H_1: $|\mu_{PB006} - \mu_{Tysabri}| \leq 2.1$,

where μ_x denotes the cumulative number of new active lesions over 24 weeks in the respective treatment group. Data from the PP Population will be analyzed using a negative binomial model with a logarithmic link function and fixed effects for the treatment group and stratification factors. Equivalence will be tested based on the corresponding 90% and 95% confidence intervals to address different regulatory requirements.

The following SAS code will be used:

```
proc genmod data = mri;
      class treatment gdelnum t2lnum jcvstat;
      model aval = treatment gdelnum t2lnum jcvstat /dist = negbin link = log;
      lsmeans treatment / diff cl exp alpha=0.05;
      lsmeans treatment / diff cl exp alpha=0.1;

run;
```

The 90% and 95% confidence intervals of the least-square means difference on the original scale will be compared to the equivalence margins of -2.1 and 2.1 lesions, and the null hypothesis will be rejected if both confidence intervals, rounded to three digits, are within the specified margins. Confidence limits for Exponentiated Difference between PB006 and Tysabri will be estimated using SAS NLMeans macro.

If values of stratification factors are corrected after randomization, the values at randomization will be used for analysis. Additionally, a sensitivity analysis will be carried out if the values of stratification factors of a patient have been corrected post randomization to assess the impact.

As a sensitivity analysis, the primary analysis will be repeated for the FAS Population. For this purpose, data from early discontinuation MRIs (i.e., End-of-Study Visits that occurred before or after the protocol-scheduled time point) will be incorporated into the derived cumulative endpoint i.e. all MRI results at all previous visits until the specific timepoint will be summed and used for analysis. The cumulative sum of measurements from prior timepoints will be used for analysis at other timepoints with missing MRI results. For intermittent missing MRI results (i.e. missed MRI visits but with MRI data collected at subsequent visits), no imputation will be done. This is due to medical claim that lesions from missed MRI screening visits are picked up at later MRI screenings.

8.7.2 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

All secondary efficacy endpoints will be summarized for the FAS, PP and SSW Populations.

For the following secondary endpoints, sample statistics will be displayed per planned time point:

- Cumulative number of new active lesions over 48 weeks
- Cumulative number of new GdE T1-weighted lesions over 24 and 48 weeks
- Cumulative number of new/enlarging T2-weighted lesions over 24 and 48 weeks
- Number of persistent lesions after 24 and 48 weeks treatment with PB006 or Tysabri

In addition to the summary by time points, for the above endpoints, an overall summary correcting for the total number of MRI scans per subject will also be displayed.

For the following endpoints, the frequencies and percentages of patients in each of 3 categories (no lesions of the specified type, any lesion of this type, no sufficient MRI data) will be presented:

- Number of patients without new GdE T1-weighted lesions over 24 and 48 weeks
- Number of patients without new/enlarging T2-weighted lesions over 24 and 48 weeks

The annualized relapse rate will be summarized in the following ways:

- A: Number of medically confirmed relapses per patient (frequency of categorized numbers) and overall
- B: Duration of follow-up time per patient (sample statistics) and overall. Follow-up time defined as: (last day of follow-up – day of randomization + 1) / 365.25.
- The ratio of relapses per patient-year: A/B.

For patients who completed the respective study interval, the Week 24/Week 48 Visit date will be used as the last day of follow-up. For patients who withdraw prior week 24 and week 48, respectively, from the study, the known medically confirmed relapses and the follow-up time up to the early discontinuation visit (or, if not done, the last performed scheduled visit) will be used.

Changes in EDSS after 24 and 48 weeks will be summarized as continuous measures using sample statistics. Additionally, the frequencies and cumulative frequencies of EDSS categories and shift from baseline per treatment group will be tabulated per time point.

EDSS assessments taken at unscheduled relapse assessment visits and unscheduled suspected PML visits will not be included in the EDSS summaries by time point; they will be used for relapse classification and listed.

8.7.3 SENSITIVITY ANALYSIS

To assess the effect of missing values in this study, a sensitivity analysis based on the FAS population will be carried out using imputation method. The PROC MI procedure in SAS will be used to implement this imputation.

One hundred datasets will be created using linear regression model with predictive variables including treatment, all stratification variables, sex, age, height and weight at baseline, and number of relapses the year prior to screening. In case of convergence issues, the included variables may be revised accordingly. The MINIMUM and ROUND options in the monotone statement will be used to restrict imputation results to non-negative integer values.

All available data, including early discontinuation data, will be used for analysis. Only post-baseline timepoints with completely missing MRI data and no subsequent MRI screening (monotone missing) will be imputed. No imputation will be done for baseline measurements. Imputation will be done only for patients with baseline and at least one post-baseline MRI result. Sensitivity analyses will be performed for the primary endpoint using the negative binomial model described in Section 8.7.1.

8.7.4 COVID-19 ANALYSIS CONSIDERATIONS

In order to assess the impact of COVID-19 on safety and efficacy of this study the following will be done:

- Study discontinuations and protocol deviations due to COVID-19 will be summarized
- Demography data for confirmed COVID-19 patients will be summarized
- Protocol deviations due to COVID-19 will be summarized by country
- A sensitivity analysis will be performed on the pre-COVID PP population. Multiple imputation as described in section 8.7.3 will be performed for this population. Sensitivity analysis will be done for the primary endpoint using imputed data for this population.

8.8 SAFETY ENDPOINTS AND ANALYSES

Safety analyses will be performed using the SAF and SSW Populations.

8.8.1 ADVERSE EVENTS

All AEs will be coded using MedDRA version 23.0.

Events will be regarded as treatment-emergent AEs (TEAE) if they start or worsen in severity after the start of the first infusion of the study drug, regardless of relationship to the study drug. If the start date is incomplete or missing, events will be flagged as treatment emergent unless sufficient data is available to conclude that the start/worsening occurred before the treatment was started.

AEs of special interest (AESI) (i.e., PML, JCV GCN, opportunistic infections, liver injury, hypersensitivity, encephalitis, meningitis, and ARN; see Protocol Section 8.10.7) will be flagged as such in the eCRF and analyzed according to these flags.

AEs reported to be “not related” or “unlikely related” to the study drug will be considered as unrelated for the purpose of statistical analysis. AEs reported as “possibly related”, “probably related”, “related”, or without information on relationship will be analyzed as related.

In addition, all COVID-19 related adverse events will be identified and summarized.

A summary table will present the number and percentage of patients per treatment arm and overall for the following:

- Any TEAE
- Any treatment-emergent AESI
- Any related TEAE
- Any TEAE of grade 3 or higher
- Any treatment-emergent Non-SAE
- Any treatment-emergent related Non-SAE
- Any treatment-emergent SAE
- Any treatment-emergent related SAE
- Any TEAE leading to temporary study drug interruption
- Any TEAE leading to permanent study drug discontinuation
- Any TEAE leading to study withdrawal
- Any fatal TEAE

Tables showing data by SOC and PT for each treatment arm and overall will include the number and percentage of patients, as well as the number of events and the exposure-adjusted event rate (in events per 100 patient-years).

The exposure-adjusted event rate will be defined as follows:

Rate = 100 * [number of events in group] / [sum of exposure time for all patients in group]

One patient’s exposure time will be defined as follows:

Exposure time (years) = [(date of last treatment + 28) – (date of first treatment) + 1] / 365.25

Specifically, for the exposure-adjusted event rate, only events occurring during the derived period will be considered. If a patient is not followed up for 28 days after the last study treatment due to one of the reasons given below, the day of last treatment in the denominator calculation above is

replaced as follows:

- If the patient dies, the date of death will be used.
- If the patient does not complete the study for other reasons, the date of the Early Discontinuation Visit will be used.
- If no such visit has been performed, the date of the last performed visit (except PML follow-up) will be used.

The exposure time, will in any of the above listed cases be calculated as:

Exposure time (years) = [(date of last treatment) – (date of first treatment) + 1] / 365.25.

Such tables will be displayed for the following:

- All TEAEs
- Treatment-emergent AESIs
- Related TEAEs
- Treatment-emergent SAEs
- Treatment-emergent related SAEs
- TEAEs of grade 3 or higher
- TEAEs leading to permanent study drug discontinuation or study withdrawal
- Fatal TEAEs

Additionally, the incidences and percentages of TEAEs and treatment-emergent SAEs will be tabulated according to the worst severity observed per patient for each SOC and PT. Each patient will only appear once per PT/SOC/overall summarization level, with the patient's event of highest grade being shown. If all occurrences of a SOC or PT for a subject has missing grade, then it will be displayed under a 'Missing' entry.

A Standardised MedDRA Queries (SMQ) analysis of TEAEs will be done for anaphylactic reactions and hypersensitivity. All TEAEs related to these SMQs will be identified and summarized by SMQ name and scope (narrow or broad). Analysis will be based on SMQ version 23.0.

All deaths will be listed separately.

8.8.2 SERUM CHEMISTRY AND HEMATOLOGY

Summary statistics of quantitative laboratory results and changes from baseline will be summarized per scheduled time point by treatment group. Frequencies and percentages of markedly abnormal values will be tabulated per scheduled assessment time point, where applicable. Shift tables of worst post-baseline assessments (including unscheduled observations) vs. baseline will be presented. Where available, National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grades will be summarized in similar frequency and shift tables.

Patients who fulfil the protocol criteria for liver abnormalities (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3x upper limit of normal [ULN] and total bilirubin > 2x ULN at

the same visit) will be listed.

All test results will also be listed.

8.8.3 URINALYSIS

The following tests will be performed as part of the urinalysis: pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, and cells.

(Quasi-) continuous results will be summarized together with changes from baseline by sample statistics per visit, and categorical results will be summarized in frequency tables by visit. Tests for which normal ranges are provided will also be summarized by means of frequency and shift tables in the same way as the hematology results. Test results including pregnancy tests will also be listed.

8.8.4 VITAL SIGNS

Summary statistics of quantitative vital signs (systolic and diastolic blood pressure, heart rate, temperature) and weight and their changes from baseline will be summarized per scheduled time point by treatment group. Patients with markedly abnormal values for vital signs will be tabulated. The following ranges will be applied:

Pulse	>120 beats per minute or increase of ≥20 bpm from baseline < 50 beats per minute or decrease of ≥20 bpm from baseline
Systolic blood pressure	≥ 160 mm Hg or increase of ≥20 mm Hg from baseline ≤ 90 mm Hg or decrease of ≥20 mm Hg from baseline
Diastolic blood pressure	≥ 100 mm Hg or increase of ≥ 15 mm Hg from baseline ≤ 50 mm Hg or decrease of ≥15 mm Hg from baseline
Temperature	> 38.3 °C / 101 °F
Body weight	> 110 kg or ± 10% from baseline weight < 45 kg or ± 10% from baseline weight

8.8.5 PHYSICAL EXAMINATION

The frequency of patients with new abnormal physical examination assessments after baseline will be tabulated by body system over the whole study period.

Further details of physical examination findings will be presented in data listings.

8.8.6 COLUMBIA-SUICIDE SEVERITY RATING SCALE

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used at Screening, week 24, and End-of-Study or Early Discontinuation Visits. At Screening, the “lifetime” version of the questionnaire will be used to collect information on the time the patient felt most suicidal.

The following items will be collected:

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide
- Category 11 – Non-Suicidal Self-Injurious Behavior

As a summary of the above items, frequencies of the Suicidal Ideation Score (defined as the maximum suicidal ideation category [Categories 1-5] on the C-SSRS, score of 0 if no ideation is present) per time point and for the overall post-baseline period will be calculated as follows:

- Suicidal ideation: A “yes” answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior: A “yes” answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A “yes” answer at any time during treatment to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.
- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) during treatment from not having suicidal behavior (Categories 6-10) prior to treatment (screening “lifetime” C-SSRS scale).
- Treatment-emergent suicidal ideation compared to all prior history: An increase in the maximum suicidal ideation score during treatment from the maximum suicidal ideation score prior to treatment (screening “lifetime” C-SSRS scale).

The frequencies of Non-Suicidal Self-Injurious Behavior (Category 11) responses will be summarized in the same way.

8.8.7 ANTI-NATALIZUMAB ANTIBODIES

The proportion of patients with positive ADA (transient and persistent) results and the proportion of patients with positive (transient and persistent) neutralizing ADA results during the study will be summarized at each visit for the SAF and SSW Populations. Missing ADA results will be presented in the missing category at each visit, if any.

A positive ADA patient will be defined as a patient who has at least 1 positive ADA result in any post-baseline sample. These patients will be further categorized as follows:

- Transiently positive: defined as a patient with confirmed positive ADAs in 1 sample at a post-dose visit.

- Persistently positive: defined as a patient with confirmed positive ADAs in 2 or more consecutive positive ADA samples at post-dose visits.

Exact 95% confidence intervals will be calculated for the differences between PB006 and Tysabri in the incidence rates of positive, persistent and positive neutralizing ADA over 24 and 48 weeks and for the 24 weeks after re-randomization between patients who switch to PB006 at week 24 and patients who remain on Tysabri. Other ADA incidence rates will be summarized descriptively.

In addition, a shift table for titer results (titer ≤1 and titer>1), if available, will be presented for shifts from baseline to each post-treatment visit.

8.8.8 ANTI-JOHN CUNNINGHAM VIRUS ANTIBODIES

The incidence rates of positive anti-JCV antibody samples by JCV index level (≤0.9, >0.9 and ≤1.5 and >1.5) will be summarized descriptively by visit and for the duration of the study.

8.8.9 LUMBAR PUNCTURE

Results of the CSF sample from lumbar puncture at PML Follow-Up Visits will be listed.

8.9 OTHER ENDPOINTS AND ANALYSIS

8.9.1 PHARMACOKINETICS

Natalizumab trough concentration in serum will be summarized descriptively per time point in the FAS and PP population.

In addition to the sample statistics defined in Section 8.1, the following summaries will be tabulated: coefficient of variation (%), geometric mean, and number of samples below the lower limit of quantification.

For sample statistics except geometric mean, results below the limit of quantification will be set to zero. For geometric mean calculations, such results will be set to the lower limit of quantification.

8.10 RISK MANAGEMENT SUPPORT

To support the risk management process, the following analyses will be performed in addition to the ones described previously for the SAF.

Number of patients and patient-years of exposure to PB006 will be summarized overall and by categorized duration of exposure (<1 month, 1 to <3 months, 3 to <6 months, 6 to< 9 months, 9 to <12 months, over a year), Age group (18 to 25 years, >25 to 35 years, >35 to 45 years, >45 to 60 years old), race and ethnicity (per categories collected in the eCRF).

Similar summaries will be created for exposure to Tysabri. Patients who switch treatments will be counted in both summaries, with their respective durations for each of the drugs.

9. PRIMARY AND FINAL ANALYSIS

Following the protocol amendment (Protocol Version 4.0), no interim analysis will be performed for this study.

The final analysis is planned when all patients have completed the End-of-Study Visit (Visit 13 /Week 48) or have discontinued.

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The protocol states in Section 9.6.4 “SAEs that occur after the start of the first infusion and through the last infusion date of the study drug (Visit 13, End-of-Study Visit), will be summarized”. As the last infusion of study drug is planned for Visit 12/Week 44, SAE data will actually be collected and analyzed through 4 weeks after the last infusion, which is when the End-of-Study Visit (Visit 13/Week 48) will occur.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the *protocol number* will be presented. On the next line, a *table/listing number* followed by the *title* of the table/listing and *population* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* will appear at the bottom left corner in a string, and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of the table/listing will appear at the bottom left corner under to the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.

The list of tables, listings, and figures is given in the section below. Shells for unique tables and listings are provided in a separate Mock-Up TFLs document.

12. LIST OF TABLES, LISTINGS, AND FIGURES

Tables, figure and listings for this study are contained in a separate document (PB006-03-01 Mock TFLs).

13. REFERENCES

Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple

sclerosis. *N Engl J Med*. 2003; 348(1):15-23.

Nilsson ME, Suryawanshi S, Gassmann-Mayer C, Dubrava S, McSorley P, and Jiang K. Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0 (Finalized February 2013).

14. APPENDIX I. TIME AND EVENTS SCHEDULE

Study Period	**Screening[a]**	**Treatment**												**End-of-Study Visit/ Early Discontinuation Visit**	**Unscheduled Relapse Assessment Visit[b]**	**Unscheduled Suspected PML Visit[b]**	**PML Follow-Up Visit[c]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/Subsequent to discontinuation**			**14**
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**68**
Permitted visit window (days)	-	-	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**			**± 14**
Informed consent	X																
Assessment of eligibility	X																
Randomization		X						X[d]									
Demographics & medical history	X																
MRI	X[e]	X[e]		X[e]		X[e]	X[e]	X[e]						X[e]		X[e,f]	X[g]
EDSS	X	X						X						X	X	X	
C-SSRS	X							X						X			
Anti-natalizumab antibodies[g]		X	X	X		X		X	X	X				X			
Natalizumab C_{trough}		X		X		X		X		X				X			

Anti-JCV antibodies	X							X						X		

Study Period	**Screening[a]**	**Treatment**												**End-of-Study Visit/ Early Discontinuation Visit**	**Unscheduled Relapse Assessment Visit[b]**	**Unscheduled Suspected PML Visit[b]**	**PML Follow-Up Visit[c]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/Subsequent to discontinuation**			**14**
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**68**
Permitted visit window (days)	-	-	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**			**± 14**
Physical examination	X_i	X_i	X	X	X	X	X	X_i	X	X	X	X	X	X[i]			X[j]
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum pregnancy test[k]	X																
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum chemistry[l] serology[m], urinalysis	X	X		X		X		X		X		X		X	X	X	
Hematology	X	X		X		X		X		X		X		X	X	X	

Lumbar puncture for CSF sample															X	
Concomitant therapy / medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[n]
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[o]
12-lead ECG	X															
Study drug		X	X	X	X	X	X	X	X	X	X	X	X			
Study Period	**Screening[a]**	**Treatment**												**End-of-Study Visit/ Early Discontinuation Visit**	**Unscheduled Relapse Assessment Visit[b]**	**Unscheduled Suspected PML Visit[b]**	**PML Follow-Up Visit[c]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/Subsequent to discontinuation**			**14**
Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**68**
Permitted visit window (days)	-	-	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**			**± 14**
Biobank samples (blood and urine)	X							X						X[p]			

ALC=absolute lymphocyte count; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EDSS=expanded disability status scale; HIV=human immunodeficiency virus; JCV= John Cunningham virus; MRI=magnetic resonance imaging; PML=progressive multifocal leukoencephalopathy. a. After obtaining informed consent, Screening will consist of 2 parts:

1. Samples for anti-John Cunningham virus (JCV) antibodies and biobank samples (blood and urine) will be taken. When JCV test results come back:

a. JCV index >1.5: The patient will be considered a screen failure. b. JCV index ≤1.5: Proceed with part 2.

2. For patients with JCV index ≤1.5, the Investigator or designee will set up a second visit for all other screening procedures that will be completed for each patient prior to randomization for study treatment.

b. Unscheduled Relapse Assessment Visit and Unscheduled Suspected PML Visit are only scheduled from visit 1 through visit 13/Subsequent to discontinuation.

c. In case of symptoms suggestive for PML, a PML Follow-Up visit is scheduled earlier. If PML diagnosis is confirmed, no further PML Follow-Up visit is scheduled. Otherwise, the patient will be followed up at week 24 ± 2 weeks after last infusion.

d. Re-randomization of Tysabri group to either Tysabri or PB006 (automatically through randomization system).

e. e. Assessed by the central reading center.

f. If PML is suspected based on the MRI scan, the MRI should not be repeated.

g. If PML is suspected, only. Only locally assessed.

h. Analysis includes testing for neutralizing antibodies for ADA positive sample.

i. Include height and weight measurement at Screening and weight measurement at other noted visits. j. For any symptoms suggestive for PML.

k. Only for females of childbearing potential. Serum pregnancy test to be performed at Screening and if a urine pregnancy test is positive.

l. If ALC is confirmed to be $<0.2 \times 10^9$/L on 2 consecutive tests within 2 weeks, treatment will be interrupted until ALC is $>0.5 \times 10^9$/L. m. HIV-1 and serology tests only performed at Screening.

n. Medications for MS treatment, only.

o. PML or AEs related to or suggestive for PML, only.

Samples are not taken at an Early Discontinuation Visit scheduled due to withdrawal of informed consent.