Polpharma Biologics S.A.

Product PB006

Protocol No. PB006-03-01

EudraCT No. 2018-004751-20

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

Document type:	Clinical Study Protocol
Development Phase:	3
Release date of original protocol:	05 FEB 2019
Release date of Version 2.0	04 SEP 2019
Release date of Version 3.0	05 FEB 2020
Release date of Version 4.0	15 JUL 2020
Sponsor	Polpharma Biologics S.A. ul. Trzy Lipy 3 80-172 Gdansk Poland

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If any contact information is changed during the course of the study, this will be done with written notification to the Investigator(s), and will not require (a) protocol amendment(s).

Synopsis

Name of the Sponsor/Company Polpharma Biologics S.A.	**Study Number** PB006-03-01
Name of Investigational Medicinal Product PB006	**EudraCT No.** 2018-004751-20
Development Phase of the Study Phase 3	

TITLE OF THE STUDY

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

STUDY POPULATION

Adult patients with Relapsing-Remitting Multiple Sclerosis (RRMS)

OBJECTIVES

Primary objective

- Evaluate and compare the cumulative number of new active lesions over 24 weeks

Secondary objectives

- 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 Expanded Disability Status Scale (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 (C_{trough}) over time
- Evaluate and compare the safety profile (physical examination, vital sign measurements, and clinical laboratory tests) over 24 and 48 weeks

OVERALL 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 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.

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

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=up to 34); and PB006 group (n= up to 130).

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. In addition, a progressive multifocal leukoencephalopathy (PML) Follow-Up Visit (Visit 14, Week 68) will be performed 24 weeks after the last infusion or earlier in case of new signs and symptoms suggestive for PML. All patients who withdraw prematurely from the study and received at least 1 infusion of study drug will also be required to return to the clinic 24 weeks after the last infusion for the PML Follow-Up Visit or earlier in case of symptoms suspicious for PML.

Magnetic resonance imaging (MRI) will be performed at Screening, prior to treatment at Visit 1 (Week 0), and at Weeks 8, 16, 20, 24, 48 and the End-of-Study Visit (Visit 13, Week 48), at unscheduled visits in case of suspected PML and at the PML Follow-Up Visit if PML is suspected (up to 24 weeks after last study drug infusion). Serum samples for ADA and neutralizing antibody formation will be collected prior to treatment at Visit 1 (Week 0), and at Weeks 4, 8, 16, 24, 28, 32, and 48. 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 48. Blood samples and urinalysis for safety laboratory assessments will be collected at Screening, prior to treatment at Visit 1 (Week 0), and every 8 weeks through Week 48 and 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 to be evaluated after 24 and 48 weeks include radiologic response criteria using MRI, 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).

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

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

The Time and Events Schedule follows this synopsis.

TEST DRUG – BIOSIMILAR

PB006 – natalizumab biosimilar, 20 mg/mL concentrate for solution for IV infusion

COMPARATOR DRUG

Tysabri (International Nonproprietary Name [INN]: natalizumab), 20 mg/mL concentrate for solution for IV infusion

NUMBER OF PATIENTS

Approximately 260 patients are planned to be randomized.

NUMBER OF STUDY CENTERS

Approximately 55 study sites in 7 countries (Belarus, Croatia, Georgia, Moldova, Poland, Serbia, and Ukraine).

STUDY PERIOD

The total study period for each patient will be approximately 52 weeks (4 weeks of screening and 48 weeks of treatment). In addition, patients are required to come for a PML Follow-Up Visit 24 weeks after last study drug infusion.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Male and female patients (age ≥18 to 60 years), with RRMS defined by the 2010 revised McDonald criteria (Appendix 1).
2. At least 1 documented relapse within the previous year and either ≥1 GdE T1-weighted brain lesions or ≥9 T2-weighted brain lesions at Screening.
3. Kurtzke EDSS score from 0 to 5 (inclusive) at Screening.
4. At Screening, females of childbearing potential must be non-pregnant and non-lactating; or females should be of non-childbearing potential (either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1 year post-menopausal [amenorrhea duration of 12 consecutive months]); non-pregnancy will be confirmed for all females of childbearing potential by a serum pregnancy test conducted at Screening.
5. Female patients of childbearing potential, with a fertile male sexual partner, must use adequate contraception from Screening until 90 days after the last dose of study drug (Visit 12, Week 44, or earlier, if treatment is discontinued sooner). Adequate contraception is defined as using hormonal contraceptives or an intrauterine device, combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the subject, is acceptable.
6. Male patients who are sexually active with women of childbearing potential agree they will use adequate contraception from Screening until 90 days after the last dose of study

drug (at Visit 12, Week 44, or earlier, if treatment is discontinued sooner) if not surgically sterilized at least 6 months before Screening (with a post-vasectomy semen analysis negative for sperm). Male patients must not donate sperm until 90 days after the last dose of study drug (Visit 12, Week 44, or earlier, if treatment is discontinued sooner). Adequate contraception for the male subject and his female partner of childbearing potential is defined as using hormonal contraceptives or an intrauterine device, combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the subject, is acceptable.

7. Signed and dated Informed Consent Form (ICF).

Exclusion Criteria

1. Manifestation of multiple sclerosis (MS) other than RRMS.
2. Relapse within the 30 days prior Screening and until administration of the first dose of study drug.
3. Prior treatment with natalizumab, alemtuzumab, ocrelizumab, daclizumab, rituximab, cladribine, or other B- and T-cell targeting therapies.
4. Prior total lymphoid irradiation or bone marrow or organ transplantation.
5. Any prior treatment within the following time period prior to Screening:

- 30 days: systemic corticosteroids or interferon-β or glatiramer acetate
- 2 months:
  - fingolimod
  - any other sphingosine-1-phosphate receptor modulator (e.g., siponimod)
  - any tumor necrosis factor-alpha (TNF-α) inhibitors
- 2 months: dimethyl fumarate
- 3.5 months: teriflunomide
- 12 months: immunosuppressive therapy for indications other than MS (e.g., cytarabine, azathioprine, methotrexate, cyclophosphamide, cyclosporine, cladribine)

6. Any prior treatment with mitoxantrone
7. Active infections requiring oral or parenteral antibiotic treatment within 2 weeks prior to Screening
8. Increased risk of opportunistic infections; exclusion determination to be made after consultation with the Medical Monitor.
9. Patients with JCV index >1.5 at Screening.
10. Past or current PML diagnosis.
11. Presence of malignancies or neoplastic diseases; past history of malignancies within 5 years prior to Screening (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved).
12. History or known presence of recurrent or chronic infection other than recurring urinary tract infections (i.e., hepatitis A, B, or C, human immunodeficiency virus [HIV], tuberculosis).
13. Clinically relevant, severe cardiac or pulmonary diseases, uncontrolled hypertension, or poorly controlled diabetes.
14. Severe renal function impairment as defined by serum creatinine values >120 μmol/L.

15. Elevated liver markers:

- Alanine aminotransferase (ALT) >3x upper limit of normal (ULN),
- Aspartate aminotransferase (AST) >3x ULN, or
- Total bilirubin 2x ULN.

Patients with documented Gilbert syndrome can be enrolled after approval by the Medical Monitor.

16. Decreased white blood cell counts (WBCs) at Screening:

- WBC $<3.0 \times 10^9$/L, or
- Absolute neutrophil count (ANC) $<1.0 \times 10^9$/L, or
- Absolute lymphocyte count (ALC) $<0.5 \times 10^9$/L.

17. Unable to understand the patient information and ICF.
18. Unable or unwilling to comply with the protocol requirements.
19. Alcohol or drug dependence within 1 year prior to study entry.
20. Self-reported symptoms of depression and/or suicidal thoughts based on the Columbia-Suicide Severity Rating Scale (C-SSRS)
21. Any investigational drug within 3 months prior to enrollment or within 5 times of its half-life, whichever is longer.
22. Unable to undergo MRI scans due to claustrophobia or metallic implants incompatible with MRI.
23. Unable to receive Gd-based MRI-contrast agents due to history of hypersensitivity to Gd-based contrast agents or severe renal insufficiency.
24. Has a known contraindication and (or) hypersensitivity to any of the constituents of the study drug or comparator drugs, including their excipients.

ENDPOINTS

Primary Endpoint

- Cumulative number of new active lesions over 24 weeks

Secondary Endpoints

- 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 and after switching
- 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

STATISTICAL METHODS

Primary Endpoint

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

$$H0: |\mu_{PB006} - \mu_{Tysabri}| > 2.1 \text{ vs. } H1: |\mu_{PB006} - \mu_{Tysabri}| \leq 2.1,$$

where μ_x denotes the cumulative number of new active lesions over 24 weeks in the respective treatment group. Data will be analyzed using a negative binomial model and equivalence will be tested based on the corresponding 90% and 95% confidence intervals to address different regulatory requirements.

Secondary Endpoints

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. All other endpoints will only be analyzed descriptively using summary statistics or frequency tables depending on the type of variable.

Planned Sample Size

A total of 230 evaluable patients (115 in each group), i.e., patients who complete the 24-week treatment period without relevant 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 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 260 patients will be randomized to either Tysabri or PB006. At Week 24, the 130 patients in the Tysabri group will be re-randomized. 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=up to 34); and PB006 group (n=up to 130).

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 RRMS or secondary progressive MS. An equivalence margin 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.

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. 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.

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

SIGNATURE PAGE FOR SPONSOR

Protocol: PB006-03-01

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

Reviewed and approved by the following:

[redacted]

[redacted] *Director Clinical Research and Development, Polpharma Biologics S.A.*

20-Jul-2020
Date

[redacted]

[redacted] *Director Regulatory Affairs, Polpharma Biologics S.A.*

20-Jul-2020
Date

[redacted]

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
ADA	anti-drug (natalizumab) antibodies
AE	adverse event
AESI	adverse event of special interest
ALB	albumin
ALC	absolute lymphocyte count
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARN	acute retinal necrosis
AST	aspartate aminotransferase
AT	aminotransferase
ATC	anatomical therapeutic chemical
CNS	central nervous system
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DIS	dissemination in space
DIT	dissemination in time
DSMB	Data Safety Monitoring Board
DW	diffusion weighted
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ePMF	electronic project master file
EU	European Union
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FLAIR	fluid attenuation inversion recovery
GCN	granule cell neuronopathy
GCP	Good Clinical Practice
Gd	gadolinium
GdE	gadolinium-enhancing
GGT	gamma-glutamyl transferase

GRAS	generally recognized as safe
HDL	high-density lipoprotein
Hct	hematocrit
HCV	anti-hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
INN	International Nonproprietary Name
INR	international normalized ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
IV	intravenous
IWRS	interactive Web response system
JCV	John Cunningham virus
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MAdCAM	mucosal addressin cell adhesion molecule
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI	National Cancer Institute
PCR	polymerase chain reaction
PD	proton density
PI	product information
PML	progressive multifocal leukoencephalopathy
PP	per-protocol population
RBC	red blood cell count
RMP	Risk Management Plan
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SPMS	secondary progressive multiple sclerosis
TEAE	treatment-emergent adverse event

TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
VCAM	vascular cell adhesion molecule
VZV	varicella zoster virus
WBC	white blood cell count

1. ETHIC CONSIDERATIONS

1.1. STATEMENT OF COMPLIANCE

The Sponsor conducts its studies according to the highest ethical and scientific standards in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), the Declaration of Helsinki, and any additional relevant ethics committee or regulatory agency-required procedures, whichever represents the greater protection for the individual. The protocol articulates standards to which investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

It is expected that investigators understand and comply with the protocol. This includes but is not limited to adhering to diagnostic or other procedures as specified in the protocol. The study will be conducted under a protocol reviewed and approved by an IEC and Regulatory Agency, where applicable. Investigators will apply due diligence to avoid protocol deviations; no waivers will be permitted.

The protocol, ICF, recruitment materials, and all participant materials will be submitted to the IEC for review and approval. Approval of both the protocol and the ICF must be obtained before any participant is enrolled and before any study-related tests or evaluations are performed.

Any amendment to the protocol will require review and approval by the IEC and Regulatory Agency, where applicable, before the changes are implemented to the study. However, the IEC/Regulatory Agency may be notified for amendments containing only administrative changes.

All changes to the ICF will require review and approval by the IEC and Regulatory Agency, where applicable. A determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved ICF.

The study will be conducted by scientifically and medically qualified persons. All personnel involved in the conduct of this study must complete Human Subjects Protection and ICH GCP training.

1.2. INDEPENDENT ETHICS COMMITTEE

Before implementing this study, the protocol, the ICF, and other information that will be given to patients must be reviewed by an IEC.

A signed and dated statement that the protocol and ICF have been approved by the IEC must be filed in the electronic project master file (ePMF) before study initiation.

The IEC as required by local law, will approve any amendments to the protocol, which need formal approval. The IEC may be notified for all other amendments (i.e., administrative changes).

The name and occupation of the chairperson and the members of the IEC (preferred) must be filed in the ePMF.

1.3. INFORMED CONSENT AND PATIENT INFORMATION

No patient can enter the study before his/her informed consent has been obtained.

The Investigator will explain to each patient the nature of the research study, its purpose, the procedures involved, the expected duration, alternative treatment, the potential risks and benefits involved and any discomfort, which may occur. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient should read and consider the statement before signing and dating it. The Investigator or designee can read the text to an eligible patient who cannot read but is not mentally challenged. The patient will be given a copy of the signed and dated document.

If written consent from the patient is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form, provided this is acceptable with local laws. The Investigator must document the date the patient or witness(es) signs the ICF in the patient's medical record.

In addition, patients undergoing dummy test magnetic resonance imaging (MRI) scans will have to sign a separate MRI ICF after being instructed carefully by the local MRI staff on the purpose, risks, and procedures of the test scan.

1.4. PATIENT CONFIDENTIALITY

[redacted]

2. INTRODUCTION

2.1. BACKGROUND INFORMATION ABOUT RELAPSING-REMITTING MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. Indeed, it affects up to 2.5 million people worldwide. Its prevalence rate varies between races and geographical latitudes, ranging from more than 100 per 100,000 in Northern and Central Europe to 50 per 100,000 in Southern Europe (Multiple Sclerosis International Federation, 2013).

It is characterized by multifocal recurrent events of neurological symptoms and signs, with variable recovery. Eventually, the majority of subjects develop a progressive clinical course (Acheson, 1977; Phadke and Downie, 1987; Paty and Ebers, 1998).

The exact cause of MS is unknown, although an autoimmune process has been implicated. Genetic susceptibility plays a role in disease initiation (Ebers and Sadovnick, 1994; Sadovnick et al., 1996), but currently unidentified environmental factors also are involved (Sadovnick and Ebers, 1993). One hypothesis is that CNS auto-reactive lymphocytes are triggered outside the CNS, become active and proliferate in the peripheral secondary lymphoid organs. Upon migration via the blood circulation, the expression of adhesion molecules on the surface of these encephalitogenic lymphocytes permits adhesion to activated brain or spinal cord endothelial cells, with subsequent migration into the CNS compartment. These cells again proliferate upon interacting with CNS myelin antigens, and initiate a pro-inflammatory cascade within the brain that results in either target-directed immune damage or bystander damage. Important cellular and humoral elements are T- and B-lymphocytes, macrophages, microglial cells, and metalloproteinases, chemokines and cytokines, including interferon (IFN)-gamma and tumor necrosis factor-alpha (TNF-α) (Beck et al., 1988; Ota et al., 1990; Martin et al., 1992).

Four clinical forms of MS are recognized: primary progressive, progressive-relapsing, secondary progressive, and relapsing-remitting (Lublin and Reingold, 1996; Paty and Ebers, 1998). Primary progressive subjects encompass about 10% of the MS population; their disease is characterized by slow and steady accumulation of neurological deficits from onset without

superimposed events. A smaller percentage of patients will have a similar onset but with occasional MS attacks (progressive-relapsing).

Patients with relapsing-remitting MS (RRMS) have acute exacerbations or MS attacks with subsequent variable recovery (remission). At the onset of MS, 80% to 85% of patients will have the relapsing-remitting form of the disease. Expanded Disability Status Scale (EDSS) scores are below 4 in most cases of RRMS. Approximately 10% of patients have benign MS, a subset of RRMS characterized by the lack of accumulation of significant residual neurological deficit over time, with EDSS scores of <3 after 10 to 15 years of disease.

Fifty percent (50%) of patients with RRMS will convert to secondary progressive MS (SPMS) within 10 years of onset (Runmarker and Andersen, 1993), with the peak time of conversion being at about 8 years after disease onset (Paty and Ebers, 1998). The proportion of patients with RRMS progressing to SPMS approaches 80% at 25 years. SPMS is characterized by the steady accumulation of significant and persistent neurological deficit, with or without superimposed MS attacks. Response to first-line therapy may differ based on whether MS attacks continue to occur in SPMS. The majority of patients with EDSS scores of 6.0 or higher has SPMS. Patients at the early stage of SPMS, generally with an EDSS score between 4 and 6, present normally still relapses, which however are not characterized by a full recovery of the previous functionality or a stage of remission. This group of subjects is called Relapsing MS (RMS).

2.2. BACKGROUND INFORMATION ABOUT PB006

PB006 is developed as a natalizumab biosimilar in the same dosing regimen, route of administration, and presentation as the reference medicinal product, Tysabri® (Biogen), currently approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) in RRMS and additionally by the FDA for the treatment of moderately to severely active Crohn's disease.

PB006 has the same amino acid sequence as the reference product Tysabri. The biochemical and physicochemical characteristics as well as secondary and tertiary structure of PB006 and the reference product Tysabri are comparable; minor differences are not expected to affect biological activity, pharmacokinetic and pharmacodynamic properties, or immunogenicity. An alternative formulation has been developed for PB006. The alternative formulation contains well-characterized generally recognized as safe (GRAS) excipients only. Given the high degree of analytical comparability between Tysabri and PB006, no differences in clinical safety and efficacy should be expected.

The clinical development program is designed following the relevant international guidelines and following interactions with FDA, EMA, and the Paul-Ehrlich-Institute in Germany. The clinical studies will provide final confirmation regarding similarity between the biosimilar candidate PB006 and the reference medicinal product Tysabri.

Natalizumab is a humanized monoclonal IgG4 antibody that selectively binds to the α4-integrin component of adhesion molecules found on lymphocytes, monocytes, and eosinophils. The α4-integrin is a subunit of the leukocyte adhesion molecules α4β1 and α4β7. Natalizumab inhibits the interaction of α4β1 with vascular cell adhesion molecule (VCAM)-1 and of α4β7 with mucosal addressin cell adhesion molecule (MAdCAM)-1. VCAM-1 and MAdCAM-1 are found on endothelial cells and interact with α4β1 and α4β7 on leukocytes for firm adherence of leukocytes to endothelial cells, a requisite step for their extravasation into inflamed tissue. As VCAM-1 is expressed on inflamed cerebrovascular endothelial cells, α4β1 is considered to be the critical target of natalizumab in preventing leukocyte migration into the CNS in MS. Further details regarding the mode of action of natalizumab are provided in the PB006 Investigator's Brochure (IB) and in the Tysabri product information (PI) (Tysabri PI, 2018).

Natalizumab therapy is to be initiated and continuously supervised by specialized physicians experienced in the diagnosis and treatment of neurological conditions, in sites with timely access to MRI. Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months.

Refer to the current PB006 IB for additional information regarding relevant nonclinical, microbiology, pharmacology, and clinical studies.

2.3. RISKS AND BENEFITS

Tysabri is indicated as monotherapy for the treatment of patients with RRMS to delay the progression of physical disability and to reduce the frequency of relapse.

Progressive multifocal leukoencephalopathy (PML) is a known risk to patients receiving Tysabri (Tysabri PI, 2018). PML is a rare, often fatal viral disease, caused by the JCV, with a slow onset resulting in inflammation and demyelination in the white matter of the brain. Acquired by 60% to 80% of the adult population, JCV is a human DNA polyoma virus (papovavirus) that resides latently in tubular epithelial cells of the kidneys and bone marrow. Immune system suppression can reactivate the virus and cause PML (Pietropaolo et al., 2018).

Approximately 50% of the JCV-positive MS population noted above have a JCV antibody index >0.9; approximately 30% have a JCV antibody index >1.5. Pooled data from large clinical studies suggest that, in patients with no prior immunosuppressant use, the level of anti-JCV antibody response (index) relates to the level of risk for PML (EMA, 2016). Risk estimates for PML in JCV antibody positive patients treated with Tysabri are shown in Table 1. For JCV antibody negative patients the risk is 0.1 per 1000. Based on the inclusion/exclusion criteria (e.g., JCV index ≤1.5, Tysabri naïve, no prior treatment with immunosuppressants), the risk for patients in this study is minimized.

Table 1 PML Risk Estimates per 1,000 Patients in Anti-JCV Antibody Positive Patients

Duration of Tysabri Use	No Prior Use of Immunosuppressants				Prior Use of Immunosuppressants
	No Index Value	Index ≤0.9	Index 0.9 to 1.5	Index >1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Source: EMA, 2016 (Original source: Tysabri Physician Information and Management Guidelines)

There is no specific screening test for PML. For this study, investigators will use a combination of patient history, physical examination, and radiologic evidence using MRI, EDSS, hematology results, and results of testing for JCV DNA presence in CSF to determine a diagnosis of PML. See details in Section 2.4.

There is no consistently effective treatment for PML. Treatments include cytarabine, cidofovir, topotecan, mefloquine, and interleukin-2. The goals of treatment are to stop Tysabri administration and to treat the underlying disease.

2.4. RISK MANAGEMENT PLAN FOR PML

Use of Tysabri has been associated with an increased risk of PML (EMA, 2019). PML also has been reported following discontinuation of Tysabri in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of Tysabri.

Three factors that are known to increase the risk of PML in natalizumab-treated patients have been identified:

- Presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.
- Longer treatment duration, especially beyond 2 years. There is a limited experience in patients who have received more than 6 years of natalizumab treatment.
- Either have used an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil) before starting Tysabri, or have not used immunosuppressants and have a high JCV antibody index.

These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab.

Due to the increased risk of developing PML in patients treated with natalizumab, the Sponsor has developed a Risk Management Plan (RMP) for PML. There is no prevention or cure for PML. Rapid recognition of PML and early discontinuation of natalizumab are key interventions. Therefore, the RMP is focused on early clinical detection and management of PML, including discontinuation of study drug, if applicable.

2.4.1. PROCESS AND ASSESSMENTS OF EARLY DETECTION

To ensure success of the RMP program, training will be provided for study personnel prior to start of the study to recognize the signs and symptoms of PML.

The benefits and risks of Tysabri treatment should be individually evaluated by the Investigator and discussed with the patient. Patients will receive training, including how to recognize the specific neurological signs and symptoms of PML, how to report these without delay, and educational materials prior to receiving study drug. The ICF will contain specific information on the risk of PML.

A baseline anti-JCV antibody test and MRI will be performed for comparison to subsequent MRI scans. Prior to the administration of each dose of study drug and until the PML Follow-Up Visit, each patient will be assessed for signs and symptoms of PML that may be suggestive of PML. Any signs and symptoms of PML will be recorded in the eCRF.

Symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months.

During the study, patients who suspect they are experiencing new or worsening neurological symptoms, including a possible relapse or PML, are required to call the study site neurologist as soon as possible (preferably 24 hours) after onset of the symptoms to set up an Unscheduled Relapse Assessment Visit (Section 7.4) or an Unscheduled Suspected PML Visit if the Investigator feels the patient is in fact experiencing a relapse or suspected PML, respectively. If symptoms occur after the End-of-Study Visit or after the Early Discontinuation Visit, a PML Follow-Up Visit is scheduled instead of an Unscheduled Relapse Assessment Visit or an

Unscheduled Suspected PML Visit. The visits and the PML Follow-Up Visit should be performed as soon as possible within the next 3 days.

Table 2 Diagnosis of MS Relapse vs PML presents certain clinical features that may help differentiate between an MS relapse and PML.

Table 2 Diagnosis of MS Relapse vs PML

	MS Relapse	**PML**
Onset	Acute	Subacute
Evolution	• Over hours to days • Normally stabilize • Resolve spontaneously or with treatment	• Days to weeks • Progressive
Clinical presentation	• Diplopia • Paresthesia • Paraparesis • Optic neuritis • Myelopathy	• Cortical symptoms/signs • Behavioral and neuropsychological alteration • Retrochiasmal visual deficits • Seizures • Hemiparesis

Source: Tysabri, 2013.

In addition to PML and MS, other medical and CNS conditions including other infections should be considered when evaluating patients with new neurological symptoms.

2.4.2. ACTION STEPS IF PML IS SUSPECTED

2.4.2.1. Study Drug Interruption

The study drug must be interrupted immediately in all cases when PML is suspected. Natalizumab dosing should only be resumed if the diagnosis of PML is excluded.

2.4.2.2. PML Diagnosis

To determine a diagnosis of PML, investigators will use a combination of the following test from Visit 1 through the End-of-Study Visit or Early Discontinuation Visit:

- Patient history
- EDSS
- Serum chemistry, hematology, and urinalysis
- MRI will be performed (FLAIR, T1- and T2-weighted sequences, with or without Gd); if findings during a scheduled MRI suggest PML, the MRI may not be repeated
- Local radiologist will alert the site, CRO, and central MRI reader
- Central MRI reader will alert the site, Sponsor representative, and CRO
- The CRO and Sponsor will inform the Data Safety Monitoring Board (DSMB)
- Lumbar puncture with evaluation of CSF for detection of JCV DNA

If clinical suspicion of PML remains despite the negative evaluation, then CSF assessment should be repeated to exclude the diagnosis of PML.

If diagnosis remain uncertain and suspicion of PML remains high, further investigations will be performed according to the local standards. Cases of PML diagnosed based on MRI findings and the detection of JCV DNA in the CSF in absence of clinical signs and symptoms have been reported (Tysabri, 2016). Many of these patients become subsequently symptomatic. Periodic monitoring for radiologic signs consistent with PML should be considered to allow for an early

diagnosis of PML. Lower PML-related mortality and morbidity have been reported following natalizumab discontinuation in patients with PML who are initially asymptomatic at diagnosis.

2.4.3. ACTION STEPS IF PML IS CONFIRMED

2.4.3.1. Study Drug Discontinuation

The study drug must be discontinued immediately in all cases when PML is confirmed.

Confirmed PML cases should be reported as SAEs/AESIs to the CRO/Sponsor immediately (within 24 hours).

2.4.3.2. Treatment of PML

Plasma exchange may be considered as a means to accelerate the clearance of natalizumab. Three sessions of plasma exchange over 5 to 8 days were shown to accelerate natalizumab clearance in clinical studies. Additional plasma exchanges (up to a total of 5 over a 10-day period) may more consistently reduce natalizumab plasma concentration.

AEs that may occur during plasma exchange include clearance of other medications and volume shift, which have the potential to lead to hypotension or pulmonary edema.

Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in the majority of patients who developed PML and subsequently discontinued natalizumab. In almost all cases, IRIS occurred within days to several weeks after plasma exchange was used to accelerate natalizumab clearance. However, natalizumab has not been associated with IRIS in patients discontinuing treatment with natalizumab for reasons unrelated to PML.

IRIS usually presents as an unanticipated clinical decline that may be rapid and severe, can lead to serious neurological complications, and may be fatal. IRIS is often associated with characteristic changes in the MRI.

IRIS should be reported as an SAE to CRO/Sponsor immediately (within 24 hours).

2.4.4. FURTHER FOLLOW-UP FOR PML

After the End-of-Study Visit or after the Early Discontinuation Visit, patients are further followed up for PML.

Physicians should monitor 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 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.

Outcomes of the PML Follow-Up Visit will be recorded in the source data and on an extra eCRF page. Data on the extra eCRF page will be kept separately from data in the clinical database. Cases of confirmed PML will be included as an addendum to the clinical study report.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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 (C_{trough}) over time
- Evaluate and compare the safety profile (physical examination, vital sign measurements, and clinical laboratory tests) over 24 and 48 weeks

4. INVESTIGATIONAL PLAN

4.1. OVERALL 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 RRMS.

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

1. Samples for anti-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 the Time and Events Schedule).

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

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).

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 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.

MRI will be performed at Screening, prior to treatment at Visit 1 (Week 0), and 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 ADA and neutralizing antibody formation will be collected prior to treatment at Visit 1 (Week 0), and at Weeks 4, 8, 16, 24, 28, 32, and 48. 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. Blood samples and urinalysis 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 and at unscheduled visits in case of a relapse and at unscheduled visits if PML is suspected.

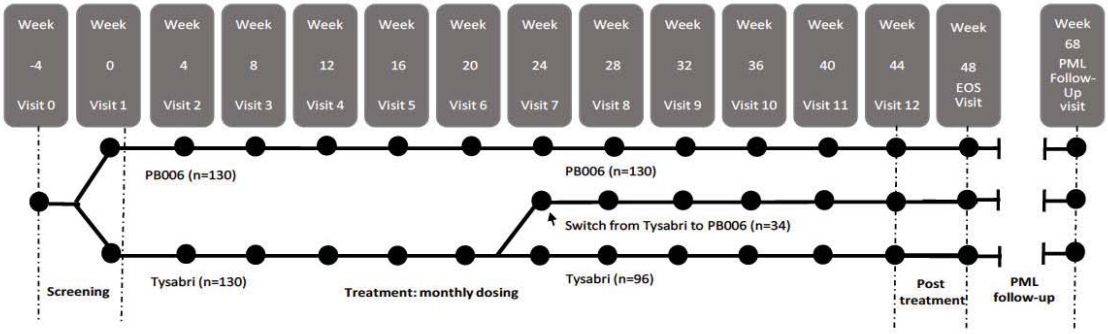
The primary endpoint will be the radiologic response as measured by the cumulative number of new active lesions over a 24-week treatment period, starting with the first infusion at Week 0 to Week 24. Secondary endpoints to be evaluated after 24 and 48 weeks include radiologic response criteria, clinical 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).

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) (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. The Time and Events Schedule for all of the study visits follows the synopsis.

Figure 1 Overall Study Flowchart



4.2. RATIONALE FOR THE STUDY DESIGN

The goal of the study is to support the demonstration of biosimilarity between PB006 and Tysabri. In particular, the study aims to confirm that there are no clinically meaningful differences between PB006 and Tysabri. Therefore, an equivalence design has been chosen in line with the applicable biosimilar guidelines.

4.3. NUMBER OF PATIENTS

Approximately two hundred sixty (260) patients will be randomized in this study.

4.4. REPLACEMENT OF PATIENTS

Randomized patients who prematurely discontinue study treatment for any reason prior to the Week 48 visit will not be replaced.

4.5. RANDOMIZATION

Investigators are required to register all patients who sign the ICF in the eCRF with the date the ICF is signed. The Investigator/designee will obtain a patient number using an electronic data capture (EDC) system. Patients who are screened will be entered into a screening log. Patients who do not meet eligibility criteria will be registered as screen failures in the eCRF along with the date and reason for screen failure. Patients who meet all eligibility requirements and who have signed an ICF will be randomly assigned (using the eCRF Randomization Form) to one of the two treatment groups in a 1:1 ratio. Randomization will be used to avoid bias in assigning patients to treatment, to increase the likelihood that known and unknown patient attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Randomization will be stratified by the following factors at Screening:

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

Once assigned, patient numbers for any screening failures, non-treated, non-evaluable, or discontinued patients will not be re-used.

If a patient experiences a relapse during screening, re-screening will be allowed and the patient will receive a new patient number.

At Week 24, the 130 patients in the Tysabri group will be re-randomized (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=up to 34); and PB006 group (n=up to 130).

4.6. BLINDING AND UNBLINDING PROCEDURES

This study will be double-blinded with regard to the study drug. The unblinded pharmacist/designee will be responsible for maintaining accountability, blinding, and dispensing the study drugs according to the handling instructions. Study center personnel, with the exception of the unblinded pharmacist/designee, will remain blinded to the identity of the study drug until the database has been locked and the study has been unblinded.

Individual patient numbers, indicating the treatment for each randomized patient, will be available to the investigators or pharmacists from the IWRS. Procedures will be described in the IWRS user manual that will be provided to each center.

To maintain Investigator blinding, the treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. In such a case, the patient should receive all appropriate medical care. Prior to any unblinding, the Investigator should contact the Medical Monitor (see Contact Information) to discuss options. The unblinding procedure will be done through the IWRS system. As soon as possible and without revealing the patient's study drug assignment (unless important to the safety of patients remaining in the study), the Investigator must notify the Sponsor if the blind is broken for any reason and the Investigator was unable to contact the Sponsor prior to unblinding. The Investigator will record in the source documentation the date and reason for revealing the blinded treatment assignment for that patient; the treatment assignment itself should not be entered into source documentation.

The Sponsor may break the code for SAEs that are unexpected and are believed to be causally related to study drug and that potentially require expedited reporting to regulatory authorities. In such cases, the minimum number of Sponsor personnel will be unblinded. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented and databases have been locked.

4.7. INTERRUPTION AND STOPPING RULES

4.7.1. INTERRUPTION AND DISCONTINUATION OF STUDY DRUG

Table 3 presents when to interrupt or discontinue treatment.

Table 3 Interruption and Discontinuation of Study Drug

Disease/Condition	Diagnosis Stage/Labs	Treatment Interruption	Testing Required	Resume Treatment	Withdrawal From Study Drug and Early Discontinuation Visit
PML	Suspected	X	Schedule confirmatory testing within 3 days (i.e., patient history, physical examination, MRI, EDSS, hematology, test for JCV DNA presence in CSF)		
	Not diagnosed during confirmatory testing			X	
	Confirmed				X
JCV GCN	Suspected (same symptoms as PML)	X			
	Confirmed				X
Opportunistic infections (as defined in Section 8.10.7.3)					X
Liver injury	Jaundice ALT or AST >5x ULN (until confirmation)	X	Perform repeat lab tests		
	Normal lab results			X	
	ALT or AST >8x ULN (not confirmed) ALT or AST >5x ULN (confirmed, retest required within 14 days) ALT or AST >3x ULN (confirmed) in conjunction with elevated total bilirubin >2x ULN or international normalized ratio (INR) >1.5, or				X

Disease/Condition	Diagnosis Stage/Labs	Treatment Interruption	Testing Required	Resume Treatment	Withdrawal From Study Drug and Early Discontinuation Visit
	ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia				
Hypersensitivity (not including infusion-related reactions)					X
Encephalitis					X
Meningitis					X
ARN	Suspected (Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye)	X	Refer for retinal screening for ARN		
	Confirmed				X
Low lymphocyte count	ALC <0.2 $\times 10^9$/L on 2 consecutive tests within 2 weeks	X			
	ALC returns to >0.5 $\times 10^9$/L			X	
Suicidal ideation/suicidal behaviors	At any C-SSRS test post screening, the score is "yes" on any item of the Suicidal Ideation section or "yes" on any item of the Suicidal Behavior section.		Refer patient to a mental health professional for further assessment and/or treatment. The decision on whether the study drug should be discontinued is to be taken by the Investigator in consultation with the mental health professional		To be determined

ALC=absolute lymphocyte count; ALT= alanine aminotransferase; ARN=acute retinal necrosis; AST= aspartate aminotransferase; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; EDSS=expanded disability status scale; GCN=granule cell neuronopathy; JCV= John Cunningham virus; MRI=magnetic resonance imaging; PML=progressive multifocal leukoencephalopathy; ULN=upper limit of normal.

4.7.2. WITHDRAWAL FROM THE STUDY

Every reasonable effort should be made to encourage retention of patients in the study, maximize compliance with the study protocol requirements, and facilitate attendance at all scheduled study visits.

All patients have the right to refuse further participation in the study at any time and for any reason. A patient's participation must, therefore, be terminated immediately upon his/her request.

The Investigator will make every attempt to ascertain the reason(s) for withdrawal and to document this in detail in the source documentation and the appropriate sections of the eCRF. Patients should be withdrawn from the study due to any of the following reasons:

- Patient withdraws consent
- Patient is noncompliant, defined as refusal or inability to adhere to the study procedures
- Patient becomes pregnant
- Unacceptable or intolerable treatment-related AEs
- Use of any other investigational treatment
- Any illness or circumstance (e.g., incarceration) that would substantially impact the study procedures or outcome measures
- At the request of the Sponsor, regulatory agencies, or IEC
- Loss to follow-up, i.e., the patient did not return to the clinic and attempts to contact the patient were unsuccessful; three attempts to contact the patient must be documented (i.e., 2 attempts by phone and 1 attempt by registered letter)
- Patients who discontinue study drug treatment permanently as listed in Table 3

In case of premature withdrawal of the patient from the study, he/she will be asked to perform the Early Discontinuation Visit assessments (Time and Events Schedule). Withdrawn patients who received at least 1 dose of study drug will be followed up for PML for 24 weeks (+/- 2 weeks).

4.8. EXPECTED STUDY DURATION

The total study period for each patient will be approximately 52 weeks (4 weeks of screening and 48 weeks of treatment). In addition, patients are required to come for a PML Follow-Up Visit 24 weeks after last study drug infusion.

5. STUDY POPULATION SELECTION

The specific inclusion and exclusion criteria for enrolling patients in this study are described in the following sections.

5.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible to participate in the study:

1. Male and female patients (age ≥18 to 60 years), with RRMS, defined by the 2010 revised McDonald criteria (Appendix 1).

2. At least 1 documented relapse within the previous year and either ≥1 GdE T1-weighted brain lesions or ≥9 T2-weighted brain lesions at Screening.

3. Kurtzke EDSS score from 0 to 5 (inclusive) at Screening.

4. At Screening, females of childbearing potential must be non-pregnant and non-lactating; or females should be of non-childbearing potential (either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1 year post-menopausal [amenorrhea duration of 12 consecutive months]); non-pregnancy will be confirmed for all females of childbearing potential by a serum pregnancy test conducted at Screening.

5. Female patients of childbearing potential, with a fertile male sexual partner, must use adequate contraception from Screening until 90 days after the last dose of study drug (Visit 12, Week 44, or earlier, if treatment is discontinued sooner). Adequate contraception is defined as using hormonal contraceptives or an intrauterine device, combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the subject, is acceptable.

6. Male patients who are sexually active with women of childbearing potential agree they will use adequate contraception from Screening until 90 days after the last dose of study drug (at Visit 12, Week 44, or earlier, if treatment is discontinued sooner) if not surgically sterilized at least 6 months before Screening (with a post-vasectomy semen analysis negative for sperm). Male patients must not donate sperm until 90 days after the last dose of study drug (Visit 12, Week 44, or earlier, if treatment is discontinued sooner). Adequate contraception for the male subject and his female partner of childbearing potential is defined as using hormonal contraceptives or an intrauterine device, combined with at least one of the following forms of contraception: a diaphragm or cervical cap, or a condom. Total abstinence from heterosexual activity, in accordance with the lifestyle of the subject, is acceptable.

7. Signed and dated ICF.

5.2. EXCLUSION CRITERIA

Patients who exhibit any of the following exclusion criteria will not be eligible for admission into the study:

1. Manifestation of MS other than RRMS.

2. Relapse within the 30 days prior Screening and until administration of the first dose of study drug.

3. Prior treatment with natalizumab, alemtuzumab, ocrelizumab, daclizumab, rituximab, cladribine, or other B- and T-cell targeting therapies.

4. Prior total lymphoid irradiation or bone marrow or organ transplantation.

5. Any prior treatment within the following time period prior to Screening:

    - 30 days: systemic corticosteroids or interferon-β or glatiramer acetate
    - 2 months:
        - fingolimod
        - any other sphingosine-1-phosphate receptor modulator (e.g., siponimod)

  - any tumor necrosis factor-alpha (TNF-α) inhibitors
- 2 months: dimethyl fumarate
- 3.5 months: teriflunomide
- 2 months: dimethyl fumarate
- 12 months: immunosuppressive therapy for indications other than MS (e.g., cytarabine, azathioprine, methotrexate, cyclophosphamide, cyclosporine, cladribine)

6. Any prior treatment with mitoxantrone.

7. Active infections requiring oral or parenteral antibiotic treatment within 2 weeks prior to Screening.

8. Increased risk of opportunistic infections; exclusion determination to be made after consultation with the Medical Monitor.

9. Patients with JCV index >1.5 at Screening.

10. Past or current PML diagnosis.

11. Presence of malignancies or neoplastic diseases; past history of malignancies within 5 years prior to Screening (except basal cell and in situ squamous cell carcinomas of the skin that have been excised and resolved).

12. History or known presence of recurrent or chronic infection other than recurring urinary tract infections (i.e., hepatitis A, B, or C, human immunodeficiency virus [HIV], tuberculosis).

13. Clinically relevant, severe cardiac or pulmonary diseases, uncontrolled hypertension, or poorly controlled diabetes.

14. Severe renal function impairment as defined by serum creatinine values >120 μmol/L.

15. Elevated liver markers:

    - Alanine aminotransferase (ALT) >3x upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) >3x ULN, or
    - Total bilirubin 2x ULN

Patients with documented Gilbert syndrome can be enrolled after approval by the Medical Monitor.

16. Decreased white blood cell counts (WBCs) at Screening:

    - WBC $<3.0 \times 10^9$/L
    - Absolute neutrophil count (ANC) $<1.0 \times 10^9$/L, or
    - Absolute lymphocyte count (ALC) $<0.5 \times 10^9$/L.

17. Unable to understand the patient information and ICF.

18. Unable or unwilling to comply with the protocol requirements.

19. Alcohol or drug dependence within 1 year prior to study entry.

20. Self-reported symptoms of depression and/or suicidal thoughts based on the Columbia-Suicide Severity Rating Scale (C-SSRS).

21. Any investigational drug within 3 months prior to enrollment or within 5 times of its half-life, whichever is longer.

22. Unable to undergo MRI scans due to claustrophobia or metallic implants incompatible with MRI.

23. Unable to receive Gd-based MRI-contrast agents due to history of hypersensitivity to Gd-based contrast agents or severe renal insufficiency.

24. Has a known contraindication and (or) hypersensitivity to any of the constituents of the study drug or comparator drugs, including their excipients.

6. TREATMENT OF PATIENTS

6.1. DESCRIPTION OF STUDY DRUGS

6.1.1. TEST DRUG – BIOSIMILAR - PB006

The test drug, PB006, 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.

6.1.2. 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.

6.1.3. PREPARATION AND ADMINISTRATION

Both study drugs will be diluted with 100 mL sodium chloride solution (0.9%), resulting in a natalizumab concentration of approx. 2.6 mg/mL for administration.

After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C to 8˚C and infused within 8 hours of dilution. If the diluted study drug is stored at 2˚C to 8˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.

The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 mL/minute. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/mL (0.9%) solution for injection.

For further details regarding preparation and administration, consult the Pharmacy Manual.

6.1.4. STORAGE, HANDLING, AND ACCOUNTABILITY

All study drug(s) and preparation/administration materials (infusion sets, catheters, transfer syringes, needles and isotonic saline bottles) will be supplied to the investigators. The Investigator or designee must confirm appropriate temperature conditions have been maintained

during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive the study drug and only authorized site staff may supply or administer study intervention. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For details of storage and handling, please refer to the Pharmacy Manual.

6.2. PRIOR AND CONCOMITANT MEDICATIONS

All medications taken within 30 days prior to Screening, and all concomitant therapy administered during the study, should be recorded on the relevant eCRF page(s), along with the reason for, and details of, therapy use.

The patient's complete MS medication history should be recorded on the relevant eCRF page(s), along with the reason for, and details of, therapy use.

6.2.1. ALLOWED MEDICATIONS

The following medications are allowed during this study:

- Corticosteroids (IV methylprednisolone 1g once daily) for 3 to 5 days for treatment of relapses
- Symptomatic MS treatments, if they are stable for at least 3 months prior to Screening

6.2.2. PROHIBITED MEDICATIONS

The use of medications is restricted from Screening through the End-of-Study Visit/ Early Discontinuation Visit.

Study drug (PB006 or Tysabri) should not be administered in combination with other disease-modifying agents, including natalizumab, alemtuzumab, ocrelizumab, daclizumab, rituximab, cladribine, and other B- and T-cell targeting therapies, interferons, glatiramer acetate, fingolimod, any other sphingosine-1-phosphate receptor modulator (e.g., siponimod), any TNF-α inhibitors, teriflunomide, dimethyl fumarate, immunosuppressive therapy (e.g., cytarabine, azathioprine, methotrexate, cyclophosphamide, cyclosporine, cladribine), mitoxantrone, or any other investigational treatment.

Systemic corticosteroid therapy or adrenocorticotropic hormone, except for treatment of relapses as defined in 6.2.1.

Corticosteroids that are by non-systemic routes (e.g., topical, inhaled, intra-articular) are allowed.

6.3. TREATMENT COMPLIANCE

Treatment compliance will be documented by recording the infusion time in the eCRF (start/end time plus any complications during the infusion) and by drug accountability.

7. STUDY ACTIVITIES BY VISIT

The study is divided into phases with associated evaluations and procedures that must be performed at specific time points, as described in the following sections. The Time and Events Schedule summarizes the frequency and timing of study events.

As soon as the patient is considered for this study, and prior to any other study procedures, the patient will have the nature of the study explained to them, and will be asked to give written informed consent (Section 1.3). Informed consent must be obtained prior to any procedures that do not form a part of the patient's normal care.

All patients (withdrawn or completed) will have evaluations and procedures performed as described for the End-of-Study Visit.

7.1. SCREENING PHASE

Written informed consent must be obtained before any study-related procedures are performed.

Patients will be evaluated for entry criteria during the screening period within 4 weeks prior to administration of study drug.

Screening will consist of the following 2 parts:

1. Samples for anti-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 the following screening procedures that will be completed for each patient prior to randomization for study treatment:

- Assessment of eligibility
- Demographics and baseline characteristics
- Medical history
- MRI
- EDSS
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Physical examination, including height and weight
- Vital signs (heart rate, body temperature, blood pressure)
- Serum pregnancy test for females of childbearing potential only
- Clinical laboratory tests (serum chemistry, serology, hematology, and urinalysis)
- Review and documentation of prior (within the previous 30 days) medications, any medications used for MS treatment, and concomitant medications
- Assessment of AEs
- 12-lead electrocardiogram (ECG)

If a patient relapses during the screening process, re-screen after 30 days of the relapse and provide a new patient number.

7.2. TREATMENT PHASE

This period begins with randomization (Section 4.4) of the patients found to be eligible for the study during the Screening Phase.

The first administration of study drug (either PB006 or Tysabri, 300 mg dose) will be given at Visit 1, Week 0 and continues through the end-of-visit 12, Week 44 (±3 days). Each patient should remain at the site for 1 hour after the first infusion is complete to monitor for any infusion/hypersensitivity reactions (Section 8.10.7).

During the Treatment Phase, the following evaluations will be conducted and the data will be collected and recorded on the eCRF at each scheduled visit (or as indicated).

Visit 1 Week 0

- MRI
- EDSS
- ADA
- Physical examination, including weight
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C_{trough})
- Assessment of concomitant medications
- Assessment of AEs (including infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 2 Week 4 (±3 days)

- ADA
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 3 Week 8 (±3 days)

- MRI
- ADA
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)

- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C_{trough})
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 4 Week 12 (±3 days)

- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 5 Week 16 (±3 days)

- MRI
- ADA
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C_{trough})
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 6 Week 20 (±3 days)

- MRI
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 7 Week 24 (±3 days)

At Week 24, patients previously receiving Tysabri will be re-randomized and may be switched to receive PB006 for the remaining treatment period (Approximately 34 out of the 130 patients in the Tysabri group will be switched to PB006). The switching of patients to the PB006 group will be done automatically by the randomization system in a blinded manner.

In addition, the following evaluations will be performed at Week 24:

- MRI
- EDSS
- C-SSRS
- ADA
- Anti-JCV antibodies (should the JCV index value be >1.5 the Investigator should re-evaluate the risk and benefits of continuing natalizumab treatment)
- Physical examination, including weight
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C_{trough})
- Biobank samples (blood and urine)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 8 Week 28 (±3 days)

- ADA
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 9 Week 32 (±3 days)

- ADA
- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)

- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C^{trough})
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 10 Week 36 (±3 days)

- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 11 Week 40 (±3 days)

- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

Visit 12 Week 44 (±3 days)

- Physical examination
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)
- Study drug administration

7.3. END-OF-STUDY VISIT OR EARLY DISCONTINUATION VISIT

The End-of-Study Visit will be scheduled at Visit 13 Week 48 (±3 days) for all patients treated in the study.

All patients who withdraw or who are withdrawn must be asked to attend an Early Discontinuation Visit as soon as possible after withdrawal.

- MRI
- EDSS
- C-SSRS
- ADA
- Anti-JCV antibodies
- Physical examination, including weight
- Vital signs (heart rate, body temperature, blood pressure)
- Urine pregnancy test for females of childbearing potential only (serum test to be performed if urine test is positive)
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Samples to determine natalizumab trough concentration (C_{trough})
- Biobank samples (blood and urine, except in case of patients' withdrawal of informed consent)
- Assessment of concomitant medications
- Assessment of AEs (including assessing for new neurological signs/symptoms of PML and infusion/hypersensitivity reactions 1 hour post infusion)

7.4. UNSCHEDULED RELAPSE VISIT

7.4.1. DEFINITION OF RELAPSE

The general definition of relapse is the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (National Clinical Guidelines Center, 2014). The abnormality must be present for at least 24 hours and have occurred in the absence of fever (<37.5° C) or infection.

7.4.2. PROCEDURES FOR EVALUATION OF SUSPECTED RELAPSE

In case of suspected relapse from Visit 1 through the End-of-Study Visit or Early Discontinuation Visit, patients are required to contact the site to be evaluated for relapse and need to have easy access to schedule an appointment. The study coordinator must be able to coordinate patient and physician assessments for unscheduled relapse visits. The visit must be scheduled as soon as possible within 3 days.

A relapse must be confirmed by the blinded rater (examining neurologist; see Section 8.3). It is recommended that this occurs within 3 days of the onset of symptoms. A relapse is confirmed when it is accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different Functional Systems of the EDSS or 2 points on one of the Functional Systems (excluding Bowel/Bladder or Cerebral Functional System).

After the relapse is confirmed, a post-baseline EDSS should be conducted 4 weeks after confirmation.

Relapses should be managed according to usual clinical practice. If treating a relapse with corticosteroids:

- A single short course of methylprednisolone can be considered for cases in which PML is unlikely on clinical grounds
- Progression of symptoms, despite treatment with corticosteroids, should trigger further investigations

If a corticosteroid is used to treat the relapse, the study-related MRI scans should be obtained before corticosteroid therapy is initiated. If this cannot be done, the MRI scan is to be taken 14 days or more after the last corticosteroid dose.

7.4.3. PROCEDURES AFTER A RELAPSE

7.4.3.1. During Screening

In case of relapse during screening, the patient can be re-screened and will receive a new patient number. Prior to re-screening the patient will sign again the currently approved version of the ICF. In case some of the screening procedures will not need to be repeated, this will be explained to the patient.

7.4.3.2. After Enrollment

The Investigator must discuss with the patient the risk/benefit of continuing participation in the study post relapse. This discussion and the decision of the patient regarding further study participation must be noted in the source documents.

7.5. UNSCHEDULED PML VISIT

If PML is suspected, from Visit 1 through the End-of-Study Visit or Early Discontinuation Visit, study drug will be interrupted and the Investigator will schedule confirmatory testing as soon as possible within 3 days. For more details, see the RMP for PML (Section 2.4).

7.6. PML FOLLOW-UP VISIT

Upon completion of, or early termination from the study, all patients (also those withdrawn due to other reasons than PML) who have received at least 1 infusion of study drug will be required to return to the clinic for a PML Follow-Up Visit 24 weeks ± 2 weeks after the last infusion of study drug. Patients should contact the study site in case they experience symptoms suggestive for PML. If patients experience symptoms suggestive for PML after the End-of-Study or Early Discontinuation Visit but before 24 ± 2 weeks after the last infusion, a PML Follow-Up Visit is scheduled as soon as possible within 3 days. If during a PML Follow-Up Visit PML diagnosis is confirmed, no further PML Follow-Up Visit is scheduled. Otherwise, patients will be followed up further until 24 ± 2 weeks after last infusion.

- Physical examination for any symptoms suggestive for PML
- MRI (only in case of symptoms suggestive for PML). MRI to be assessed locally, only
- Assessment for medications for MS treatment
- PML or AEs related to or suggestive for PML, only

8. STUDY PROCEDURES

The Time and Events Schedule summarizes the frequency and timing of the study events listed in this section.

8.1. DEMOGRAPHICS AND MEDICAL HISTORY

Once the signed ICF (Section 1.3) is obtained, the inclusion/exclusion criteria have been assessed (Sections 5.1 and 5.2), and the patient has been randomized, the Investigator or designee will collect the demographic information (e.g., age, gender) and enter it into the eCRF.

Relevant medical findings will be collected from the patient's medical history, which may include age at initial diagnosis of MS, and specific information concerning prior or existing medical conditions.

8.2. MAGNETIC RESONANCE IMAGING

Brain MRI scans to provide radiologic response data for assessing lesions will be done at each site. Identification of GdE T1-weighted lesions and T2-weighted lesions will be done by a trained and certified radiology reviewer according to standard procedures at the MRI central reading center.

Before any site can screen patients, they will be required to perform test ("dummy") scans. The purpose of the dummy scan is to ensure that adequate image quality, consistent patient positioning, and measurements reproducibility are obtained through the use of appropriate MRI pulse sequence parameters.

Patients undergoing these test scans will have to sign a separate Dummy MRI ICF after being instructed carefully by the local MRI staff on the purpose, risks, and procedures of the test scan. For appropriate and safe conduct of the test scans, the MRI staff is to follow the procedures in the MRI Manual. The test scans will be prepared and filed at the MRI site and in the ePMF.

The image quality of each scan (test scans and trial scans) will be reviewed at the MRI central reading center with predetermined criteria; unsatisfactory images will be rejected and, in such cases, a repeat scan will be requested. If a repeat scan is necessary for the Screening visit, it is imperative that it is acquired as soon as possible and before the first study dose, as applicable.

For each patient evaluated in this study, scans will be performed using the same machine and similar operational parameters throughout the trial, if possible.

To preserve patient confidentiality, the full name of the patient must not appear on the images. The scans should contain at least the following identifiers: patient number, study site number, date of investigation, and visit number. A comment line should specify the name and the volume of the contrast agent delivered.

Baseline (Visit 1) MRI must be conducted on the day of dosing (randomization date) and prior to study drug administration. MRI scans for Week 8 to Week 48 should be planned as per the dosing date from the Baseline visit (Visit 1) of each patient.

MRI for each of these visits must be performed before dosing and within the visit window.

Early Discontinuation Visit (Visit 13) MRI must be performed as soon as possible after withdrawal.

Unscheduled visits for suspected PML MRI must be performed within 3 days of suspected PML. If PML is clinically suspected from Visit 1 through the End-of-Study Visit or the Early Discontinuation Visit, the local radiologist should alert the Investigator who will schedule an Unscheduled Suspected PML Visit with the patient within 3 days. If PML was suspected based on a scheduled MRI scan, a new MRI should not be acquired for the unscheduled visit. For further details regarding MRI acquisition windows, consult the Central MRI Reader Manual.

Brain MRI scans performed at a PML Follow-Up Visit will be assessed locally, only.

8.2.1. CONTRAST AGENT

The EMA has provided recommendations on restriction of use of linear Gd agents in body scans based on a scientific review that found Gd deposition in the brain and other tissues (EMA, 2017) following use of gadolinium contrast agents. The EMA has stated that there is currently no evidence that Gd deposition in the brain has caused any harm to patients; however, EMA has recommended restrictions for some IV linear agents in order to prevent any risks that could potentially be associated with Gd brain deposition. The EMA recommended that use of the IV linear products gadodiamide, gadopentetic acid, and gadoversetamide be suspended in the EU.

Another class of Gd agents known as macrocyclic agents (gadobutrol, gadoteric acid, and gadoteridol) are more stable and have a lower propensity to release Gd than linear agents. The EMA recommended that these products can continue to be used in their current indications but at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable (EMA, 2017).

Based on the EMA recommendations, a macrocyclic Gd-based contrast agent (gadobutrol, gadoteric acid, or gadoteridol) will be administered as an IV infusion of 0.1 mmol/kg. The administration of Gd, including the brand used and the dose given will be documented in the eCRF.

Creatinine/estimated glomerular filtration rate (eGFR) values should be available during screening visit and within 3 months prior to each MRI scan with contrast agent to allow safe administration of contrast agent in accordance with patient's renal function.

For patients with acceptable eGFR values (i.e., eGFR values ≥50 mL/min/1.73m^2) obtained at the baseline (Visit 1) and subsequent Visits 3, 5, 6 and 7, the eGFR value obtained at Visit 7 remains valid until EOS MRI assessment.

For patients without stable eGFR values throughout the previous period (i.e., any eGFR value <50 mL/min/1.73m^2), an additional (local) creatinine test and eGFR value needs to be obtained in order to ensure the MRI with contrast agent can safely be taken at EOS Visit.

8.2.2. SUSPECTED PML

If PML is clinically suspected from Visit 1 through the End-of-Study Visit or Early Discontinuation Visit, the local radiologist will alert the Investigator who will schedule an Unscheduled Suspected PML Visit with the patient within 3 days. MRI scans will immediately be reviewed by the central reading center. The results of the review will be communicated to the site, Sponsor, and CRO immediately. For more details, see the RMP for PML (Section 2.4).

If PML is suspected after the End-of-Study Visit or Early Discontinuation Visit, a PML Follow-Up Visit is scheduled.

8.2.3. MS RELAPSES / CORTICOSTEROID TREATMENT

In the event of a relapse, the study-related MRI scans should be obtained before corticosteroid therapy is initiated. If this cannot be done, the MRI scan is to be taken 14 days or more after the last corticosteroid dose.

8.3. KURTZKE EXPANDED DISABILITY STATUS SCALE

The Kurtzke EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. Based on a standard neurological examination, the 7 functional systems (plus "other") are rated. These ratings are then used in conjunction with observations and information concerning gait and use of assistive devices to rate the EDSS.

EDSS ratings will be performed by independent examining neurologists. The independent neurologists have no access to other patient data. Training (through Neurostatus, level C certification) must be documented in the ePMF. Preferably, and if feasible, the same rater should examine the same patient throughout the course of the study. The examining physician should have a back-up if the primary physician is unavailable.

8.4. COLUMBIA-SUICIDE SEVERITY RATING SCALE

The rater/clinician-administered versions of the C-SSRS assess severity and intensity of suicidal ideation, types of suicidal behaviors, and lethality of suicide attempts. There are 11 categories defined in the C-SSRS (5 subtypes of suicidal ideation, 5 subtypes of suicidal behavior, and self-injurious behavior without suicidal intent). The ratings will be assessed per the instructions.

At Screening, the C-SSRS result will be used to determine study eligibility.

After randomization, a positive outcome on the C-SSRS would require that the patient be referred to a mental health professional for further assessment and/or treatment. The decision on whether the study drug should be discontinued is to be taken by the Investigator in consultation with the mental health professional and should be documented in the eCRF.

8.5. PHYSICAL EXAMINATION

Physical examinations will include the following assessments:

- Weight (kg) (to be collected at Screening, and Weeks 0, 24, 48) and height (cm) (to be collected at the Screening visit only)
- Examination of the injection site and draining nodes (at all visits except screening visit)
- Head/ears/eyes/nose/throat examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Assessment for neurological deficits
- Musculoskeletal assessment

Any abnormalities will be recorded in the eCRF.

8.6. VITAL SIGNS

Vital signs (heart rate, body temperature, and blood pressure) will be measured in the sitting position after resting for at least 5 minutes.

If blood samples are scheduled at the same time, vital signs should be measured before the blood draw.

Blood pressure may be measured manually or with an automated device, preferably in the non-dominant arm. The same measurement technique should be used throughout the study for each patient.

Body temperature will be measured with an electronic device.

8.7. 12-LEAD ELECTROCARDIOGRAM

For the Screening 12-lead ECG, the patient should be in a supine position (lying down) for at least 5 minutes prior to and during the recording. The ECG will be assessed as normal or abnormal by the Investigator; any abnormal findings will be described in the eCRF and the Investigator will assess clinical significance. The ECG recording strip will be signed and dated by the Investigator and stored in the medical records.

The ECG should be performed prior to the blood draws.

8.8. PREGNANCY AND CONTRACEPTION

During Screening, one criterion of the patient's eligibility to be included in the study is if they are willing to practice contraception from Screening until 90 days after the last dose of study drug at Visit 12, Week 44 (or earlier, if treatment is discontinued sooner).

Female patients are to be:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea), or
- Surgically sterilized or physiologically incapable of becoming pregnant and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative pregnancy test at Screening, and using or agreeing to use adequate methods of contraception (see description below) from Screening until 90 days after the last dose of study drug at Visit 12, Week 44 (or earlier, if treatment is discontinued sooner), if they have a fertile male sexual partner.

Male patients are to be:

- Surgically sterilized at least 6 months before Screening (with a post-vasectomy semen analysis negative for sperm), or
- Using or agreeing to use adequate methods of contraception (see description below) from Screening until 90 days after the last dose of study drug at Visit 12, Week 44 (or earlier, if treatment is discontinued sooner), if they have a fertile female sexual partner.

Male patients must not donate sperm until 90 days after the last dose of study drug (Visit 12, Week 44 or earlier, if treatment is discontinued sooner).

Adequate contraception is defined as using hormonal contraceptives or an intrauterine device, combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence from heterosexual activity, in accordance with the lifestyle of the subject, is acceptable.

Also, female patients must not be lactating.

A serum pregnancy test for human chorionic gonadotropin will be performed on female patients of childbearing potential at Screening.

A urine dipstick pregnancy test for human chorionic gonadotropin will be performed on female patients of childbearing potential at all visits during the Treatment Phase, and at the End-of-Study/Early Discontinuation Visit. A serum pregnancy test will be performed if the urine pregnancy test is positive.

In case of pregnancy of the patient or the patient's partner, the Investigator or designee will need to submit it via the Pregnancy Report Form and then follow-up to determine outcome of the pregnancy and condition of the infant. In case of pregnancy of the patient's partner, the partner will be asked to complete an ICF allowing the Investigator to collect information about the course of the pregnancy and the birth and health of the infant, or until the pregnancy is terminated.

A female patient who becomes pregnant during study participation will be withdrawn from the study.

8.9. PREVIOUS AND CONCOMITANT MEDICATION

At Screening, all medications (including nonprescription medications, and complementary and alternative medications) taken within 30 days before Screening are to be reviewed and recorded

in the eCRF. However, any medications used for MS treatment should be recorded. At each visit after Screening, any medication taken by the patient is to be recorded in the eCRF.

8.10. ADVERSE EVENT ASSESSMENTS

Clinical events occurring before starting study treatment but after signing the ICF are recorded on the Medical History/Current Medical Conditions eCRF page.

8.10.1. DEFINITIONS

An AE is any untoward medical occurrence which can be any undesirable sign, symptom, clinically significant laboratory abnormality if associated with clinical symptoms or require therapy, or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related.

Information about all AEs, whether reported by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the adverse event eCRF page and followed as appropriate. Monitoring, collection and recording of AEs should continue until the End-of-Study Visit or Early Discontinuation Visit. PML, AEs related to or suggestive for PML are monitored, collected and recorded until 24 weeks (+/- 2 weeks) after the last infusion of the study drug or until PML is diagnosed, whatever comes earlier.

AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (National Cancer Institute, 2010). If CTCAE grading does not exist for an AE, the intensity of mild (1), moderate (2), severe (3), and life-threatening (4) will be used.

Medical conditions/diseases present prior to the ICF being signed are only considered AEs if they worsen after the ICF is signed.

As far as possible, each AE will also be described by:

1. Description
2. Duration (start and end dates)
3. CTCAE grade 1-4 or intensity
4. Relationship to the study drug – attribution (by categories below) and actions taken regarding the study drug
5. Action(s) taken to treat the AE
6. Outcome

Insufficient clinical response, i.e., lack of therapeutic efficacy should NOT be recorded as an AE.

Relapses are to be documented on the specific eCRF page(s).

8.10.2. SEVERITY

The Investigator, or qualified designee, responsible for the care of the patient will assess an AE for severity and seriousness. Severity is not equivalent to seriousness, which is based on patient/reaction outcome or action criteria usually associated with reactions that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. The Investigator will determine the severity of each AE using

the CTCAE Version 4.03. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE Version 4.03 as stated below (National Cancer Institute, 2010).

Grade Descriptions:

1. Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only

2. Grade 2: moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)

3. Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden)

4. Grade 4: life-threatening consequences; urgent intervention indicated

5. Grade 5: death related to AE

8.10.3. RELATIONSHIP

The relationship of each AE to study drug will be defined as "not related," "unlikely related," "possibly related," "probably related," or "related." The Investigator is responsible for determining the study drug relationship for each AE that occurs during the study. Assessments are to be recorded on the appropriate eCRF page.

Not Related

AEs that are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment, etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possibly, Probably, or Related.

Unlikely Related

An AE may be considered unlikely related if it includes at least the first 2 features:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

Possibly Related

An AE may be considered possibly related if it includes at least the first 2 features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

Probably Related

An AE may be considered probably related if it includes at least the first 3 features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental, or toxic factors or other modes of therapy administered to the subject.
- It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia).
- It follows a known pattern of response to the suspected drug.

Related

An AE may be considered related if it includes all of the following features:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreases on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug. For example: bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.
- It follows a known pattern of response to the suspected drug.
- It reappears or worsens if the drug is re-administered.

The actions taken in response to an AE are described in the following way. One or more of these are to be selected:

1. No action taken
2. Study drug temporarily interrupted
3. Study drug permanently discontinued due to this AE
4. Withdrawal from the study

8.10.4. EXPECTEDNESS

An adverse reaction, the nature or severity of which is not consistent with the applicable PI (IB or Tysabri SmPC) should be considered as unexpected.

8.10.5. CLINICAL LABORATORY ADVERSE EVENTS

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy, in which case they should be recorded on the adverse events eCRF page and should include the signs, symptoms, or diagnosis associated with them.

8.10.6. SERIOUS ADVERSE EVENTS

An SAE is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one

of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Pre-planned surgeries or other pre-planned measures requiring hospitalization will not be considered SAEs for this study unless hospitalization is longer than planned.

Instructions for Expedited Notification of Serious Adverse Events

Any SAE occurring in a patient after providing informed consent until the End-of-Study Visit/ Early Discontinuation Visit must be reported.

Each SAE must be reported by the Investigator within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related, assessing the causal relationship to study drug treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The follow-up reporting should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation.

The [redacted] may contact the Investigator to obtain further information on a reported SAE. If warranted, an Investigator alert may be issued, to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.10.7. ADVERSE EVENTS OF SPECIAL INTEREST

The following AEs will be considered as AESI and can lead to withdrawal from the study treatment: PML, JCV GCN, opportunistic infections, liver injury, hypersensitivity, encephalitis, meningitis, and ARN.

If an AESI occurs, the Investigator should treat according to the standard of care, report the event as an AESI in the format and timelines as for SAEs, and contact the Medical Monitor with any further questions.

If an AESI fulfills the criteria of an SAE (serious criterion) then it should be reported as an SAE, only.

Steps for handling study drug interruption or discontinuation for all AESIs can be found in Table 3.

8.10.7.1. *Progressive Multifocal Leukoencephalopathy*

For more details about PML, see the RMP for PML (Section 2.4).

8.10.7.2. *John Cunningham Virus Granule Cell Neuronopathy*

According to the Tysabri PI (2018), "JCV also causes granule cell neuronopathy (GCN) which has been reported in patients treated with TYSABRI. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome, although cerebellar atrophy may be a differential feature on MRI), and diagnosis and management of JCV GCN should follow guidance provided for PML".

8.10.7.3. *Opportunistic Infections*

According to the Tysabri PI (2018), "[…] opportunistic infections with use of TYSABRI […] cannot currently be excluded." Certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginitis, tooth infections, tonsillitis, and herpes infections, occurred more often in Tysabri-treated patients than in placebo-treated

patients. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received Tysabri.

Patients should be informed that natalizumab may lower the ability of their immune system to fight infections. Patients should be instructed of the importance of contacting their doctor if they develop any symptoms of infection.

The study drug should be permanently discontinued if the opportunistic infection is confirmed.

8.10.7.4. *Liver Injury*

According to the Tysabri PI (2018), "Spontaneous suspect adverse drug reactions of liver injury, including severe liver injury, have been reported from the market. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose. Signs of liver injury have also been reported for the first time after multiple doses, including cases with rechallenge. In these patients recovery of liver function occurred following cessation of therapy. If liver injury occurs during treatment with TYSABRI the drug should be discontinued and investigation of cause undertaken. TYSABRI should be initiated with caution in patients with a history of liver disease and liver function tests should be regularly monitored in these patients."

Liver safety monitoring and assessment information can be found in Appendix 2.

8.10.7.5. *Hypersensitivity*

According to the Tysabri PI (2018), "TYSABRI has been associated with hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions, which occurred at an incidence of <1%. These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion, but there have been occasional post-market reports of delays of up to 2 weeks in symptom onset. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypertension, hypotension, dyspnea and chest pain. Generally, these reactions are associated with antibodies to TYSABRI. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to TYSABRI following an initial short exposure (up to three infusions) and extended period (three months or more) without treatment. Neurologists should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered."

Natalizumab IV should be administered by a healthcare provider prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measure should be available for immediate use. Patients should be observed during the infusion and for one hour after each infusion.

Patients and caregivers will be instructed to report the development of rash, hives, pruritus, flushing, urticarial, redness and / or swelling, etc. that may represent an administration-related reaction (i.e., infusion-related reaction) to study drug. Patients will be asked to report administration-related AEs to the sites immediately as they are experienced or after having received appropriate medical care. Appropriate treatment and follow-up will be determined by the Investigator. If signs or symptoms of an administration-related reaction are observed during the administration of study drug, it should be immediately discontinued and the patient treated as medically appropriate.

Patients who have experienced a hypersensitivity reaction to the study drug must be permanently discontinued from the study drug.

In all cases of administration-related reaction, the Medical Monitor must be informed as soon as practical.

8.10.7.6. Encephalitis/Meningitis

Natalizumab increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster virus. Serious, life-threatening, and sometimes fatal cases have been reported in the post marketing setting in MS patients receiving Tysabri. If herpes encephalitis or meningitis occurs, the study drug should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

8.10.7.7. Acute Retinal Necrosis

ARN is a rare fulminant viral infection of the retina caused by the family of herpes virus (e.g., varicella zoster). ARN has been observed in patients being administered Tysabri and can be potentially blinding. Patients presenting with eye symptoms such as decreased visual acuity, redness and painful eye should be referred for retinal screening for ARN. Following clinical diagnosis of ARN, study drug discontinuation should be discontinued.

8.11. CLINICAL LABORATORY TESTS

8.11.1. BLOOD CHEMISTRY AND HEMATOLOGY

All samples will be collected in accordance with acceptable laboratory procedures at the time points specified in the Time and Events Schedule.

Clinical chemistry and hematology tests will include the following and will be carried out by a central laboratory as presented in Table 4.

Table 4 Clinical Chemistry, Serology and Hematology Tests

Hematology:	Serum Chemistry:
Hematocrit (Hct)	Albumin (ALB)
Hemoglobin (Hgb)	Alkaline phosphatase (ALK-P)
Platelet count	Alanine aminotransferase (ALT)
White blood cell (WBC) count full and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)	Aspartate aminotransferase (AST)
	Creatinine
	Gamma-glutamyl transferase (GGT)
Absolute lymphocyte count (ALC)	Lactate dehydrogenase (LDH)
Absolute neutrophil count (ANC)	Total protein
Red blood cell (RBC) count	Calcium
	Chloride
Serology:	Inorganic phosphorus
JCV antibodies	Total bilirubin
HIV-1 and HIV-2 antibodies (only at Screening)	Direct bilirubin
	Total cholesterol
Varicella zoster virus (VZV) immunoglobulin (Ig) (only at Screening)	Triglycerides
	High-density lipoprotein (HDL)
Anti-hepatitis A virus	Low-density lipoprotein (LDL)
Hepatitis B surface antigen	C-reactive protein (CRP)
Anti-hepatitis B core antigen	
Anti-hepatitis C virus (HCV) IgG or IgM	

Screening labs (outside the requested range) can be repeated (Medical Monitor should be contacted).

Liver safety monitoring and assessment information can be found in Appendix 2.

8.11.2. URINALYSIS

A urinalysis will be performed to measure pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, and cells. A microscopic examination will be performed, if necessary.

8.12. ANTI-JCV ANTIBODY SAMPLES

Blood samples for anti-JCV antibodies will be collected as specified in the Time and Events Schedule.

Samples will be sent to a central laboratory to determine the presence or absence of JCV antibodies using a validated assay.

Anti-JCV antibody status evaluation will be performed every 6 months.

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

8.13. ANTI-NATALIZUMAB ANTIBODY SAMPLES

Serum samples for ADA will be collected as specified in the Time and Events Schedule.

Samples will be sent to a central laboratory to determine the presence or absence of antibodies using a validated assay.

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

8.14. NATALIZUMAB TROUGH CONCENTRATION

Samples to determine natalizumab trough concentrations (C_{trough}) over time will be collected as specified in the Time and Events Schedule.

Samples will be sent to a central laboratory. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

If study drug is supposed to be administered at the visit, the samples should be taken before study drug administration.

8.15. BIOBANK SAMPLES

Biobank samples (blood and urine) will be collected as specified in the Time and Events Schedule. [redacted]

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

8.16. CEREBRAL SPINAL FLUID LUMBAR PUNCTURE

If PML is suspected from Visit 1 through the End-of-Study Visit/Early Discontinuation Visit, a lumbar puncture will be performed to draw CSF for JCV DNA ultrasensitive polymerase chain reaction (PCR). The CSF sample will be sent to the central laboratory.

Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

8.17. DATA SAFETY MONITORING BOARD

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

9. PLANNED STATISTICAL METHODS

9.1. GENERAL CONSIDERATIONS

Prior to unblinding, a detailed statistical analysis plan (SAP) will be completed and approved. This will contain a detailed explanation of the methodology used in the statistical analyses and provide rules and data handling conventions to perform the analyses and how to handle missing data.

The analysis will be conducted when all patients have completed the End-of-Study Visit (Visit 13, Week 48) or have discontinued.

9.2. DETERMINATION OF SAMPLE SIZE

A total of 230 evaluable patients (115 in each group), i.e., patients who complete the 24-week treatment period without relevant 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 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 260 patients will be randomized to either Tysabri or PB006.

At Week 24, the 130 patients in the Tysabri group will be re-randomized (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=up to 34); and PB006 group (n=up to 130).

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 MS. An equivalence margin 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.

9.3. ANALYSIS POPULATIONS

9.3.1. SAFETY POPULATION

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

9.3.2. 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 Population. Patients in this group will be analyzed as treated after re-randomization, also considering treatment before re-randomization.

9.3.3. FULL ANALYSIS SET POPULATION

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.

9.3.4. PER-PROTOCOL POPULATION

Only patients participating in this study who complete the 24-week treatment period without major protocol deviations, which potentially affect the analysis of the primary endpoint, and for whom sufficient post-baseline MRI data are available will be included in the Per-Protocol (PP) population. Further details on the definition of the PP Population will be specified in the SAP.

9.4. ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics such as age, sex, race, weight, and medical history will be summarized by treatment group in all populations using mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables. Use of prior and concomitant medications will be coded and tabulated by treatment group on the Anatomical Therapeutic Chemical (ATC) 2, ATC 4, and preferred name level.

9.5. ANALYSIS OF DISPOSITION AND PATIENT CHARACTERISTICS

Patient disposition (enrollment, discontinuations from the study), study drug administered, premature discontinuations from study drug, withdrawals from the study, and major protocol deviations will be summarized by treatment group in the FAS population.

9.6. ANALYSIS OF ENDPOINTS

Generally, analyses will be performed per treatment arm (according to the first and second randomization) and overall, using mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentages for categorical variables, unless specified otherwise.

9.6.1. PRIMARY 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:

$$H0: |\mu_{PB006} - \mu_{Tysabri}| > 2.1 \text{ vs. } H1: |\mu_{PB006} - \mu_{Tysabri}| \leq 2.1,$$

where μ_x denotes the cumulative number of new active lesions over 24 weeks in the respective treatment group. Data will be analyzed using a negative binomial generalized linear model with fixed effects for the treatment group and stratification factors with log link on the PP Population. Parameters will be estimated using a maximum likelihood approach. Equivalence will be tested based on the corresponding 90% (for FDA) and 95% (for EMA) confidence intervals to address different regulatory requirements. This analysis will be repeated for the FAS Population and the corresponding 90% and 95% confidence intervals will be derived.

9.6.2. SECONDARY ENDPOINTS

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 and after switching
- 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

All secondary endpoints will only be analyzed descriptively without formal comparison between treatment groups. Further details will be provided in the SAP.

9.6.3. ANALYSIS OF EFFICACY ENDPOINTS

Secondary efficacy analysis will be performed on the FAS and PP Populations.

All lesion numbers will be summarized as continuous measures as well by categories (details will be specified in the SAP) per analysis time point.

The number and percentage of patients without new/enlarging T2-weighted lesions will be tabulated. The number and percentage of patients without new GdE T1-weighted lesions will be tabulated.

The annualized relapse rate will be based on a denominator of 365.25 days and summarized as a continuous measure.

Absolute values and change from baseline of EDSS will be tabulated, and categorical summaries for each analysis time point will be presented.

The outcomes and shifts of the C-SSRS will be summarized per time point.

9.6.4. ANALYSIS OF SAFETY

Safety analysis will be performed using the Safety Population and Safety-Switch Population.

The number and percentage of patients with treatment-emergent adverse events (TEAEs; defined as any AEs starting or worsening after the start of the first infusion of the study drug, regardless of relationship to study drug), AESIs (i.e., PML, JVC GCN, opportunistic infections, liver injury, hypersensitivity, encephalitis, meningitis, ARN, see Section 8.10.7), and SAEs that occur after the start of the first infusion and through 4 weeks after the last infusion date of the study drug (Visit 13, End-of-Study Visit), will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity. In addition to incidence rates, exposure adjusted AE rates will be summarized as well.

Change from baseline in clinical laboratory tests and vital signs will be summarized by treatment group. Patients with markedly abnormal values for laboratory tests and vital signs will be tabulated.

Physical examination findings will be presented in data listings.

9.6.5. ANALYSIS OF ANTI-NATALIZUMAB ANTIBODIES

The proportions of patients with positive ADA (transient and persistent) persistent ADA and positive (transient and persistent) neutralizing ADA during the study will be summarized at each visit based on the Safety Population.

A positive ADA patient is defined as a patient who has at least 1 positive ADA result in any post-baseline sample, and is further categorized as:

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

9.6.6. ANALYSIS OF NATALIZUMAB TROUGH CONCENTRATION

Natalizumab trough concentration in serum will be summarized descriptively.

9.6.7. ANALYSIS OF ANTI-JCV ANTIBODIES

Anti-JCV antibodies incidence rates by JCV index level will be summarized descriptively.

9.7. ANALYSES

The analysis of all primary and secondary endpoints is planned when all patients have completed the End-of-Study Visit (Visit 13, Week 48) or have discontinued.

9.8. HANDLING OF DROPOUTS AND MISSING DATA

Every effort will be made to collect all data at specified times. A detailed description of the handling of dropouts and missing data (including loss to follow-up) for all efficacy and safety evaluations will be provided in the SAP.

9.9. DEVIATIONS FROM THE ANALYSIS PLAN

If any deviations from the planned statistical analysis are deemed necessary, a justification for all decisions will be provided in the clinical study report.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. MONITORING PROCEDURES

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the investigators and their staff. During the study, the site monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to ICH GCP, the progress of enrollment, and also to ensure that the study drugs are being stored, dispensed, and accounted for according to specifications.

The Investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study center. The Sponsor's monitoring standards require full

verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary activity and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

10.2. PROTOCOL VIOLATIONS/DEVIATIONS

No waivers for protocol violations or deviations will be granted.

10.3. RECORDING OF DATA AND RETENTION OF DOCUMENTS

Data on patients collected on eCRFs during the study will be documented in a pseudonymous fashion and the patient will only be identified by the patient number. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, both the Sponsor and the Investigator are bound to keep this information confidential.

All the information required by the protocol should be provided; any omissions require explanation. All eCRFs should be completed and available for collection within a timely manner, preferably no more than 2 days after the patient's visit, so that the site monitor/clinical research associate may check the entries for completeness, accuracy, and legibility, ensure the eCRF is signed by the Investigator, and transmit the data to Sponsor. eCRFs must be completed in English.

The Investigator must maintain source documents for each patient in the study. All information on eCRFs will be traceable to these source documents, which are generally maintained in the patient's file.

Essential documents, as listed below, will be retained by the Investigator for as long as needed to comply with national and international regulations. Refer to the Clinical Study Site Agreement for the Sponsor's requirement on record retention. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments
2. IB and updates
3. Copies of regulatory and IEC approvals for the study protocol and all amendments (blanks and all signed copies)
4. All source documents and laboratory record
5. eCRF copies
6. Curricula vitae of investigative team members and delegation of responsibilities list
7. FDA Form 1572
8. Normal values ranges/values for medical/laboratory/technical procedures
9. SAE forms and safety updates
10. Interim reports to ethics committees and authorities in accordance with local requirements
11. Patients' signed and dated ICF(s)

12. Patient Screening and Patient Identification logs

13. Study drug accountability records

14. Any other pertinent study document

10.4. DATA MANAGEMENT

Additional information regarding data management will be included in the Data Management Plan.

10.4.1. DATA COLLECTION

Monitors or designees will review the eCRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The eCRFs will be available in the EDC system to the Sponsor and data management staff or its designee for review.

10.4.2. DATABASE MANAGEMENT AND QUALITY CONTROL

The eCRF information entered into the database will be systematically checked by data management staff following the Sponsor's or its designee's data management procedures. Errors, omissions, or requests for clarification will be queried; queries will be generated in the eCRF and addressed to the investigational site for resolution.

Use of prior and concomitant medications will be coded and tabulated by treatment group on the ATC 2, ATC 4, and preferred name level. Co-existing medical conditions, AEs, and other medical events will be coded using the latest version of the MedDRA dictionary. The same version of the MedDRA dictionary will be used throughout the study.

When the database has been declared to be complete and accurate, the database will be locked. The data will be locked in EDC on "by visit" and "by-patients" level. Additional information on the database lock procedure will be included into the Data Management Plan. Any changes to the database after database lock can be made only by joint written agreement of the Sponsor study team.

10.5. COMPENSATION, INSURANCE, AND INDEMNITY

There will be no charge to study patients. The Sponsor will pay all costs of tests and re-tests, procedures, and treatments that are part of the study procedures. The Sponsor may reimburse the cost of patient travel to the study visits and the PML Follow-Up visits.

[redacted]

10.6. AUDITING PROCEDURES

In addition to the routine monitoring procedures, the Sponsor or its designees may conduct audits of clinical research activities in accordance with internal standard operating procedures to evaluate compliance with the principles of ICH GCP. The Sponsor, its designee, or a regulatory authority may wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the Investigator will inform the Sponsor and CRO immediately that this request has been made.

10.7. PUBLICATION OF RESULTS

Publication of any study-related information will be outlined in the Investigator agreement.

10.8. FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.9. INVESTIGATOR CONFIDENTIALITY

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor, in strict confidence and to request similar confidentiality from his/her staff and the IEC. Study documents provided by the Sponsor (protocols, IBs, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study.

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Appendix 1: 2010 Revised McDonald Criteria for Diagnosis of MS

Clinical (Attacks)	Lesions	Additional Criteria to Make Diagnosis
≥2 attacks[a]	Objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]	Objective clinical evidence of 1 lesion	DIS, demonstrated by: • ≥1 T2 lesion in at least 2 of 4 MS-typical CNS regions (periventricular, juxtacortical, infratorial, spinal cord)[d]; **OR** • Await further clinical attack[a] implicating a different CNS site
1 attack[a]	Objective clinical evidence of ≥2 lesions	DIT, demonstrated by: • Simultaneous presence of asymptomatic GdE and non-enhancing lesions at any time ; **OR** • A new T2 and/or GdE lesions(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; **OR** • Await a second clinical attack[a]
1 attack[a]	Objective clinical evidence of 1 lesion (clinically isolated syndrome)	DIS and DIT, demonstrated by: For DIS: • ≥1 T2 lesion in at least 2 of 4 MS-typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord)[d]; **OR** • Await a second clinical attack[a] implicating a different CNS site **AND** DIT, demonstrated by: • Simultaneous presence of asymptomatic GdE and non-enhancing lesions at any time; **OR** • A new T2 and/or GdE lesions(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; **OR** • Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)		1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: • Evidence for DIS in the brain based on ≥1 T2 lesion in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions; • Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord; • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Source: Polman, 2011, Table 4

MS=multiple sclerosis; CNS=central nervous system; CSF=cerebrospinal fluid; DIS=dissemination in space; DIT=dissemination in time; GdE=gadolinium-enhancing; IgG=immunoglobulin G; MRI=magnetic resonance imaging; PPMS=primary progressive multiple sclerosis. If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is ‘‘MS’’; if suspicious, but the criteria are not completely met, the diagnosis is ‘‘possible MS’’; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is ‘‘not MS.’’

[a] An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b] Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d] GdE lesions are not required; symptomatic lesions are excluded from consideration in patients with brainstem or spinal cord syndromes.

Appendix 2: Liver Safety Monitoring and Assessment

Any patient enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases AT to >3x ULN, or bilirubin >2x ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, and total bilirubin). Testing should be repeated within 48 to 72 hours of notification of the test results. Alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the site, Sponsor, and CRO. Patients should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST	Total Bilirubin
Moderate	>3x ULN	≤2x ULN
Severe[1]	>3x ULN	>2x ULN

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST >8x ULN (not confirmed)
- ALT or AST >5x ULN for >2 weeks (confirmed, retest required within 14 days)
- ALT or AST >3x ULN (confirmed) in conjunction with elevated total bilirubin >2x ULN or INR >1.5
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia.

Discontinuation of study drug should be considered for the lab values above.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the patient may require additional monitoring and follow-up or may be discontinued from the study drug.

In addition, if close monitoring for a patient with moderate or severe hepatic laboratory tests is not possible, the study drug should be discontinued.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination, and laboratory tests.

[1] Hy's Law definition (Temple, 2016): Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant). The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations >3x ULN ("2x ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, should be reported as an AESI. The CRO/Sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset diseases should be recorded as AEs on the adverse event page of the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities, should be noted. Non-alcoholic steatohepatitis is seen in obese hyperlipoproteinemic and / or diabetic patients and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the Medical History eCRF page captures any illness that pre-dated study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medications, complementary and alternative medications).
- Based on the patient's history, other testing may be appropriate including:
    - acute viral hepatitis (A, B, C, D, E or other infectious agents)
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR and direct bilirubin
    - consider gastroenterology or hepatology consultations

Electronic Signature Page

[redacted]

Document title: Statistical Analysis Plan (version 1.1)

Sign-off status: FINAL

Digitally signed by:

NAME, POSITION	ROLE	DATE TIME STAMP
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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
Author:	[redacted]

DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
Final 1.0	01APR2021
Final 1.1	28APR2021

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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Author: [redacted]

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Clinical Trial Lead: [redacted]

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Clinical Program Statistician: [redacted]

Signature: ..... Date: .....

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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).

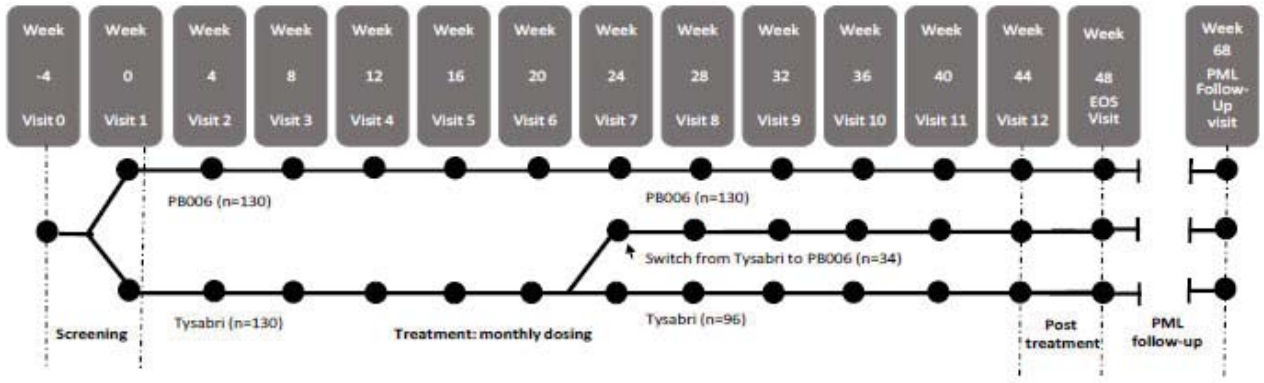
No stratification factors will be considered for the re-randomization for switch.

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.