COVER PAGE

Official Title:	A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration
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PROTOCOL NUMBER: 101MS329

PHASE OF DEVELOPMENT: 3b

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SPONSOR SIGNATURE PAGE

Protocol 101MS329 was approved by:

[redacted]

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Date (dd - MONTH - yyyy)

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1. SYNOPSIS

Protocol Title:	A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing (EID) of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration
Protocol Number:	101MS329
Version Number:	4.0
Name of Study Treatment:	BG00002 (natalizumab; Tysabri®)
Study Phase:	3b
Study Indication:	Relapsing-remitting multiple sclerosis (RRMS)
Study Rationale:	Extending the dosing interval of natalizumab (e.g., to 6 weeks) has been practiced by some physicians in anti-John Cunningham virus antibody-positive patients with the intention of improving the benefit/risk of the treatment by reducing the exposure-dependent risk of progressive multifocal leukoencephalopathy while maintaining efficacy. Whether extending the dosing interval of natalizumab can potentially improve benefit/risk for some patients remains to be established as there are no prospective, randomized, controlled studies assessing the efficacy of extended interval dosing (EID). This study aims to assess the following: the initial efficacy, safety, and tolerability of switching to EID (dosing interval every 6 weeks [Q6W]) after at least 12 months of disease stability on standard interval dosing (SID) [dosing interval every 4 weeks (Q4W)] compared to the continuation of SID; and the long-term efficacy, safety, and tolerability of EID when natalizumab is delivered by subcutaneous (SC) or intravenous (IV) administration. This study has 2 parts. • Part 1 is a randomized, controlled, rater-blinded analysis designed to compare the efficacy, safety, and tolerability of natalizumab EID and SID outcomes. • Part 2 is a randomized open-label extension (OLE) designed to assess subject preference for SC natalizumab EID treatment

and explore long-term efficacy, safety, and tolerability of EID.

Study Objectives and Endpoints:

Part 1

The primary objective of Part 1 of the study is to evaluate the efficacy of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment, with the goal of estimating the difference between SID and EID, with high precision and a narrow 95% confidence interval, to support the treatment decision based on individualized benefit/risk assessments.

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

Secondary objectives and endpoints for Part 1 of the study are as follows:

- To evaluate additional relapse-based clinical efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
  - Time to first relapse (relapses will be adjudicated by an Independent Neurology Evaluation Committee)
  - Annualized relapse rate at Week 72
- To evaluate disability worsening of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
  - Time to Expanded Disability Status Scale (EDSS) worsening (confirmed after at least 24 weeks)
- To evaluate additional magnetic resonance imaging (MRI)-lesion efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.
  - Number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48
  - Number of new gadolinium (Gd)-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72
- To evaluate the safety of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months in relation to continued SID treatment.

- Safety assessments of adverse events (AEs) and serious adverse events (SAEs)

[redacted]

Part 2

The following endpoints will be evaluated between subjects randomized to crossover of SC versus IV routes of natalizumab administration.

The primary objective and endpoint of Part 2 are as follows:

- To evaluate subject preference for SC versus IV route of natalizumab administration.
  - Proportion of subjects indicating a preference for natalizumab SC administration at the end of Part 2

The secondary objectives and endpoints of Part 2, to be assessed between 6 months of SC treatment and 6 months of IV treatment in the randomized crossover period, are as follows:

- To compare treatment satisfaction with SC versus IV route of administration.
  - Total score on Treatment Satisfaction Questionnaire for Medication (TSQM)
- To compare drug preparation and administration time between SC and IV routes of natalizumab administration.
  - Mean time for drug preparation and administration
- To evaluate the safety and immunogenicity of SC versus IV routes of natalizumab administration.
  - The proportion of subjects with treatment emergent AEs
  - The proportion of subjects who develop anti-natalizumab antibodies
- To evaluate the efficacy of SC versus IV routes of natalizumab administration.
  - Number of new or newly enlarging T2 hyperintense lesions
  - Time to first relapse
  - Annualized relapse rate
  - Change in EDSS score
  - Number of new Gd-enhancing lesions

- Number of new T1 hypointense lesions
- Percentage of brain volume change and change in cortical and thalamic brain region volume

- To characterize the pharmacokinetics and pharmacodynamics of SC versus IV routes of natalizumab administration.
  - Trough serum natalizumab concentration
  - Trough α4 integrin saturation

[redacted]

Study Design: Part 1 is a prospective, randomized, interventional, controlled, open-label, rater-blinded study of IV natalizumab administered under SID and EID.

Part 2 is an OLE study of natalizumab EID delivered by SC and IV administration in a randomized crossover design that is available to all qualified subjects who have completed Part 1. New subjects who did not participate in Part 1 but meet Part 1 enrollment criteria and satisfy the requirements for enrollment in Part 2 are also eligible.

Study Location: Approximately 100 sites in North America, the United Kingdom, the European Union, Israel, and Australia are planned for Part 1; approximately 45 sites outside of the United States are planned for Part 2.

Number of Planned Subjects:

Part 1

Approximately 480 subjects are expected to be enrolled with approximately 240 subjects per treatment group (natalizumab SID; natalizumab EID).

Part 2

Up to approximately 200 subjects who have completed Part 1 study treatment and are qualified for Part 2 are expected to be enrolled. New subjects may also be enrolled to ensure adequate sample size for the study analysis.

Study Population:

Part 1

This study will be conducted in subjects aged 18 to 60 years old, inclusive, with a diagnosis of RRMS, who have been treated with natalizumab that is consistent with the approved dosing for a minimum of 12 months prior to randomization. Subjects must have an EDSS score $\leq$ 5.5 at Screening and have had no relapses in the 12 months prior to randomization. At Screening, subjects must not be MRI-

positive for Gd-enhancing lesions or positive for anti-natalizumab antibodies.

Part 2

Subjects who have completed treatment in Part 1 under their original randomized treatment assignment to SID or EID, are qualified, and have consented are eligible to be enrolled. Subjects who switched from EID to SID in Part 1 will not be eligible to participate in Part 2.

Detailed eligibility criteria for Part 2 are described in Section 8.3 and Section 8.4.

If required to ensure adequate sample size to power the study, additional new subjects who did not take part in Part 1 may be permitted to enroll in Part 2. Any new subjects need to meet the eligibility criteria for Part 1 detailed in Section 8.1 and Section 8.2.

[redacted]

Treatment Groups:

Part 1

SID group: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion Q4W (28 [-2/+5] days).

EID group: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion Q6W (42 [-2/+5] days).

Part 2

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

Duration of Treatment and Follow-Up:

Part 1

Study duration for each subject enrolled only in Part 1 will be approximately 102 weeks, comprising the following:

- 6-week screening period
- 72-week treatment period
- 12-week follow-up period
- Follow-up safety phone call 12 weeks after the follow-up period (24 weeks after the last dose of study treatment)

Subjects who enroll in Part 2 do not need to have the Week 12 follow-

up visit or follow-up safety phone call 24 weeks after the last dose of study treatment in Part 1.

Part 2

Study duration for subjects enrolled in Part 2 after completing Part 1 and for new subjects will be approximately 108 weeks, comprising the following:

- 36-week period of IV Q6W treatment
- 48-week randomized crossover treatment period comprising 24 weeks SC Q6W and 24 weeks IV Q6W
- 12-week follow-up period
- Follow-up safety phone call 12 weeks after the follow-up period (24 weeks after the last dose of study treatment)

The total duration of study participation for subjects who participate in both Part 1 and Part 2 will be approximately 186 weeks.

The Part 2 Screening, informed consent, and eligibility assessment should be performed during Week 72 of Part 1. In the event that the Part 2 Screening cannot be performed at that time, a separate Part 2 Screening may occur within 6 weeks prior to Week 78 or Week 84, whichever visit and infusion is the first Part 2 administration of study treatment to the subject. Subject randomization to crossover sequence in Part 2 will occur at the Week 108 visit to confirm crossover treatment allocation.

After Week 84, subjects are not eligible for enrollment in Part 2 of the study.

2. LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough serum concentration of natalizumab
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
EDSS	Expanded Disability Status Scale
EID	extended interval dosing
EOS	end of study
[redacted]	[redacted]
ET	early termination
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Gd	gadolinium
Hep	hepatitis
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INEC	Independent Neurology Evaluation Committee
IRT	interactive response technology
IV	intravenous(ly)
JCV	John Cunningham virus
KM	Kaplan-Meier
mAb	monoclonal antibody
mITT	modified intent to treat
MMRM	mixed model of repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PBVC	percentage of brain volume change
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPQ	Patient Preference Questionnaire
PRO	patient-reported outcome
Q4W	every 4 weeks
Q6W	every 6 weeks
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
[redacted]	[redacted]
SID	standard interval dosing
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TSQM	Treatment Satisfaction Questionnaire for Medication
USA	United States
VCAM-1	vascular cell adhesion molecule 1

3. SPONSOR INFORMATION

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For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. INTRODUCTION

Natalizumab is a recombinant humanized anti-α4 integrin antibody, derived from a monoclonal antibody (mAb) [AN100226m] raised against human α4 integrin. The murine mAb (AN100226m) was humanized by complementarity-determining region grafting of the hypervariable region of the gene encoding AN100226m onto a human immunoglobulin G4 framework, producing the humanized immunoglobulin G4/kappa antibody, natalizumab.

Natalizumab has been approved under the propriety name Tysabri® and was licensed for use in relapsing forms of multiple sclerosis (MS) by the United States (US) Food and Drug Administration on 23 November 2004. Natalizumab was authorized in the US on 05 June 2006, in the European Union on 27 June 2006 (Austria, Belgium, Bulgaria, Croatia [15 December 2008], Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom), and in multiple other countries in the rest of the world (Algeria, Argentina, Australia, Azerbaijan, Bahrain, Bosnia and Herzegovina, Brazil, Canada, Chile, Colombia, Costa Rica, Dominican Republic, El Salvador, Georgia, Guatemala, Honduras, Hong Kong, Iceland, India, Israel, Japan, Jordan, Kazakhstan, Kuwait, Lebanon, Libya, Malaysia, Mexico, Morocco, New Zealand, Norway, Oman, Panama, Peru, Qatar, Russia, Serbia, Singapore, South Africa, South Korea, Switzerland, Syria, Taiwan, Tunisia, Ukraine, the United Arab Emirates, Uruguay, and Venezuela).

4.1. Overview of Multiple Sclerosis

MS is a progressive, degenerative disease of the central nervous system (CNS) characterized by a variety of clinical courses. Approximately 90% of patients present with episodic neurological symptoms and will have bouts of disease activity (exacerbations) separated by periods of total or partial remission (relapsing-remitting phase). A typical patient will have 1 or 2 exacerbations per year with variable duration, lasting from several weeks to more than a month. This relapsing-remitting phase may last many years but, in most patients, is eventually followed by a period of chronic progressive decline (secondary progression), with increasing disability and with or without exacerbations. Approximately 10% of patients will have progression from the onset of the disease (primary progression), without acute exacerbations.

MS is an inflammatory disease of the CNS characterized by areas of demyelination (lesions), which give rise to the clinical symptoms of the disease. Although lesions can occur throughout the CNS, certain sites seem particularly vulnerable, such as the optic nerve, brainstem, spinal cord, and periventricular regions. Lesions are believed to occur when activated T lymphocytes cross the blood-brain barrier and, once in the parenchyma, initiate a series of events leading to activation of endothelial cells, recruitment of additional lymphocytes and monocytes, release of proinflammatory cytokines, and subsequent demyelination [Ffrench-Constant 1994]. Trafficking of leukocytes across the blood-brain barrier involves interaction of the cell adhesion molecule α4 integrin, expressed on lymphocytes and monocytes, with its counter receptors vascular cell adhesion molecule 1 (VCAM-1) and fibronectin on brain endothelial cells. In

particular, VCAM-1 is expressed on inflamed brain endothelial cells and on activated microglial cells, while fibronectin is expressed around inflamed brain microvessels [Hartung 1995].

Blockade of these cell adhesion interactions is assumed to either prevent trafficking of leukocytes across the vascular endothelium, into parenchyma tissue, and subsequently into inflamed tissue; or prevent their activation by ligands in the parenchyma. It is believed that the clinical progression of MS is related to the demyelination caused by leukocyte injury to the myelin sheaths. Thus, inhibiting or preventing leukocyte entry into the CNS and subsequent leukocyte activation is expected to be of therapeutic benefit in MS.

4.2. Current Therapies for Multiple Sclerosis

Approved therapies for MS include the following:

- interferon
- glatiramer acetate
- dimethyl fumarate
- teriflunomide
- alemtuzumab
- fingolimod
- ocrelizumab
- cladribine
- mitoxantrone
- natalizumab
- diroximel fumarate
- siponimod
- ozanimod

4.3. Profile of Previous Experience With Natalizumab

See the Investigator's Brochure (IB) for detailed information on relevant nonclinical and clinical studies.

4.3.1. Nonclinical Experience

The pharmacology, pharmacokinetics (PK), and toxicology of natalizumab have been characterized in nonclinical in vitro and in vivo experimental systems. Nonclinical studies are outlined in the accompanying natalizumab IB.

4.3.2. Clinical Experience

Natalizumab has been used extensively in relapsing-remitting multiple sclerosis (RRMS) and Crohn's disease, both in clinical studies as well as in the postmarketing setting.

As of 07 August 2017, natalizumab has been administered for MS to approximately 5064 subjects in clinical studies and approximately 171,630 patients in the postmarketing setting. Approximately 1639 and 1688 subjects have received natalizumab for Crohn's disease in clinical studies and in the postmarketing setting, respectively. Additionally, subjects have received natalizumab in clinical studies for rheumatoid arthritis (231 subjects), acute ischemic stroke (210 subjects), and multiple myeloma (6 subjects).

The efficacy of natalizumab in subjects with relapsing forms of MS has been established in 3 controlled studies: a Phase 2 dose-comparison study as well as 2 Phase 3 efficacy and safety studies. These studies show that treatment with natalizumab has a profound impact on disability worsening and relapse rate and markedly attenuates brain magnetic resonance imaging (MRI) measures of inflammation and tissue destruction in subjects with relapsing forms of MS. Moreover, the data indicate that efficacy is realized early and persists throughout the treatment period.

4.4. Benefit-Risk Assessment

After more than 10 years of postmarketing experience, natalizumab continues to demonstrate a high level of efficacy with a well-characterized safety profile and a significant beneficial impact on the quality of life in patients with RRMS. In pivotal clinical studies, natalizumab demonstrated a 67% reduction in annualized relapse rate and a 42% reduction in the risk of disability progression over 2 years. Since the marketing of natalizumab, publications from multiple independent groups, as well as publications from the Sponsor, have further demonstrated the clinical effectiveness of natalizumab when used in patients with MS with high disease activity despite treatment with first-line therapies [Belachew 2011; Morrow 2010; Oturai 2009; Sangalli 2011].

Extensive safety data from clinical studies and the postmarketing setting have resulted in a well-characterized safety profile for natalizumab. Infusion and hypersensitivity reactions and anti-natalizumab antibody production are important safety concerns; however, they are manageable in routine clinical practice. Serious herpes infections and hepatic events are additional safety concerns that are also included in product labeling; however, the incidence of these adverse events (AEs) is low.

The most important AE affecting natalizumab benefit-risk assessment is the occurrence of progressive multifocal leukoencephalopathy (PML). Three established risk factors for the development of PML have been identified and are currently included in the product labeling: that PML risk is increased with the presence of anti-John Cunningham virus (JCV) antibodies, treatment duration (especially beyond 2 years of therapy), and prior use of an immunosuppressant therapy. These 3 risk factors, as well as information about anti-JCV antibody index in anti-JCV antibody-positive patients without any prior immunosuppressant use, can be utilized to further stratify the risk of PML and therefore provide an important tool for physicians and patients when making individual benefit-risk decisions regarding initiation or continuation of natalizumab therapy.

Overall, the benefit-risk ratio for natalizumab in treating RRMS remains positive.

4.5. Study Rationale

The safety and efficacy of the currently recommended dose (300 mg natalizumab administered intravenously [IV] every 4 weeks [Q4W]) has been well established through clinical trials and in real-world clinical practice.

Extending the dosing interval of natalizumab (e.g., to every 6 weeks [Q6W]) has been practiced by some physicians in anti-JCV antibody-positive patients with the intention of improving the benefit/risk of the treatment by reducing the exposure-dependent risk of PML while maintaining efficacy. In a prespecified, retrospective analysis of anti-JCV antibody-positive patients treated with natalizumab in the US TOUCH (Tysabri® Outreach: United Commitment to Health) program (n = 18,755), the risk of PML was compared between patients treated with standard interval dosing (SID) and patients treated with extended interval dosing (EID) for at least 6 months (300 mg with an average dosing interval of 5 to 6 weeks). The majority of patients were treated with SID for at least 1 year before switching to EID (median of 25 SID infusions prior to switch). The analysis demonstrated a clinically and statistically significant reduction in the risk of PML in patients treated with EID. Whether extending the dosing interval of natalizumab can potentially improve benefit/risk for some patients remains to be established as there are no prospective, randomized, controlled studies assessing efficacy of EID.

This study will be conducted in 2 parts: Part 1 is a randomized, controlled, rater-blinded, analysis designed to assess the efficacy, safety, and tolerability of switching to EID (Q6W dosing) after at least 12 months of disease stability on SID (Q4W dosing);Part 2 is a randomized open-label extension (OLE) designed to assess preference for SC natalizumab EID treatment and explore long-term efficacy, safety, and tolerability of EID.

5. SCHEDULE OF ACTIVITIES

5.1. Part 1 – Schedule of Activities

Please note that SID and EID schedule of activities (Table 1 and Table 2, respectively) differ only with respect to natalizumab administration throughout the study [redacted]. These differences are highlighted in gray in the schedules that follow.

Table 1: Part 1 Schedule of Activities – SID

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted], 2) clinical and neurological assessments, [redacted], and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit.

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call 96[3]**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
Informed Consent Form	X																							
Eligibility Criteria Check	X	X																						
Randomization		X																						
Medical History	X																							
Physical Examination	X	X[6]						X						X						X	X		X	X
Body Weight	X	X[6]						X						X						X	X		X	X
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HIV, Hep B, and Hep C Testing	X																							
[redacted]																								

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call 96[3]**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																								
C-SSRS[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
[redacted]																								
EDSS	X							X						X						X	X		X	X
Neurological Examination (MS Signs & Symptoms)	X							X						X						X	X		X	X
Blood Hematology[9]	X							X						X						X	X			X
Blood Chemistry[10]	X																				X			X
Serum Pregnancy Test[11]	X																							
Serum FSH[12]	X																							
Urine Pregnancy Test[13]		X																						
[redacted]																								

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call 96[3]**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																								
Brain MRI[15]	X							X						X						X			X	X
Natalizumab Administration (SID)[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
AEs		Record as per Section 15.3 of the protocol																						
SAEs	Record as per Section 15.3 of the protocol																							
Concomitant Therapy and Procedures		Record as per Section 11.5 of the protocol																						

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call 96[3]**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
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Assessment of New Neurological Symptoms[17]																								X

[redacted], AE = adverse event; [redacted]; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; EDSS = Expanded Disability Status Scale; EOS = end of study; [redacted]; ET = early termination; FSH = follicle-stimulating hormone; Gd = gadolinium; Hep = hepatitis; HIV = human immunodeficiency virus; [redacted]; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; PML = progressive multifocal leukoencephalopathy; SAE = serious adverse event; [redacted]; SID = standard interval dosing; [redacted]

1 Informed consent can be obtained any time between Day -42 and the day of the last prestudy dose of natalizumab. The last prestudy dose of natalizumab must occur between Days -33 and -26 from the baseline visit. Some screening assessments must be performed immediately prior to the last prestudy dose of natalizumab (see footnote 9). All other screening assessments can occur any time between the day of the last prestudy natalizumab dose and baseline.

2 Week 72 will be the last Part 1 visit for subjects who enroll in Part 2; those subjects will then follow the Part 2 visit schedule in Section 5.2, Table 3.

3 Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.

4 If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12 weeks (± 10 days) and the follow-up safety phone call at 24 weeks after the final dose of study treatment.

5 Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours pf the onset of symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit). The samples will be named NW1 and NW2.

6 If a screening test is performed within 72 hours of the Baseline Visit, the assessment does not have to be repeated at Baseline.

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

8 The "baseline/screening" C-SSRS must be completed at the Screening Visit; at all other visits, the "since last visit" C-SSRS must be used.

[9] Sample to be collected prior to dosing.

[10] If a subject experiences signs and symptoms suggestive of liver injury (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.

[11] Required for women of childbearing potential. Results must be known prior to Day 0/Baseline.

[12] For postmenopausal subjects only.

[13] Required for women of childbearing potential. Follow-up testing throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (over 1 month between menstrual periods), a urine pregnancy test should be performed.

[redacted]

[15] The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs, with the exception of the one conducted at the Neurological Worsening and Relapse Assessment, are to be completed within a 7-day window of the dosing visit. MRIs conducted at the Neurological Worsening and Relapse Assessment must be completed prior to dosing with rescue therapy, but can be completed on the same day. If a subject's MRI is scheduled to occur <4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so that it is performed either before the steroid treatment of between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early study termination for a pregnancy, a Gd-enhancing MRI should not be conducted.

[16] Please refer to the Directions for Handling and Administration (DHA) located in the Study Reference Guide for details of postdose observation requirements.

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

Table 2: Part 1 Schedule of Activities – EID

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted], 2) clinical and neurological assessments, [redacted], and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit.

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[3] 96**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**42 (-2/ +5)**	**84 (-2/ +5)**	**126 (-2/ +5)**	**168 (-2/ +5)**	**210 (-2/ +5)**	**252 (-2/ +5)**	**294 (-2/ +5)**	**336 (-2/ +5)**	**378 (-2/ +5)**	**420 (-2/ +5)**	**462 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
Informed Consent Form	X																	
Eligibility Criteria Check	X	X																
Randomization		X																
Medical History	X																	
Physical Examination	X	X[6]				X				X				X	X		X	X
Body Weight	X	X[6]				X				X				X	X		X	X
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HIV, Hep B, and Hep C Testing	X																	
[redacted]																		
C-SSRS[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[3] 96**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**42 (-2/ +5)**	**84 (-2/ +5)**	**126 (-2/ +5)**	**168 (-2/ +5)**	**210 (-2/ +5)**	**252 (-2/ +5)**	**294 (-2/ +5)**	**336 (-2/ +5)**	**378 (-2/ +5)**	**420 (-2/ +5)**	**462 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																		
EDSS	X					X				X				X	X		X	X
Neurological Examination (MS Signs & Symptoms)	X					X				X				X	X		X	X
Blood Hematology[9]	X					X				X				X	X			X
Blood Chemistry[10]	X														X			X
Serum Pregnancy Test[11]	X																	
Serum FSH[12]	X																	
Urine Pregnancy Test[13]		X																
[redacted]																		

Study Week	**Screening Visit[1] -6 to -1**	**Baseline Visit 0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72[2]**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[3] 96**	**ET Visit[4]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]**
Study Day	**-42 to -1**	**0**	**42 (-2/ +5)**	**84 (-2/ +5)**	**126 (-2/ +5)**	**168 (-2/ +5)**	**210 (-2/ +5)**	**252 (-2/ +5)**	**294 (-2/ +5)**	**336 (-2/ +5)**	**378 (-2/ +5)**	**420 (-2/ +5)**	**462 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																		
Brain MRI[15]	X					X				X				X			X	X
Natalizumab Administration (EID)[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
AEs		Record as per Section 15.3 of the protocol																
SAEs	Record as per Section 15.3 of the protocol																	
Concomitant Therapy and Procedures		Record as per Section 11.5 of the protocol																
Assessment of New Neurological Symptoms[17]																		X

[redacted], AE = adverse event; [redacted]; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; EDSS = Expanded Disability Status Scale; EID = extended interval dosing; EOS = end of study; [redacted]; ET = early termination; FSH = follicle-stimulating hormone; Gd = gadolinium; Hep = hepatitis; HIV = human immunodeficiency virus; [redacted]; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; PML = progressive multifocal leukoencephalopathy; [redacted]; SID = standard interval dosing; [redacted].

1 Informed consent can be obtained anytime between Day -42 and the day of the last prestudy dose of natalizumab. The last prestudy dose of natalizumab must occur between Days -33 and -26 from the baseline visit. Some screening assessments must be performed immediately prior to the last prestudy dose of natalizumab (see footnote 9). All other screening assessments can occur anytime between the day of last prestudy natalizumab dose and baseline.

2 Week 72 will be the last Part 1 visit for subjects who enroll in Part 2; those subjects will then follow the Part 2 visit schedule in Section 5.2,Table 3 .

[3] Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.

[4] If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12 weeks (± 10 days) and the follow-up safety phone call at 24 weeks after the final dose of study treatment.

[5] Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of the symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit). The samples will be named NW1 and NW2.

[6] If a screening test is performed within 7 days of the Baseline Visit, the assessment does not need to be repeated at Baseline.

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

[8] The "baseline/screening" C-SSRS must be completed at the Screening Visit; at all other visits, the "since last visit" C-SSRS must be used.

[9] Sample to be collected prior to dosing.

[10] If a subject experiences signs and symptoms suggestive of liver injury (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.

[11] Required for women of childbearing potential. Results must be known prior to Day 0/Baseline.

[12] For postmenopausal subjects only.

[13] Required for women of childbearing potential. Follow-up testing throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (over 1 month between menstrual periods), a urine pregnancy test should be performed.

[R] [redacted]

[15] The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs, with the exception of the one conducted at the Neurological Worsening and Relapse Assessment, are to be completed within a 7-day window of the dosing visit. MRIs conducted at the Neurological Worsening and Relapse Assessment must be completed prior to dosing with rescue therapy, but can be completed on the same day. If a subject's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the previous MRI was performed within the previous 4 weeks. In the event of an early study termination for a pregnancy, a Gd-enhancing MRI should not be conducted.

[16] Subjects are to continue with their natalizumab SID until they have received their baseline dose. Please refer to the DHA located in the Study Reference Guide for details of postdose observation requirements.

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

5.2. Part 2 – Schedule of Activities

For subjects who completed Part 1 treatment and enrolled in Part 2, the schedule of activities for Part 2 (Table 3) does not differ for subjects randomized to SC/IV or IV/SC with the exception of the order of treatment administration during the crossover period.

For new subjects enrolled in Part 2, the initial screening, inclusive of select assessments, differs from those subjects who participated in Part 1 but is otherwise the same beginning at Week 78 through the end of Part 2 (Table 4).

Table 3: Part 2 Schedule of Activities – EID SC vs. IV OLE for Subjects Who Participated in Part 1

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted], 2) clinical and neurological assessments, 3) PK/PD [redacted] collection, and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit.

Study Week	**78**	**84**[1]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[2]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[3]	**Follow-Up Safety Phone Call 180**[4]
Study Day	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
Informed Consent Form for Part 2[5]	---- X ----																	
Eligibility Criteria Check for Part 2[5]	---- X ----																	
Randomization						X												
Vital signs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[1]		X				X				X				X	X	X	X	
Body Weight[1]		X				X				X				X				
C-SSRS[1,7]		X																
[redacted]																		
TSQM						X				X				X				
[redacted]																		

Study Week	**78**	**84**[1]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[2]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[3]	**Follow-Up Safety Phone Call 180**[4]
Study Day	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
EDSS		X				X				X				X		X	X	
Neurological Examination (MS Signs & Symptoms)		X				X				X				X		X	X	
Blood Hematology[8]		X				X				X				X	X	X	X	
Blood Chemistry[9]		X													X	X	X	
Urine Pregnancy Test[10]																		
PD Assessments (whole blood)[8]				X		X	X	X	X	X	X	X	X	X				
PK Natalizumab Concentration (serum)[8]				X		X	X	X	X	X	X	X	X	X				
Anti-natalizumab Antibodies[8]						X		X		X		X		X			X	
[redacted]																		
Brain MRI[11]						X				X				X		X		

Study Week	**78**	**84**[1]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[2]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[3]	**Follow-Up Safety Phone Call 180**[4]
Study Day	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
Natalizumab EID IV infusion	X	X	X	X	X									X				
Natalizumab EID SC-IV Crossover[12]						X	X	X	X	X	X	X	X	X[13]				
PPQ[14]											X		X			X		
Safety (AEs, SAEs)	Record as per Section 15.3 of the protocol																	
Concomitant Therapy and Procedures	Record as per Section 11.5 of the protocol																	X

AE = adverse event; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; EDSS = Expanded Disability Status Scale; EID = extended interval dosing; EOS = end of study; [redacted]; ET = early termination; Gd = gadolinium; IV=intravenous; [redacted]; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; SAE = serious adverse event; SC = subcutaneous; TSQM = Treatment Satisfaction Questionnaire for Medication.

1 The Part 1 and Part 2 assessments at Week 84 are the same and should be performed only once.

2 If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12weeks (± 10 days) and the follow-up safety phone call at 24 weeks after the last dose of study treatment.

3 Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of the symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit).

4 Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.

5 The Part 2 informed consent and eligibility assessment should be performed during Week 72 of Part 1 if possible. In the event that this cannot be performed at that time, informed consent and eligibility assessment should be conducted prior to the subject starting Part 2 at the Week 78 or Week 84 visit. Randomization

to crossover study treatment should be done at the Week 108 visit to confirm crossover treatment allocation. After Week 84, subjects are not eligible for enrollment in Part 2 of the study.

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

[7] The Part 1 "baseline/screening" C-SSRS must be completed at the Part 1 screening Visit; at all other visits, the "since last visit" C-SSRS must be used.

[8] Sample to be collected prior to dosing.

[9] If a subject experiences signs and symptoms suggestive of liver failure (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.

[10] Follow-up testing for women of childbearing potential throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (more than 1 month between menstrual periods), a urine pregnancy test should be performed.

[11] All postbaseline MRIs are to be completed within a 7-day window of the dosing visit. If a subject's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early termination for a pregnancy, a Gd-enhancing MRI should not be conducted.

[12] The time required for drug preparation and drug administration should be recorded in detail for each occasion of treatment administration during the crossover period. Please refer to the DHA located in the Study Reference Guide for details of postdose observation requirements.

[13] Subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at the Week 156 visit with the route of administration being the subject’s choice.

[14] PPQ assessments at Week 138 and Week 150 must be collected after study treatment administration.

Table 4: Part 2 Schedule of Activities – EID SC vs. IV OLE for New Subjects

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted], 2) clinical and neurological assessments, 3) PK/PD [redacted] collection, and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit. This Schedule of Activities is identical to the Schedule in Table 3 after the Week 84 visit.

Nominal Study Week	**Screen**[1]	**Baseline Visit 72**	**78**	**84**[2]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[3]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[4]	**Follow-Up Safety Phone Call**[5] **180**
Nominal Study Day	**-42 to -1**	**504 (-2/ +5)**	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
Informed Consent Form for Part 2[1]	X																			
Eligibility Criteria Check for Part 2[1]	X	X																		
Randomization								X												
Medical History[1]	X																			
Physical Examination[1]	X	X		X				X				X				X	X	X	X	
Body Weight[1]	X	X		X				X				X				X				
Vital signs[6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, Hep B, and Hep C Testing	X																			
TSQM		X						X				X				X				

Nominal Study Week	**Screen**[1]	**Baseline Visit 72**	**78**	**84**[2]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[3]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[4]	**Follow-Up Safety Phone Call**[5] **180**
Nominal Study Day	**-42 to -1**	**504 (-2/ +5)**	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
[redacted]																				
EDSS	X			X				X				X				X		X	X	
Neurological Examination (MS Signs & Symptoms)	X			X				X				X				X		X	X	
Blood Hematology[7]	X			X				X				X				X	X	X	X	
Blood Chemistry[8,7]	X			X													X	X	X	
Serum Pregnancy Test[9]	X																			
Serum FSH[10]	X																			
Urine Pregnancy Test[11]		X																		
PD Assessments (whole blood)[7]		X				X		X	X	X	X	X	X	X	X	X				
PK Natalizumab Concentration (serum)[7]		X				X		X	X	X	X	X	X	X	X	X				

Nominal Study Week	**Screen**[1]	**Baseline Visit 72**	**78**	**84**[2]	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-Up EOS Visit 168**	**ET Visit**[3]	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)**[4]	**Follow-Up Safety Phone Call**[5] **180**
Nominal Study Day	**-42 to -1**	**504 (-2/ +5)**	**546** (-2/ +5)	**588** (-2/ +5)	**630** (-2/ +5)	**672** (-2/ +5)	**714** (-2/ +5)	**756** (-2/ +5)	**798** (-2/ +5)	**840** (-2/ +5)	**882** (-2/ +5)	**924** (-2/ +5)	**966** (-2/ +5)	**1008** (-2/ +5)	**1050** (-2/ +5)	**1092** (-2/ +5)	**1176** (±10)	-	-	**1260** (±10)
Anti-natalizumab Antibodies[7]	X							X		X		X		X		X			X	
[redacted]																				
Brain MRI[12]	X							X				X				X		X		
Natalizumab EID IV infusion		X	X	X	X	X	X									X				
Natalizumab EID SC-IV Crossover[13]								X	X	X	X	X	X	X	X	X[14]				
PPQ[15]													X		X			X		
Safety (AEs, SAEs)		Record as per Section 15.3 of the protocol																		
Concomitant Therapy and Procedures			Record as per Section 11.5 of the protocol																	X
Assessment of New Neurological Symptoms[16]																				X

AE = adverse event; CRF = case report form; EDSS = Expanded Disability Status Scale; EID = extended interval dosing; EOS = end of study; [redacted]; ET = early termination; FSH = follicle stimulating hormone; Gd = gadolinium; Hep = hepatitis; HIV = human immunodeficiency virus;

IV=intravenous; [redacted]; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; SAE = serious adverse event; SC = subcutaneous; TSQM = Treatment Satisfaction Questionnaire for Medication.

[1] Informed consent can be obtained any time between Day -42 and the day of the last prestudy dose of natalizumab. The last prestudy dose of natalizumab must occur between Days -33 and -26 from the baseline visit. Some screening assessments must be performed immediately prior to the last prestudy dose of natalizumab (see footnote 7). All other screening assessments can occur any time between the day of the last prestudy natalizumab dose and baseline. Randomization to crossover study treatment should be done at the Week 108 visit to confirm crossover treatment allocation.

[2] The Part 1 and Part 2 assessments at Week 84 are the same and should be performed only once.

[3] If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12 weeks (± 10 days) and the follow-up safety phone call at 24 weeks after the last dose of study treatment.

[4] Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit).

[5] Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.

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

[7] Sample to be collected prior to dosing.

[8] If a subject experiences signs and symptoms suggestive of liver failure (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.

[9] Required for women of childbearing potential. Results must be known prior to Baseline.

[10] For postmenopausal subjects only.

[11] Follow-up testing for women of childbearing potential throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (more than 1 month between menstrual periods), a urine pregnancy test should be performed.

[12] The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs are to be completed within a 7-day window of the dosing visit. If a subject's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early termination for a pregnancy, a Gd-enhancing MRI should not be conducted.

[13] The time required for drug preparation and drug administration should be recorded in detail for each occasion of treatment administration during the crossover period. Please refer to the DHA located in the Study Reference Guide for details of postdose observation requirements.

[14] Subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at the Week 156 visit with the route of administration being the subject's choice.

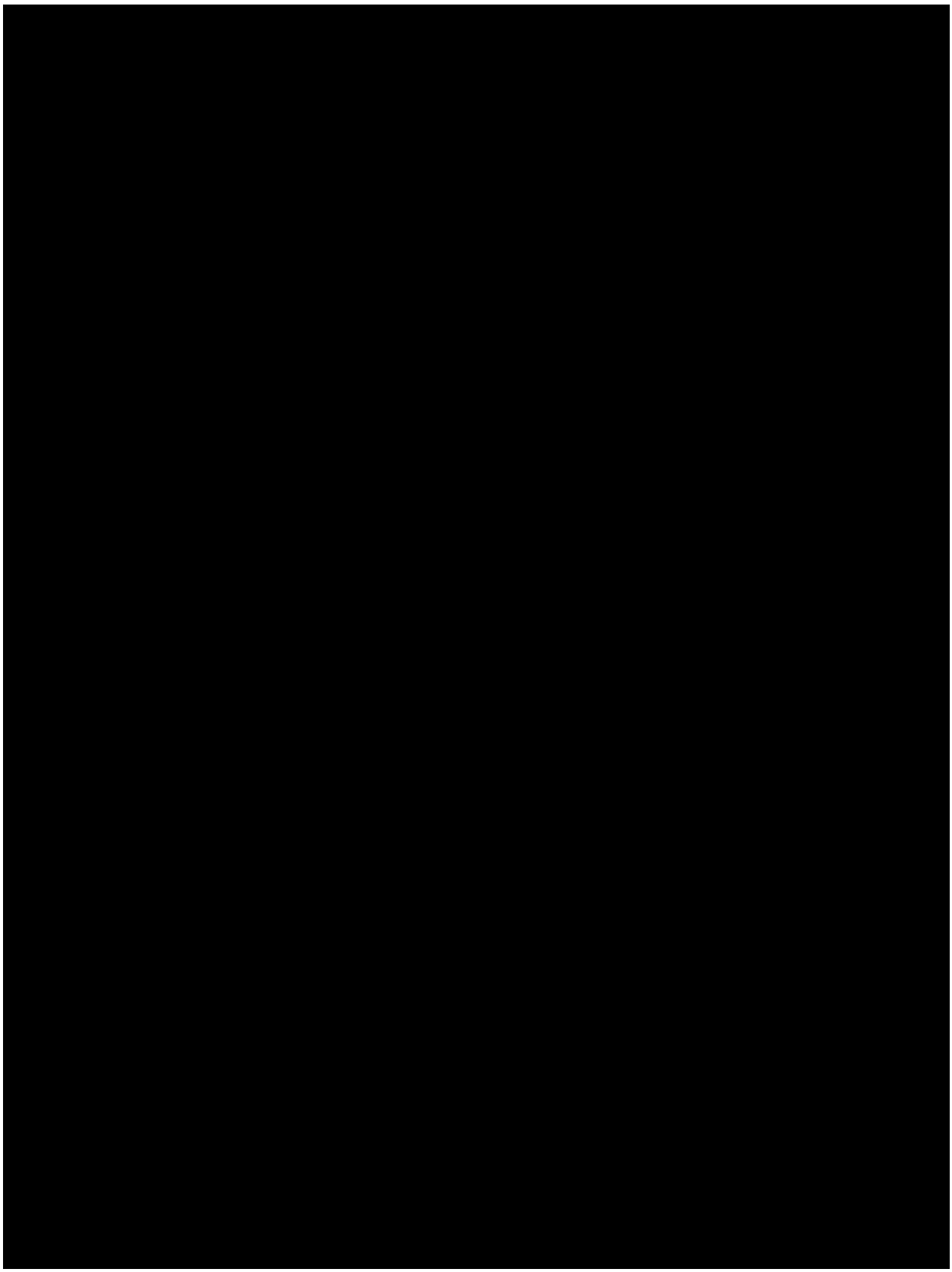
[15] PPQ assessments at Week 138 and Week 150 must be collected after study treatment administration.

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

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Part 1 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment, with the goal of estimating the difference between SID and EID, with high precision and a narrow 95% confidence interval (CI), to support the treatment decision based on individualized benefit/risk assessments.	The number of new or newly enlarging T2 hyperintense lesions at Week 72
Secondary Objectives	**Secondary Endpoints**
To evaluate additional relapse-based clinical efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	• Time to first relapse (relapses will be adjudicated by an Independent Neurology Evaluation Committee [INEC]) • Annualized relapse rate at Week 72
To evaluate disability worsening of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	• Time to Expanded Disability Status Scale (EDSS) worsening (confirmed after at least 24 weeks)
To evaluate additional MRI-lesion efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	• Number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 • Number of new gadolinium (Gd)-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72
To evaluate the safety of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months in relation to continued SID treatment.	Safety assessments of AEs and serious adverse events (SAEs)



This clinical study collects samples that may be used for future scientific and genetic research. Objectives related to this future research have not been determined.

6.2. Part 2 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate subject preference for SC versus IV route of natalizumab administration.	• Proportion of subjects indicating a preference for natalizumab SC administration at the end of Part 2
Secondary Objectives	**Secondary Endpoints**
To evaluate treatment satisfaction with SC versus IV route of administration.	• Total score on Treatment Satisfaction Questionnaire for Medication (TSQM)

To evaluate drug preparation and administration time between SC and IV routes of natalizumab administration.	• Mean time for drug preparation and administration.
To evaluate the safety and immunogenicity of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • The proportion of subjects with treatment emergent AEs • The proportion of subjects who develop anti-natalizumab antibodies
To evaluate the efficacy of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • Number of new or newly enlarging T2 hyperintense lesions • Time to first relapse • Annualized relapse rate • Change in EDSS score • Number of new Gd-enhancing lesions • Number of new T1 hypointense lesions • PBVC and change in cortical and thalamic brain region volume
To characterize PK and PD of SC versus IV routes of natalizumab administration.	All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period. • C_{trough} • Trough α4 integrin saturation
[redacted]	

7. STUDY DESIGN

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

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

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

At the completion of their 72-week treatment period, subjects in Part 1 who cannot participate, or elect not to participate, in Part 2 will enter a 12-week follow-up period, and will receive a follow-up safety phone call 12 weeks later (i.e., 24 weeks after the last dose of study treatment) before completing the study.

Part 2 is a 108-week OLE for approximately 200 subjects at approximately 45 sites in Canada, the United Kingdom, Europe, Israel, and Australia who complete their randomized treatment in Part 1, provide consent, and are eligible to participate immediately following completion of the 72-week treatment period.

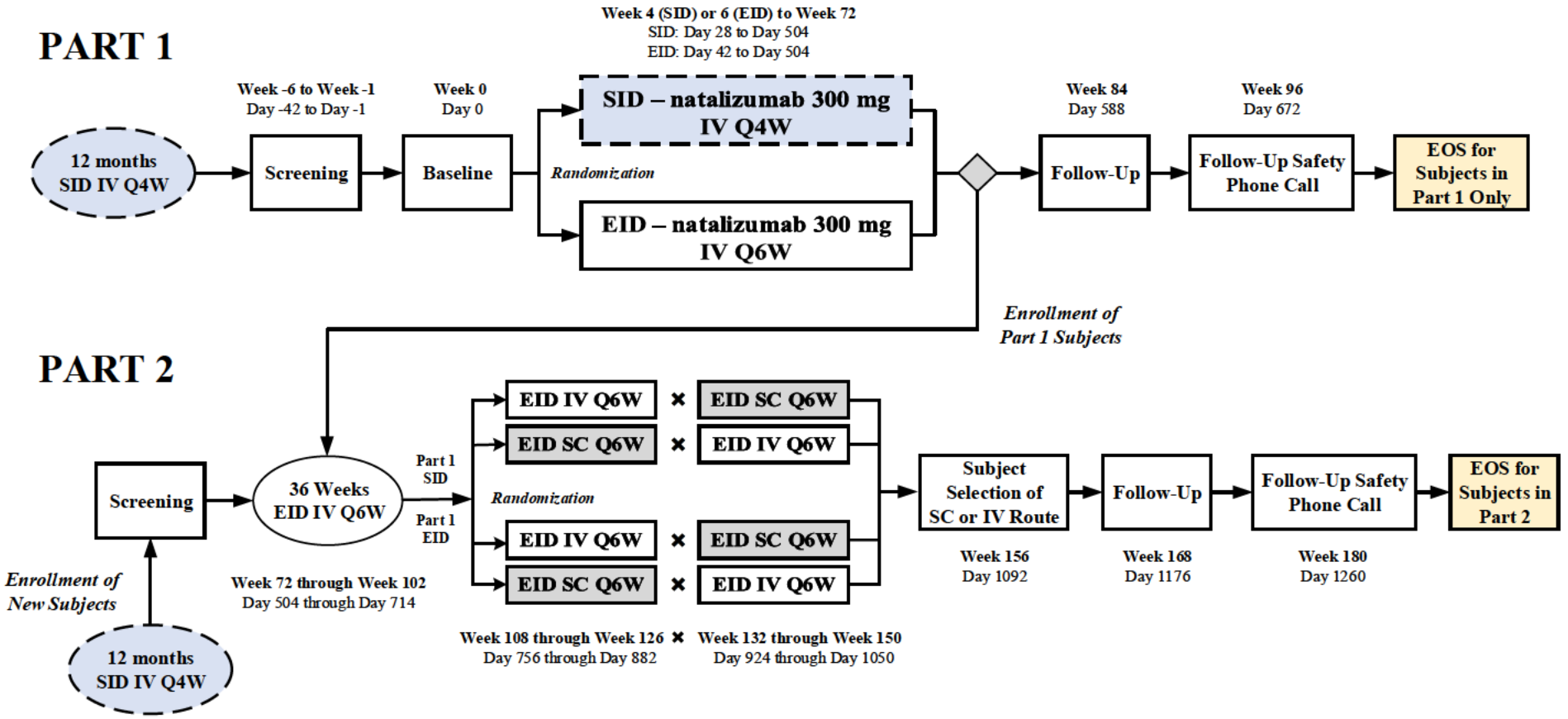
Subjects who did not participate in Part 1 but provide consent and satisfy the inclusion-exclusion and eligibility requirements of Part 1, including treatment with natalizumab SID for at least 12 months without relapses in the last 12 months, may also be enrolled in Part 2 as new subjects to ensure adequate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

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

At the completion of their 48-week crossover treatment period, subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at Week 156 with the route of administration being the subject's choice, proceed to the 12-week follow-up period, and receive a follow-up safety phone call 12 weeks later (i.e., 24 weeks after the last dose of study treatment) before completing the study.

The design of this study, inclusive of Parts 1 and 2, is presented in Figure 1.

Figure 1: Design for Study 101MS329 with Open-Label Extension



7.1. Study Duration for Subjects

7.1.1. Study Duration for Subjects Enrolled Only in Part 1

The total duration of study participation in Part 1 for subjects who do not participate in Part 2 will be up to 102 weeks. This comprises a screening period of up to 6 weeks; a treatment period of 72 weeks; a follow-up period of 12 weeks; and a follow-up safety phone call 12 weeks after the follow-up period (i.e., 24 weeks after the last dose of study treatment).

The end of study (EOS) date for a subject in Part 1 may be the last study visit, the follow-up safety phone call, or last protocol-specified assessment; if the subject has ongoing AEs that are being followed, then the date may be the date of AE resolution.

7.1.2. Study Duration for Subjects Enrolled in Part 1 and Part 2

The total duration of study participation in Part 1 for subjects who also participate in Part 2 will be up to 78 weeks, comprising a screening period of up to 6 weeks and the randomized SID or EID treatment period of 72 weeks.

The total duration of study participation in Part 2 for these subjects will be approximately 108 weeks. This comprises EID IV treatment for 36 weeks; a randomized EID SC vs. EID IV crossover treatment period of 48 weeks; a follow-up period of 12 weeks; and a follow-up safety phone call 12 weeks after the follow-up period (i.e., 24 weeks after the last dose of study treatment). The total duration of study participation for subjects who participate in both Part 1 and Part 2 will be approximately 186 weeks.

The EOS date for subjects participating in Part 1 and Part 2 may be the last study visit, the follow-up safety phone call, or last protocol-specified assessment; if the subject has ongoing AEs that are being followed, then the date may be the date of AE resolution.

7.2. Responsibilities of Study Site Staff

7.2.1. General Staff Responsibilities During Part 1 and Part 2

For each subject in Part 1 and Part 2, the Investigator of the study site will designate the following study site staff:

- A primary and backup unblinded *treating neurologist*
- An unblinded *treating nurse* (or study coordinator; may be performed by treating neurologist)
- A primary and backup blinded *examining neurologist*
- A blinded *examining technician* (may be performed by blinded examining neurologist) *(see Section 7.2.2 for changes in Part 2)*
- An unblinded *MRI technician*
- An unblinded *pharmacist* (or unblinded authorized designee)

Both the *examining neurologist* and the *treating neurologist* must have a minimum of 2 years of neurology specialty training and, at study initiation, do not anticipate leaving the study within at least 1 year. Where specified, evaluations described in this section must be performed only by the personnel indicated. Treating neurologists may review neurological examination results obtained by examining neurologists. The *examining neurologist* and *examining technician* should not administer study treatment.

The primary *treating neurologist* will be responsible for the following:

- Management of the routine neurological care of the subject, including the physical examination, management of treatment, and associated safety monitoring.
- Assessment (including assignment of causality) and treatment of AEs, SAEs, and MS relapses.
- Assessing whether the subject's study treatment should be discontinued as per the criteria detailed in Section 10.
- The treating neurologist may designate the backup treating neurologist or the treating nurse at the study site to perform some of the tests and evaluations listed under "treating neurologist." If there is more than 1 treating neurologist available at a given study site such that each one is assigned to particular subjects, then these treating neurologists may act as backup for each other.
- Review of hematology and blood chemistry data from the central laboratory to aid in the management of the subject. As with other laboratory and clinical information, these data should NOT be reviewed by the examining neurologist, the backup examining neurologist, or the examining technician.

The primary *treating nurse* (or study coordinator; may be performed by treating neurologist) will be responsible for the following:

- Assisting the treating neurologist in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs/SAEs and concomitant medications.
- Administering the PROs (TSQM, [redacted]
- Collecting blood samples.
- Obtaining vital signs.

The *examining neurologist* will be responsible for the following:

- Obtaining an EDSS score and MS signs and symptoms based on a detailed neurological examination at the scheduled timepoints required in the protocol.
- Obtaining an EDSS score at every unscheduled Neurological Worsening and Relapse Assessment Visit, if referred by the treating neurologist when there is the possibility of a relapse.
- The following guidelines must be strictly followed:

- The examining neurologist must not be involved with any other aspect of subject care and management. Furthermore, the examining neurologist is not to serve as treating neurologist for any subjects at a given study site.
- The examining neurologist must remain blinded to AEs, concomitant medications, laboratory data, MRI scan/data, and any other data that have the potential of revealing the treatment assignment.
- To ensure consistency across study sites, examining neurologists and the backup examining neurologist must receive standardized training and obtain certification of EDSS scoring prior to enrollment of subjects at their study site.
- The backup examining neurologist will conduct subject evaluations ONLY if the primary examining neurologist is unavailable due to illness, vacation, or travel. All study sites should attempt to maintain the same examining neurologist throughout the study.
- If an examining neurologist has to be replaced, the new examining neurologist must receive standardized training and obtain certification of EDSS scoring prior to performing an EDSS assessment.
- The communication of new findings on the neurological examination from the examining neurologist to the treating neurologist is permitted (because findings on the neurological examination may be important in the routine care of the subject, e.g., medical management of relapses).
- The roles of the treating and examining neurologists (primary and backup) are NOT interchangeable even for different subjects.
- The examining neurologist may also act as the examining technician (see below).
- After receiving approval from the Biogen Medical Director or designee, nurse practitioners or physician assistants who have at least 2 years of practice experience in a neurology clinic and have prior experience and certification in EDSS scoring may function as examining neurologists in this study.

The *examining technician* (or the examining neurologist) will be responsible for the following:

- [redacted]
- The following guidelines must be strictly followed:
  - The examining technician must remain blinded to AEs, concomitant medications, laboratory data, MRI scan/data, and any other data that have the potential of revealing the treatment assignment.
  - To ensure consistency across study sites, examining technicians must undergo a standardized training session prior to enrollment of subjects at their study site.
  - All study sites should attempt to maintain the same examining technician throughout the study.

- If an examining technician has to be replaced, the new examining technician must undergo a training session prior to performing any study assessment.

The *MRI technician* will be responsible for the following:

- Performing a brain MRI scan with and without contrast, in accordance with the study-specific MRI manual, at all protocol-required timepoints.

The unblinded *pharmacist* (or unblinded authorized designee) will be responsible for the following:

- Receipt, storage, distribution, and accountability of study treatment.
- Storage and security of documentation related to study treatment, dose preparation, and study treatment assignment. All treatment assignment or study treatment preparation information must be maintained strictly confidential from the examining neurologist and examining technician at all times. Measures to prevent inadvertent unblinding must be followed.
- Preparation of study treatments for IV infusion.

7.2.2. Changes in Responsibilities During Part 2

The role of examining technician is no longer required in Part 2. The blinded examining technician will need to remain blinded until the Week 84 visit has been completed for all subjects who enrolled in Part 1, all queries have been addressed, and protection of the associated database secured. The Sponsor will confirm when the blinded examining technician can be unblinded. The primary and backup blinded examining neurologist along with the central MRI rater will remain blinded throughout the study. All other roles as presented in Section 7.2.1 will remain unchanged in Part 2.

7.3. Unscheduled Visits and Treatment for MS Relapses

If an MS relapse is suspected during the study, the subject should return to the study site for an unscheduled visit and be evaluated as soon as possible (within 5 days after onset of the event) for confirmation and to determine the severity of the relapse. Relapses will be documented in the relapse assessment form.

An MS relapse will be defined as the onset of new or recurrent neurological symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological examination, and not explained solely by non-MS processes such as fever, infection, severe stress, or drug toxicity (adapted from [Schumacher 1965]).

The Unscheduled Visit for Neurological Worsening and Relapse Assessment should not modify or replace the subjects' visit schedule. If a subject's study MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so that it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the previous MRI was performed within the previous 4 weeks.

New or recurrent neurological symptoms that occur < 30 days following the onset of a protocol-defined relapse should be considered as part of the same relapse. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse, and should not be treated with high-dose corticosteroids. Laboratory tests to investigate possible causes of pseudorelapse can be done at the discretion of the Investigator.

7.3.1. Unscheduled Visits in Part 1

In Part 1, an unscheduled visit for a suspected relapse should be recorded at a Neurological Worsening and Relapse Assessment Visit, with the relapse reported on the relapse assessment form and not reported as an AE. A brain MRI should be performed before treatment of a protocol-defined relapse. The potential abnormalities must then be reviewed and confirmed by the INEC for the purposes of confirming the secondary endpoint (see Section 19.2.2). Treatment of a protocol-defined relapse may proceed at the discretion of the Investigator prior to INEC confirmation according to local standard of care and will not affect the subject's eligibility to continue in the study. At the discretion of the Investigator, treatment may include methylprednisolone 1000 mg IV administered daily for 3 to 5 days with or without an oral prednisone taper (up to 15 days).

7.3.2. Unscheduled Visits in Part 2

In Part 2, an unscheduled visit for a suspected relapse should be recorded at a Neurological Worsening and Relapse Assessment Visit with the relapse reported on the relapse assessment form and not reported as an AE. The Investigator is responsible for determining whether a protocol-defined relapse has occurred. After all Part 2 unscheduled visit assessments have been performed, relapse treatment can proceed per local standard of care without INEC review.

7.4. Study Stopping Rules

The study will be stopped if the interim futility analysis shows a statistically significant worsening of efficacy in Part 1 as gauged by new or newly enlarging T2 hyperintense lesions in the EID group relative to the SID group.

Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.5. End of Study

The EOS is defined as the last subject, last visit for final collection of data during the study.

8. SELECTION OF SUBJECTS

8.1. Part 1 Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization, or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Aged 18 to 60 years old, inclusive, at the time of informed consent.
3. Diagnosis of RRMS according to the McDonald criteria [Thompson 2018].
4. Treatment with natalizumab as disease-modifying monotherapy for RRMS that is consistent with the approved dosing for a minimum of 12 months prior to randomization. The subject must have received at least 11 doses of natalizumab in the 12 months prior to randomization with no missed doses in the 3 months prior to randomization.
5. EDSS score ≤ 5.5 at Screening.
6. No relapses in the last 12 months prior to randomization, as determined by the enrolling Investigator.
7. All women of childbearing potential must practice highly effective contraception during the study and for 3 months after their last dose of study treatment. For further details of contraceptive requirements for this study, see Section 15.5.

8.2. Part 1 Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of randomization, or at the timepoint specified in the individual criterion listed:

1. Primary- and secondary-progressive MS.
2. MRI positive for Gd-enhancing lesions at Screening.
3. Subjects for whom MRI is contraindicated (e.g., have a contraindicated pacemaker or other contraindicated implanted metal device, have suffered, or are at risk for, side effects from Gd, or have claustrophobia that cannot be medically managed).
4. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including diabetes), urologic, pulmonary, neurologic (except for RRMS), dermatologic, psychiatric, renal, or other major disease that would preclude participation in a clinical study, in the opinion of the Investigator.
5. History of human immunodeficiency virus or positive test result at Screening, or history of other immunodeficient conditions. The requirement for testing at Screening may be omitted if it is not permitted by local regulations.

6. Known history of hepatitis C (test for hepatitis C virus antibody) or hepatitis B virus (test for hepatitis B surface antigen and/or hepatitis B core antibody).
7. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).
8. History of transplantation or any antirejection therapy.
9. History of severe allergic or anaphylactic reactions or known hypersensitivity to any antibody drug therapy.
10. A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to Screening, or PML or other opportunistic infections at any time.
11. Presence of anti-natalizumab antibodies at Screening.
12. Signs or symptoms suggestive of any serious infection, based on medical history, physical examination, or laboratory testing, as determined by the Investigator.

Treatment History

13. Prior treatment with cladribine, mitoxantrone, T-cell or T-cell receptor vaccination, cyclophosphamide, cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil.
14. Prior treatment with any therapeutic mAb other than natalizumab within 24 months prior to randomization.
15. Prior treatment with total lymphoid irradiation.
16. Prior treatment with IV immunoglobulin, plasmapheresis, or cytapheresis within 12 months prior to randomization.
17. Treatment with IV or oral corticosteroids (topical or inhaled corticosteroids are acceptable) or related products (e.g., Acthar®) within 3 months prior to randomization.

Miscellaneous

18. History of drug or alcohol abuse within 2 years prior to entry, per Investigator judgment.
19. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 30 days (or 5 half-lives of the agent, whichever is longer) prior to the Baseline Visit or at any time during this study.
20. Inability to comply with study requirements.
21. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.
22. Women who are pregnant or breastfeeding, and women intending to become pregnant during the study.

8.3. Part 2 Inclusion Criteria

To be eligible to participate in Part 2, candidates previously enrolled in Part 1 must meet the following eligibility criteria at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject to understand the purpose and risks of the study and provide signed and dated informed consent for Part 2 and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Completed Part 1 Week 72 visit while remaining on their randomized treatment assignment of SID or EID.

8.4. Part 2 Exclusion Criteria

Candidates who completed Part 1 will be excluded from Part 2 entry if any of the following exclusion criteria exist at the timepoint specified in the individual criterion listed:

1. Subject treated with natalizumab EID was reverted to natalizumab SID by choice or as rescue treatment in Part 1.
2. Subject received treatment with any MS disease-modifying therapy other than natalizumab in Part 1 or in the period between Part 1 and Part 2.
3. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including diabetes), urologic, pulmonary, neurologic (except for RRMS), dermatologic, psychiatric, renal, or other major disease that would preclude participation in a clinical study, in the opinion of the Investigator.
4. History of human immunodeficiency virus or history of other immunodeficient conditions.
5. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).
6. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 30 days (or 5 half-lives of the agent, whichever is longer) prior to the Baseline Visit or at any time during this study.
7. Inability to comply with study requirements.
8. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.
9. Women who are pregnant or breastfeeding, and women intending to become pregnant during the study.

8.5. Part 2 Inclusion Criteria for New Subjects

The inclusion criteria for new subjects who did not participate in Part 1 of the study are the same as those for subjects who did participate in Part 1, as presented in Section 8.1.

8.6. Part 2 Exclusion Criteria for New Subjects

The exclusion criteria for new subjects who did not participate in Part 1 of the study are the same as those for subjects who did participate in Part 1, as presented in Section 8.2.

9. SCREENING AND RANDOMIZATION

9.1. Screening

9.1.1. Part 1 Screening

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

Screen failures are defined as subjects who sign the informed consent form (ICF) but are not subsequently randomized. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Subjects who fail screening due to clinically nonsignificant laboratory result(s) or transient infection can be rescreened once, at the discretion of the Investigator.

It is not required that all screening tests and assessments be completed during 1 pretreatment visit; however, some tests and assessments must be completed immediately prior to subjects receiving their last prestudy dose of natalizumab. Other assessments can occur anytime between the subjects receiving their last prestudy dose of natalizumab and baseline (see Section 5).

Participating study sites are required to document all screened candidates initially considered for inclusion in the study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log. A minimal set of screening failure information is required to ensure transparent reporting of screening failure to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any SAEs.

9.1.2. Part 2 Screening

Subjects must provide informed consent before any Part 2 assessments are performed (see Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study. New subjects enrolling in Part 2 of the study should follow all guidance with respect to screening as described in Section 9.1.1. New subjects who fail screening due to a clinically nonsignificant laboratory result(s) or transient infection can be rescreened once at the discretion of the Investigator.

Part 2 Screening Visit will be performed during the Week 72 visit if possible or within 6 weeks prior to Week 78 or Week 84, whichever visit/infusion is the first Part 2 study treatment administration to the subject.

Subjects who meet Part 2 inclusion/exclusion criteria and provide informed consent will be enrolled and will receive their first Part 2 study treatment at Week 78. In the event that a subject

cannot be enrolled at Week 78 for any reason, the subject can enroll up to a maximum of 12 weeks after their Week 72 visit, provided that the subject has continued to receive treatment with natalizumab between the end of Part 1 and the beginning of Part 2.

9.2. Randomization

9.2.1. Part 1 Randomization

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not continue in the study.

Randomization will be performed using interactive response technology (IRT). Subjects will be randomized to receive natalizumab SID or natalizumab EID in a 1:1 ratio. The randomization will be stratified by country/region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia), body weight (≤ 80 kg versus > 80 kg), and duration of natalizumab exposure (≤ 3 years versus > 3 years).

Refer to the Study Reference Guide for details on randomization.

9.2.2. Part 2 Randomization

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

9.3. Blinding Procedures

9.3.1. Part 1 Blinding

The designated examining neurologist, backup examining neurologist, and examining technician will be blinded to treatment assignments; however, the subjects, Investigator, Biogen, and IQVIA will know the subject's treatment assignment. The central MRI rater will remain blinded throughout the study. To maintain the rater blinding, it is imperative that subject treatment assignments, infusion dates, and laboratory data are not shared with the examining neurologist, backup examining neurologist, or examining technician.

9.3.2. Part 2 Blinding

All blinding procedures will be maintained in Part 2 until all Part 1 Week 84 data have been entered, checked, and secured. The Sponsor will notify the sites when the Part 1 examining technician can be unblinded. The examining neurologist, backup examining neurologist, and central MRI rater will remain blinded throughout the study.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.2.
- The subject develops persistent anti-natalizumab antibodies (2 consecutive readings).
- The subject develops PML or another serious opportunistic infection.
- The subject withdraws consent to continue study treatment.
- The subject experiences an AE or SAE that necessitates permanent discontinuation of study treatment.
- The subject experiences hypersensitivity or suspected allergic reaction to study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- At the discretion of the Investigator or Sponsor for noncompliance.

The primary reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF).

In Part 1, subjects who discontinue treatment may remain in the study and continue protocol-required tests and assessments. Of note, subjects who discontinue natalizumab do not need to return for visits at which only vital signs and Columbia Suicide Severity Rating Scale (C-SSRS) assessments are performed. Subjects who discontinue natalizumab should continue visits at 12-week intervals (e.g., Weeks 12, 24, 36, 48, 60, and 72).

If a subject chooses to withdraw from the study, an Early Termination (ET) Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment; in addition, all EOS assessments should be conducted at a separate EOS visit 12 weeks (± 10 days) after the final dose of study treatment is received. A follow-up safety phone call will be performed 24 weeks after the last dose of study treatment.

In Part 2, subjects who discontinue study treatment will be required to withdraw from the study. If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment. In addition, all EOS assessments should be conducted at a separate EOS Visit 12 weeks (± 10 days) after the final dose of study treatment. A follow-up safety phone call will be performed 24 weeks after the last dose of study treatment.

10.2. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the study site for a required study visit:

1. The study site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
2. In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical records.
3. Should the subject continue to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10.3. Withdrawal of Subjects From Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.
- The subject discontinues study treatment in Part 2.

The primary reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects must undergo an ET Visit unless withdrawal is due to death or withdrawal of consent.

Subjects who withdraw from the study may not be replaced.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for natalizumab IV infusion in both Parts 1 and 2 of the study; refer to the DHA for natalizumab SC injection in Part 2 of the study.

11.1.1. Part 1 Regimen

Subjects will continue to receive natalizumab either SID (300 mg IV infusion Q4W) or EID (300 mg IV infusion Q6W) for a period of 72 weeks.

11.1.2. Part 2 Regimen

Subjects will initially receive natalizumab 300 mg IV Q6W beginning on Week 78. During the treatment period beginning on Week 108, subjects will receive natalizumab 300 mg Q6W for 24 weeks by SC injection and natalizumab 300 mg by IV infusion for 24 weeks in a randomized crossover

11.2. Modification of Dose and Treatment Schedule

11.2.1. Modification of Dose

The dosage of natalizumab cannot be modified.

11.2.2. Modification of Treatment Schedule

11.2.2.1. Part 1 Modification of Treatment

If a subject treated with natalizumab EID experiences any of the following conditions, the Investigator will have the option of reverting to natalizumab SID as a rescue treatment. If a subject treated with SID experiences any of the following conditions, the Investigator will have the option of selecting another disease-modifying therapy that is available to the subject per local standard of care. Rescue treatment decisions are to occur within 4 weeks of either the date of MRI that showed the disease activity or confirmation of EDSS score worsening for at least 24 weeks, at the Investigator's discretion:

- Two or more new or enlarging T2 hyperintense lesions of any size, compared with a previous scan performed as part of this study.
- An EDSS worsening compared with previous assessment and confirmed at least 24 weeks after the initial increase meeting any of the following criteria: 1) an increase of ≥ 1.0 in EDSS as compared with previous assessment if previous EDSS was ≤ 5.5 and > 0; or 2) an increase of ≥ 1.5 in EDSS if previous EDSS was 0; or 3) an increase of ≥ 0.5 in EDSS if previous EDSS was ≥ 6.0.
- A clinical relapse with new or recurrent neurological symptoms, not associated with fever or infection, having a minimum duration of 24 hours and any of the following: 1) an increase of ≥ 1 grade in ≥ 2 functional scales of the EDSS; or 2) an increase of

≥ 2 grades in 1 functional scale of the EDSS; or 3) an increase of ≥ 1 in the EDSS if the previous EDSS was ≤ 5.5, or ≥ 0.5 if the previous EDSS was ≥ 6 (an increase of ≥ 1.5 in EDSS if previous EDSS was equal to 0).

Subjects who receive rescue treatment with natalizumab SID should remain in the study and follow the schedule of activities for SID. Subjects who receive rescue treatment different from natalizumab SID may remain in the study and follow the schedule of activities with exception of natalizumab administration. Note, for subjects who experience acute clinical relapse, high dose corticosteroid treatment as per local standard of care (up to 5 days) for relapse treatment may be administered (see Section 7.3).

11.2.2.2. Part 2 Modification of Treatment

In Part 2, there will be no protocol-defined rescue treatment; subjects who discontinue study treatment in Part 2 for any reason will be withdrawn from the study and will be treated as per local standard of care.

11.3. Precautions

Please refer to the DHA located in the Study Reference Guide for details on postdose observation requirements.

11.4. Compliance

All doses of study treatment will be administered by the study site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time of the subject's written consent and the subject's last study visit.

11.5.1.1. Allowed Concomitant Therapy

Concomitant treatment with any of the following is allowed so long as the exclusionary criteria described in Section 8.2 are observed:

- Medications necessary for the treatment of AEs.
- 4-aminopyridine if used per label and maintained on a stable regimen for at least 30 days prior to randomization and throughout the study.
- Medications used to treat MS symptoms such as spasticity, bladder impairment, pain, fatigue, or depression.
- Short courses of high-dose corticosteroids per local standard of care in the treatment of protocol-defined relapse of MS disease (see Section 7.3).
- Corticosteroids that are administered by nonsystemic routes (e.g., topical, inhaled).

- In Part 2 only, corticosteroids administered via systemic routes (e.g., oral, injected, and intravenous) are also allowed.

11.5.1.2. Disallowed Concomitant Therapy

Subjects should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations.

Concomitant treatment with any of the following is not allowed while receiving study treatment, unless as otherwise described in this protocol:

- Any nonstudy treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments. This includes, but is not limited to interferon, glatiramer acetate, dimethyl fumarate, diroximel fumarate, cyclophosphamide, methotrexate, azathioprine, cladribine, mitoxantrone, IV immunoglobulin, mycophenolate mofetil, fingolimod, siponimod, ozanimod, daclizumab, rituximab, ocrelizumab, or any therapeutic mAb.
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- In Part 1 only, systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone, except for protocol-defined treatment of relapses as described in Section 7.3. These therapies are allowed in Part 2 only.

Subjects who receive any of these restricted treatments may be required to discontinue study treatment permanently and may be withdrawn from the study as outlined in Section 10.1.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial culture) performed between the time of the subject's written consent and the subject's last study visit, unless the subject is being followed up for study-related toxicity.

11.5.2.1. Disallowed Concomitant Procedures

Treatment with any of the following concomitant procedures is not allowed while receiving study treatment, unless as otherwise described in this protocol:

- total lymphoid irradiation
- T-cell or T-cell receptor vaccination
- plasmapheresis
- cytapheresis

Subjects who receive treatment with any of these restricted procedures may be required to permanently discontinue study treatment and may be withdrawn from the study as outlined in Section 10.1.

The use of concomitant therapies or procedures defined above must be recorded in the subject's CRF, according to the instructions for CRF completion. AEs related to the administration of these therapies or procedures must be documented in the appropriate CRF.

11.6. Continuation of Treatment

There is no provision to provide study treatment after the study. Natalizumab is available commercially and subjects/Investigators can continue Tysabri treatment via a commercial source. Once subjects have completed the Part 1 or Part 2 treatment period in the study, it is up to the treating physician and subject as to what the most appropriate treatment plan is for that subject per local practice.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatments are for one-time use only; do not use any study treatment remaining in the vial for another subject.

12.1. Natalizumab

Natalizumab is a recombinant, humanized anti-α4 integrin antibody manufactured by Biogen.

Natalizumab for IV infusion is supplied as a liquid in 15 mL vials containing 300 mg of natalizumab per vial and excipient materials (sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, and polysorbate 80).

Natalizumab for SC injection is provided in a 1 mL prefilled syringe containing 150 mg natalizumab and excipient materials (sodium phosphate, sodium chloride, polysorbate 80, pH 6.0); 2 injections in succession are required to administer 300 mg.

The contents of the natalizumab label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date will be stored in the IRT system, and printable assignment reports will be available to study site staff. Study treatment should not be used after the expiration, expiry, or use-by date.

12.1.1. Natalizumab Preparation

The individual preparing natalizumab should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the container closure system or study treatment, do not use the study treatment. The drug product in question should be saved at the study site and the problem immediately reported to Biogen. Information on reporting product issues can be found in the Study Reference Guide, Pharmacy Manual, and DHA.

12.1.2. Natalizumab Storage

Study treatment must be stored in a secure location.

Natalizumab is to be stored at 2°C to 8°C (36°F to 46°F), protected from light, in a monitored and locked refrigerator with limited access. Study treatment is not to be frozen. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Natalizumab Handling and Disposal

The Investigator must return all used and unused natalizumab study treatment as instructed by Biogen unless approved for onsite destruction.

If any natalizumab supplies are to be destroyed at the study site, the institution or appropriate study site staff must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Natalizumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating the dates and amount of study treatment received, to whom study treatment was dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all study treatment both used and unused must be saved for accountability. By the end of the study, reconciliation must be made between the amount of natalizumab supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

13. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 5 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the study site to have the evaluations repeated.

13.1. Clinical Efficacy Assessments

13.1.1. Part 1 Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of natalizumab in Part 1:

MRI Efficacy Assessments

- T2 hyperintense lesion number and volume
- Gd-enhancing lesion number and volume
- T1 hypointense lesion number and volume
- [redacted]

The images will also be stored for future analyses to enable investigation of additional MRI metrics (e.g., gray matter volume, thalamic volume) [redacted].

All MRIs should also be read by the local radiologist in accordance with standard practice and any incidental findings reported to the study site Investigator. Local radiologists must provide MRI scans and/or their standard radiology report to the treating neurologists after each study MRI, in accordance with local practice and regulation. The radiology reports may include a comparison to the prior MRI scan. Locally read MRIs will not be used for endpoint analyses.

Clinical Efficacy Assessments

- Relapses (clinical relapses are assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours; see Section 7.3 for further details)
- Neurological examination and EDSS score
- [redacted]
- [redacted]
- [redacted]

13.1.2. Part 2 Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of natalizumab in Part 2:

MRI Efficacy Assessments

- T2 hyperintense lesion number and volume
- Gd-enhancing lesion number and volume
- T1 hypointense lesion number and volume
- PBVC

The images will also be stored for future analyses to enable investigation of additional MRI metrics (e.g., gray matter volume, thalamic volume) [redacted].

All MRIs should also be read by the local radiologist in accordance with standard practice and any incidental findings reported to the study site Investigator. Local radiologists must provide MRI scans and/or their standard radiology report to the treating neurologists after each study MRI, in accordance with local practice and regulation. The radiology reports may include a comparison to the prior MRI scan. Locally read MRIs will not be used for endpoint analyses.

Clinical Efficacy Assessments

- Relapses (clinical relapses are assessed as defined by new or recurrent neurologic symptoms not associated with fever or infection having a minimum duration of 24 hours; see Section 7.3 for further details)
- Neurological examination and EDSS score
- TSQM, [redacted]

Subject Preference

- Patient Preference Questionnaire (PPQ) for route of administration

13.2. Pharmacokinetic Assessments

C_{trough} will be determined to assess the PK of natalizumab in [redacted] Part 2.

13.3. Pharmacodynamic Assessments

[redacted]

[redacted]

13.3.2. Part 2 Pharmacodynamic Assessments

In Part 2, trough α4 integrin saturation will be assessed to evaluate the PD properties of natalizumab. [redacted]

14. SAFETY ASSESSMENTS

See Section 5 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of natalizumab:

In Part 1 only:

- C-SSRS

In Part 1 and for new subjects in Part 2 only,

- Medical history

In Part 1 and Part 2:

- Physical examination
- Body weight
- Vital sign measurements: temperature, systolic and diastolic blood pressures, pulse rate, and respiratory rate
- Concomitant therapy and procedure recording
- AE and SAE recording

14.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays in Part 1 and Part 2.

The following laboratory assessments will be performed to evaluate the safety profile of natalizumab:

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

14.3. Natalizumab Safety Assessments

The following assessments will be performed to determine the safety of natalizumab in [redacted] Part 2:

- Anti-natalizumab antibodies
- [redacted]

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value and/or vital sign result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the subject to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the natalizumab Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

In Part 1, any AE experienced by the subject after the first dose in this study until the follow-up safety phone call is to be recorded in the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs in the CRF.

In Part 2, any AE collected between the signing of the Part 2 ICF and EOS Visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

AEs that are ongoing when the subject completes or discontinues the study will be followed up by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome will be recorded in the CRF, as applicable.

For events related to IV infusion and SC injection, the time of AE onset should be recorded.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the follow-up safety phone call is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed up for all SAEs until the follow-up safety phone call. Thereafter, the event should be reported to Biogen only if the Investigator considers the SAE to be related to study treatment.

Any SAE that is ongoing when the subject completes or discontinues the study will be followed up by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

A report ***must be submitted*** to Biogen regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, fax a completed SAE form; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded in the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the study site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Biogen will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Progressive Multifocal Leukoencephalopathy

Due to the risk of PML in natalizumab-treated subjects, if neurological symptoms or MRIs indicate a possible pathology other than MS, the following diagnostic procedures are recommended:

- Careful evaluation of MRI, including comparison with previous MRI scans.
- [redacted].
- Timely discontinuation of treatment. If the Investigator is unable exclude PML or other opportunistic infections (viral, bacterial, or fungal), natalizumab must be discontinued.

If, in the opinion of the Investigator, a subject's individualized risk for PML requires more frequent MRI monitoring than is performed as part of this study, additional MRIs to monitor for PML may be performed at the Investigator's discretion.

15.4.2. Pregnancy

Subjects should not become pregnant after the first dose in this study and for at least 3 months after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*. In the event of early study termination for a pregnancy, an EOS Gd-enhancing MRI should not be conducted.

The Investigator must report a pregnancy occurring in a female subject between the first dose of study treatment and 3 months after the last dose of study treatment by faxing the appropriate form to Biogen within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded in the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.3. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE in the CRF; however, all overdoses must be recorded on an Overdose form and faxed to Biogen within 24 hours of the study site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an

AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed to Biogen. All study treatment-related dosing information must be recorded in the dosing CRF.

15.4.4. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standard of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.5. Contraception Requirements

All women of childbearing potential must ensure that highly effective contraception is used during the study and for at least 3 months after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
  - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as contraception that achieves a failure rate of < 1% when used consistently and correctly, and includes the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.2.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, in the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax it to Biogen within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen within 24 hours of the study site staff becoming aware of new information.
- Ensure that all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, in the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a study site can enroll any subjects, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within the required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

In this more detailed description of the associated statistical methods, the endpoints are presented in relationship to categorical assessment. The associated endpoints of primary, secondary, [redacted] importance are specifically identified under each of these categories.

16.1. Efficacy

16.1.1. Analysis Population

The modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least 1 dose of study treatment and have at least 1 postbaseline efficacy assessment, will be used for all efficacy analyses. Subjects will be analyzed in the groups to which they are randomized.

16.1.2. General Methods of Analysis

Data will be collected and analyzed in 2 parts:

1. After the completion of the randomized phase in Part 1, the primary efficacy and safety analyses will be performed. All data will be summarized by randomized treatment group (SID and EID).
2. After the completion of the randomized phase in Part 2, analyses of all Part 2 endpoints will be performed. Data from Part 1 will be combined with data from Part 2 to evaluate the long-term efficacy and safety data of natalizumab EID.

For the continuous endpoints, the summary statistics will generally include the number of subjects with data, mean, standard deviation, median, interquartile range, and overall range. For categorical endpoints, the summary statistics will generally include the number of subjects with available data and the percentage of subjects with data in each category.

In the analysis of Part 1 efficacy variables, comparisons will be made between the EID group and the SID group.

16.1.3. Part 1 Statistical Analysis

16.1.3.1. Analysis of the Primary Endpoint in Part 1

The primary endpoint, the number of new or newly enlarging T2 hyperintense lesions at Week 72, will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe, and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia) as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and

associated p-value. The treatment will be considered different if the lower limit of the 95% CI is above 1. As a secondary inference, the possibility of a 2-fold increase in the mean lesion number in the EID group as compared with the SID group will be considered ruled out if the upper limit of 95% CI is no greater than 2. The proportion of subjects with no new or newly enlarging T2 hyperintense lesions will be analyzed using logistic regression models with the same covariates as those described above.

16.1.3.2. Primary and Secondary Estimands and Handling of Intercurrent Events in Part 1

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

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

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

16.1.3.3. Analysis of the Secondary Endpoints in Part 1

Time to First Relapse

Relapses that occur after subjects have received rescue SID natalizumab prior to Week 72 will be excluded from the analyses of time to first relapse, and the subject's time in the study will be censored at the time the subject starts rescue SID natalizumab treatment. If a subject withdraws from the study prior to Week 72 and the subject did not experience relapse as adjudicated by INEC prior to withdrawal, he or she will be censored on the last day they were in the study if the reason for withdrawal is not related to lack of efficacy. For withdrawals due to lack of efficacy, the withdrawal time will be considered as event time. The start date for time to first relapse or censoring is defined as the baseline/first dose date.

The proportion of relapsed subjects will be estimated using the Kaplan-Meier (KM) product-limit method and be presented as KM curves over time. The comparison of treatment groups will be based on Cox regression models with the same covariates as those described in Section 16.1.2. The hazard ratio of relapse of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value.

Annualized Relapse Rate

The annualized relapse rate at Week 72 will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe, and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia) as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value.

EDSS Worsening

Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score ≥ 1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 that is confirmed after at least 24 weeks. Time to EDSS worsening will be analyzed using KM estimates and Cox regression models similar to the method described above for time to the first relapse.

Secondary MRI Endpoints

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

[redacted]

[redacted]

16.1.3.5. Subgroup Analyses in Part 1

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

- Baseline EDSS (EDSS score ≤ 2.0 versus EDSS score > 2.0)
- Age at baseline (age < 40 years versus age ≥ 40 years)
- Duration of natalizumab exposure (≤ 3 years versus > 3 years) at baseline
- Gender

- Country/region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)
- Baseline weight (40 to 59 kg, 60 to 79 kg, 80 to 89 kg, and ≥ 90 kg)

In addition, subgroup analysis of the primary and key secondary endpoints will be evaluated in subgroups defined by prior disease activity, the number and type of therapies prior to natalizumab, quartiles of the C_{trough} values, and α-integrin saturation levels at Weeks 24, 48 and 72.

16.1.4. Part 2 Statistical Analysis

In Part 2, the mITT population is defined as all randomized subjects in Part 2 who received at least 1 dose of SC natalizumab and completed at least the first question in the PPQ on 1 occasion.

During Part 2, the baseline of each period is defined as the last assessment before the first dose administration during that period.

16.1.4.1. Analysis of the Primary Endpoint in Part 2

Proportion of subjects indicating preference for SC versus IV administration at the end of Part 2.

For each subject, the last answer in the PPQ will be used to derive the primary endpoint of Part 2. The proportion of subjects preferring SC natalizumab at the end of Part 2 will be estimated, and the 95% CI will be calculated using the exact Binomial method. Additionally, the proportion of subjects preferring SC will be summarized by randomized arms during Part 2, i.e., the group receiving SC followed by IV and that receiving IV followed by SC.

16.1.4.2. Analysis of the Secondary Endpoint in Part 2

Mean score on TSQM.

Total TSQM value will be summarized by route of administration during Part 2. No formal comparison is planned.

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

Mean time for drug preparation and administration will be summarized by route of administration during Part 2. No formal comparison is planned.

For the remaining secondary endpoints, analysis will be performed by using data, respectively, during the first period, the second period, and both periods.

Number of new or newly enlarging T2 hyperintense lesions.

In Part 2, the number of new or newly enlarging T2 hyperintense lesions will be summarized by route of administration.

Time to first relapse

In Part 2, if a subject withdraws from the study prior to the end of either period in the crossover design and did not experience a relapse reported prior to withdrawal, the subject will be censored

on the last day in the period. The start date for time to first relapse or censoring is defined as the start date of each period.

The proportion of relapsed subjects will be estimated using the KM product limit method and be presented as KM curves over time by route of administration.

The comparisons of route will be based on Cox regression models with route of administration as the classification variable and treatment arm during Part 1 and period during Part 2 as covariates. The hazard ratio of relapse of SC versus IV (SC/IV) will be derived from the Cox model with a 95% CI and associated p-value.

Annualized relapse rate

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

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

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

The annualized relapse rate at the end of each period will be analyzed using a negative binomial regression model, with route of administration as the classification variable and the treatment arm during Part 1 and period during Part 2 as covariates. The logarithmic transformation of the number of years in the study at the end of each period will be included in the model as the "offset" parameter. The ratio of mean annualized relapse rate of SC/IV will be derived from the model with a 95% CI and associated p-value. If negative binomial regression model does not converge, a Poisson regression model with the same classification variable and covariates will be used instead.

Change in EDSS score

During each period of the crossover design in Part 2, the change in EDSS score from the start date of a period to the end date of the same period will be calculated and summarized by route of administration.

Number of new Gd-enhancing lesions

The same method for the analysis of new or newly enlarging T2 hyperintense lesions will be applied.

Number of new T1 hypointense lesions

The same method for the analysis of new or newly enlarging T2 hyperintense lesions will be applied.

PBVC and change in cortical and thalamic brain region volume

The same method for the analysis of new or newly enlarging T2 hyperintense lesions will be applied.

[redacted]

[redacted]

16.2. Pharmacokinetics

16.2.1. Analysis Population

[redacted]

In Part 2, the PK population is defined as all subjects who receive at least 1 dose of SC or IV natalizumab and have at least 1 assessment for the concentration of natalizumab in serum after randomization in Part 2.

16.2.2. Methods of Analysis

C_{trough} will be summarized using descriptive statistics for each timepoint for [redacted] Part 2. In Part 2, the data in both periods will be used and summarized by the route of administration and timepoint.

16.3. Pharmacodynamics

16.3.1. Analysis Population

[redacted]

In Part 2, the PD population is defined as all subjects who receive at least 1 dose of SC or IV natalizumab and have at least 1 assessment of the PD parameter after randomization in Part 2.

16.3.2. Methods of Analysis

[redacted]

In Part 2, the baseline of each period is defined as the last assessment before the first dose administration during that period. Data in both periods will be used, and measurement results and the changes from Baseline will be summarized by route of administration and timepoint, and mean values will be plotted over time. Parameters with non-normal distributions may be analyzed in logarithmic scale.

[redacted]

16.5. Safety

16.5.1. Analysis Population

For Part 1, the safety population is defined as all subjects who receive at least 1 dose of study treatment in Part 1.

For Part 2, the safety population is defined as all subjects who receive at least 1 dose of SC or IV natalizumab in Part 2.

16.5.2. Methods of Analysis

16.5.2.1. Adverse Events

All AEs will be collected throughout the study. These AEs will be coded using the Medical Dictionary for Regulatory Activities. The incidence of treatment-emergent clinical AEs will be summarized for Part 1 and Part 2 by the following:

- preferred term
- primary system organ class
- primary system organ class and preferred term

- severity and relationship to study treatment

In Part 2, the AEs reported in both periods will be summarized by route of administration.

16.5.2.2. Clinical Laboratory Results

Laboratory data (hematology and blood chemistry) will be summarized for each treatment group using shift tables. Tables will present changes relative to each parameter's normal ranges. Summary statistics for actual values and changes from Baseline will also be summarized by treatment group and timepoint.

16.5.2.3. Vital Signs

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

16.5.2.4. C-SSRS

C-SSRS data will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) for continuous variables, and using frequency and percentage for discrete variables.

16.6. Antigenicity/Immunogenicity Data

16.6.1. Analysis Population

[redacted]

In Part 2, the analysis population will include all subjects who receive at least 1 dose of SC or IV natalizumab and have at least 1 assessment for the specific parameter after randomization in Part 2.

16.6.2. Methods of Analysis

The percentage of subjects who develop antibodies to natalizumab will be determined and summarized by treatment group and timepoint for [redacted] Part 2.

In Part 2, data from both periods will be used. The proportion of subjects who develop antibodies to natalizumab will be determined and summarized by route of administration and timepoint.

[redacted]

16.7. Interim Analyses

An interim futility analysis, based on the number of new or newly enlarging T2 hyperintense lesions at 24 weeks, will be conducted when 50% of subjects have at least 6 months of randomized treatment in Part 1. The interim data will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight ($\leq$ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline ($\leq$ 3 years versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe, and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia) as

covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI. The study may be stopped for futility if the lower limit of the 95% CI is > 2 and a 2-fold increase in mean lesion numbers in the EID group can be concluded with 97.5% confidence.

In Part 2, no formal interim analysis will be performed; however, there may be intermittent analyses of the data as needed.

16.8. Sample Size Considerations

Historical data on MS treatments, including a meta-analysis on the relationship between new or newly enlarging T2 lesions and relapses, suggest little or no clinical relevance of a difference of 0.2 to 0.3 in mean lesion numbers over 72 weeks [Sormani and Bruzzi 2013]. With the planned sample size of N = 200/group, the precision of the estimated mean lesion numbers is sufficient to allow > 80% probability to observe the lower limit of the 95% CI for the ratio of EID to SID in the estimated mean lesion number above 1 if the true mean is 0.5 and 0.3 in the EID and SID group, respectively. If the true mean is 0.6 and 0.3 in the EID and SID group, respectively, the probability will be approximately 90%. In the other direction, the sample size provides a precision that allows approximately 90% probability to observe the upper limit of the 95% CI to be ≤ 2 if the true mean lesion numbers in both groups are 0.3. Approximately 480 subjects will be enrolled to account for a drop-out rate of approximately 17%.

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

17. ETHICAL REQUIREMENTS

Biogen, IQVIA, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator is responsible for endorsing all data on completed CRFs electronically, prior to any interim lock or database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. Biogen or designee will submit documents on behalf of the study sites in countries other than the US.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as those in the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject

or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

Written informed consent must be obtained from subjects electing to enroll in Part 2 before any assessments are performed.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

[redacted]

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical records.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race and ethnicity will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or PK profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity. [redacted]

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post-study results regardless of the outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the study sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all CRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed, and any discrepancies or omissions will be resolved. Documentation of results will be provided to Biogen in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, management of SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites in electronic CRFs by a web-based electronic data capture tool configured by the CRO and hosted by the electronic data capture vendor. PROs will be completed by the subject on paper forms and subsequently entered into the electronic CRF by study site staff.

19.1.4. Central Facility for MRI Scans

A central MRI reader has been selected by Biogen to read and interpret all MRI scans for this study. All study sites will need to perform a dummy scan for the qualification of the study site's MRI machine; a separate ICF will be used for this scan. If there is a change in the MRI machine during the study, this process will need to be repeated. The MRI central reader will be blinded to treatment allocation.

19.2. Study Committees

An Independent Data Monitoring Committee will not be used for this study because the Investigators and treating staff are not blinded to the subjects' treatment assignment, natalizumab has a well-established safety profile, and the study has built-in rescue criteria and a futility analysis to check efficacy failure.

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet at least annually to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to subject treatment assignments.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen, and participating Investigators. Biogen will designate one of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Neurology Evaluation Committee

An INEC will be formed to review and confirm potential abnormalities related to suspected relapses for the purposes of confirming the Part 1 secondary endpoint.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before the implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of the completion or termination of this study and sent a copy of the study synopsis in accordance with the necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that study site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with the destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the study site.

19.6. Study Report Signatory

Biogen will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator’s contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

20. REFERENCES

Belachew S, Phan-Ba R, Bartholomé E, et al. Natalizumab induces a rapid improvement of disability status and ambulation after failure of previous therapy in relapsing-remitting multiple sclerosis. Eur J Neurol. 2011;18(2):240-245.

Calabresi PA, Mellion M, Edwards KR, et al. Efficacy Results From the Phase 2b SYNERGY Study: Treatment of Disabling Multiple Sclerosis with the Anti-LING0-1 Monoclonal Antibody Opicinumab. Presented at the 2017 American Academy of Neurology Annual Meeting.

Ffrench-Constant C. Pathogenesis of multiple sclerosis. Lancet. 1994;343(8892):271-5.

Hartung HP, Archelos JJ, Zielasek J, et al. Circulating adhesion molecules and inflammatory mediators in demyelination: a review. Neurology. 1995;45(6 Suppl 6):S22-S32.

Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. Mult Scler. 2010;16(11):1385-92.

Oturai AB, Koch-Henriksen N, Petersen T, et al. Efficacy of natalizumab in multiple sclerosis patients with high disease activity: a Danish nationwide study. Eur J Neurol. 2009;16(3):420-3.

Sangalli F, Moiola L, Bucello S, et al. Efficacy and tolerability of natalizumab in relapsing–remitting multiple sclerosis patients: a post-marketing observational study. Neurol Sci. 2011;31(0):299-302.

Schumacher G, Beebe G, Kibler R, et al. Problems of experimental trials of therapy in multiple sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann NY Acad Sci. 1965;122(1):552-568.

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

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-173. Epub 2017/12/21.

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Controlled, Open-Label, Rater-Blinded, Phase 3b Study of the Efficacy, Safety, and Tolerability of 6-Week Extended Interval Dosing of Natalizumab (BG00002) in Subjects With Relapsing-Remitting Multiple Sclerosis Switching From Treatment With 4-Week Natalizumab Standard Interval Dosing (SID) in Relation to Continued SID Treatment - Followed by an Open-Label Crossover Extension Study Comprising Subcutaneous and Intravenous Natalizumab Administration" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date (dd - MONTH - yyyy)

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 101MS329

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

Version 4.0

Date: 20 August 2020

EUDRA CT Number: 2018-002145-11

Version 4.0 of the protocol has been prepared for this amendment, which supersedes Version 3.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 101MS329 is the addition of details regarding the Screening visit for new participants who did not participate in Part 1 of the study and are being enrolled in Part 2.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 5.2, Part 2 - Schedule of Activities, Table 4, footnote 1

Now reads:

[1] ~~The Part 2 Screening, informed consent, and eligibility assessment for a new subject should be performed within 6 weeks of the Baseline Visit.~~**Informed consent can be obtained any time between Day -42 and the day of the last prestudy dose of natalizumab. The last prestudy dose of natalizumab must occur between Days -33 and -26 from the baseline visit. Some screening assessments must be performed immediately prior to the last prestudy dose of natalizumab (see footnote 7). All other screening assessments can occur any time between the day of the last prestudy natalizumab dose and baseline.** Randomization to crossover study treatment should be done at the Week 108 visit to confirm crossover treatment allocation.

Rationale: The change was made to clarify the timing of the last prestudy dose of natalizumab and screening requirements for new participants being enrolled in the open-label extension, as well as the assessments that must be completed prior to the last prestudy dose of natalizumab.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 5.1, Part 1 - Schedule of Activities, Table 1

Change: In footnote 16, instructions for postdosing observation requirements were revised

Now reads:

[16] ~~Subjects must be observed for 1 hour after completion of infusion.~~ **Please refer to the Directions for Handling and Administration (DHA) located in the Study Reference Guide for details of postdose observation requirements.**

Rationale: Biogen has elected to specify requirements for postdosing observation in the DHA of natalizumab rather than the study protocol.

This change also affects Section 5.1, Part 1 - Schedule of Activities (Table 2, footnote 16); Section 5.2, Part 2 - Schedule of Activities (Table 3, footnote 12); Section 5.2, Part 2 - Schedule of Activities (Table 4, footnote 13); and Section 11.3, Precautions.

Section 5.2, Part 2 - Schedule of Activities, Table 4

Change: The Nominal Study Day for the Screening visit was revised.

Now reads:

-~~41~~**42** to -1

Rationale: This revision was required to align with the change in footnote 1 of this table.

Section 5.2, Part 2 - Schedule of Activities, Table 4

Change: Reference to footnote 7 was added to the Blood Chemistry assessment schedule.

Now reads:

Blood Chemistry[8,7]

Rationale: The need for reference to footnote 7 was overlooked in the previous version.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The Sponsor Signature Page was revised.

LIST OF ABBREVIATIONS

DHA	Directions for Handling and Administration

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
United States

Biogen Idec Research Limited
Innovation House
70 Norden Road
Maidenhead, Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Protocol 101MS329

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

Version 3

Date: 08 July 2020

EUDRA CT Number: 2018-002145-11

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 101MS329 is the addition of an OLE comprising a crossover analysis of natalizumab administered by IV infusion and SC injection under EID.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 7, Study Design

Now reads:

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

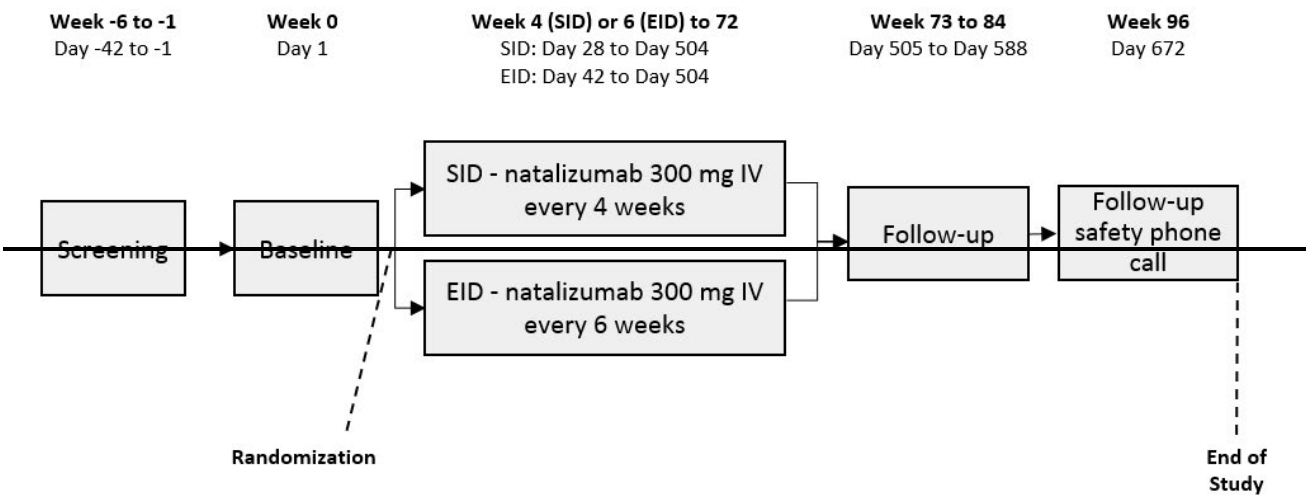
- SID: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion every 4 weeks (28 **[**-2/+5 days**]**).
- EID: approximately 240 subjects will receive natalizumab as a 300 mg IV infusion every 6 weeks (42 **[**-2/+5 days**]**).

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

At the completion of their 72-week treatment period, subjects in Part 1 who cannot participate, or elect not to participate, in Part 2 will enter a 12-week follow-up, and will receive a follow-up safety phone call 12 weeks later (i.e., 24 weeks after the last dose of study treatment) before completing the study.

~~See Figure 1 for a schematic of the study design.~~

~~**Figure 1: Study Design**~~



Part 2 is a 108-week OLE for approximately 200 subjects at approximately 45 sites in Canada, the United Kingdom, Europe, Israel, and Australia who complete their randomized treatment in Part 1, provide consent, and are eligible to participate immediately following completion of the 72-week treatment period.

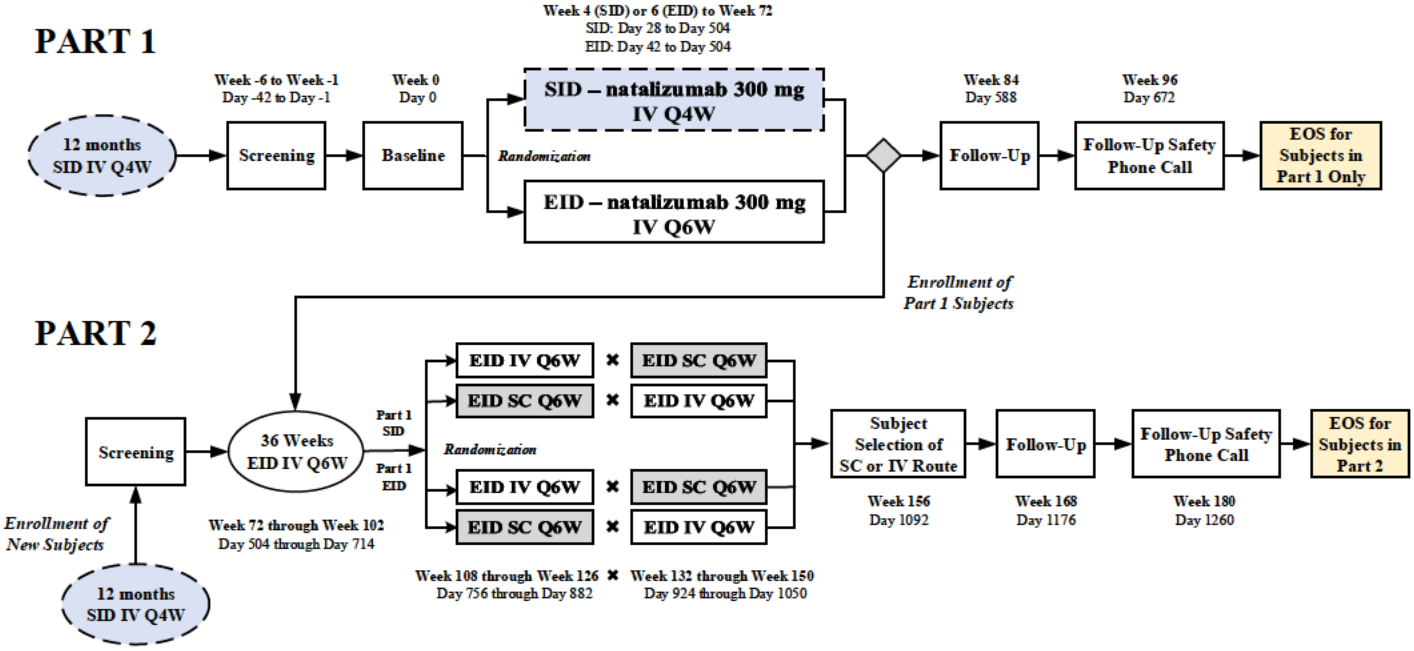
Subjects who did not participate in Part 1 but provide consent and satisfy the inclusion-exclusion and eligibility requirements of Part 1, including treatment with natalizumab SID for at least 12 months without relapses in the last 12 months, may also be enrolled in Part 2 as new subjects to ensure adequate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

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

At the completion of their 48-week crossover treatment period, subjects in Part 2 will receive a final dose of natalizumab 300 mg by IV infusion at Week 156, proceed to the 12-week follow-up, and receive a further safety follow-up by telephone 12 weeks later (i.e., 24 weeks after the last dose of study treatment) before completing the study.

The design of this study, inclusive of Parts 1 and 2, is presented in Figure 1.

Figure 1: Design for Study 101MS329 with Open-Label Extension



Rationale: Part 1 of the study is a comparison of the IV infusion of natalizumab under SID, which occurs Q4W, and infusion under EID, which occurs every 6 weeks (Q6W). The Part 2 OLE has been added to assess subject preference for natalizumab administration by IV infusion or SC injection and explore the long-term efficacy, safety, and tolerability of EID.

This change also *substantially* affects Section 1, Synopsis; Section 5, Schedule of Activities; Section 6, Study Objectives and Endpoints; Section 7.1, Study Duration; Section 7.3, Unscheduled Visits and Treatment for MS Relapses; Section 7.5, End of Study; Section 8, Selection of Subjects; Section 9, Screening and Randomization; Section 10, Discontinuation of Study Treatment and Withdrawal of Subjects from the Study; Section 11, Study Treatment Use; Section 12, Study Treatment Management; Section 13, Efficacy, Pharmacokinetic, and Pharmacodynamic Assessments; and Section 16, Statistical Methods and Determination of Sample Size.

This change *nonsubstantially* affects Section 4.5, Study Rationale; Section 7.2, Responsibilities of Study Site Staff; Section 14, Safety Assessments; Section 15, Safety Definitions, Recording, Reporting, and Responsibilities; and Section 17, Ethical Requirements.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1.1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 5, Schedule of Activities

Change: Section 5 was revised to comprise Section 5.1, Part 1 – Schedule of Activities, and Section 5.2, Part 2 – Schedule of Activities, as follows:

In Section 5.1:

- Table 1: Part 1 Schedule of Activities – SID, and Table 2: Part 1 Schedule of Activities – EID were revised to correct the timing of the Baseline Visit and the [redacted] assessments being done by the Investigator and the subject.
- A new footnote (footnote 2) was added regarding the final Part 1 visit.
- Subsequent footnotes were renumbered, and renumbered footnotes 4 and 15 were revised to include additional detail.

Now reads (in the relevant section of Tables 1 and 2):

Study Week	Screening Visit[1] -6 to -1	Baseline Visit 0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72[2]	Follow Up EOS Visit 84	Follow Up Safety Phone Call 96[3]	ET Visit[4]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[5]
Study Day	-42 to -1	~~1~~0	28 (-2/ +5)	56 (-2/ +5)	84 (-2/ +5)	112 (-2/ +5)	140 (-2/ +5)	168 (-2/ +5)	196 (-2/ +5)	224 (-2/ +5)	252 (-2/ +5)	280 (-2/ +5)	308 (-2/ +5)	336 (-2/ +5)	364 (-2/ +5)	392 (-2/ +5)	420 (-2/ +5)	448 (-2/ +5)	476 (-2/ +5)	504 (-2/ +5)	588 (±10)	672 (±10)		
[redacted]																								
C-SSRS[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

…

[2] **Week 72 will be the last Part 1 visit for subjects who enroll in Part 2; those subjects will then follow the Part 2 visit schedule in Section 5.2, Table 3.**

…

[4] If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit **at** 12 weeks (± 10 days) **and the safety follow-up phone call at 24 weeks** after the final dose of study treatment.

…

[15] The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs, with the exception of the one conducted at the Neurological Worsening and Relapse Assessment, are to be completed within a 7-day window of the dosing visit. MRIs conducted at the Neurological Worsening and Relapse Assessment must be completed prior to dosing with rescue therapy, but can be completed on the same day. If a subject's MRI is scheduled to occur <4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so that it is performed either before the steroid treatment of between 4 and 8 weeks after the last dose of steroid treatment. **MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early study termination for a pregnancy, a Gd-enhancing MRI should not be conducted.**

In Section 5.2:

- Introductory text was added to Section 5.2, Part 2 – Schedule of Activities.
- Table 3: Part 2 Schedule of Activities – EID SC vs. IV OLE for Subjects Who Participated in Part 1 was added, with supporting footnotes.
- Table 4: Part 2 Schedule of Activities – EID SC vs. IV OLE for New Subjects was added, with supporting footnotes.

Now reads:

5.2. Part 2 – Schedule of Activities

For subjects who completed Part 1 treatment and enrolled in Part 2, the schedule of activities for Part 2 (Table 3) does not differ for subjects randomized to SC/IV or IV/SC with the exception of the order of treatment administration during the crossover period.

For new subjects enrolled in Part 2, the initial screening, inclusive of select assessments, differs from those subjects who participated in Part 1 but is otherwise the same beginning at Week 78 through the end of Part 2 (Table 4).

Table 1: Part 2 Schedule of Activities – EID SC vs. IV OLE for Subjects Who Participated in Part 1

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted] 2) clinical and neurological assessments, 3) PK/PD [redacted] collection, and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit.

Study Week	78	84[1]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[2]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[3]	Follow-Up Safety Phone Call 180[4]
Study Day	546 (-2/ +5)	588 (-2/ +5)	630 (-2/ +5)	672 (-2/ +5)	714 (-2/ +5)	756 (-2/ +5)	798 (-2/ +5)	840 (-2/ +5)	882 (-2/ +5)	924 (-2/ +5)	966 (-2/ +5)	1008 (-2/ +5)	1050 (-2/ +5)	1092 (-2/ +5)	1176 (±10)	-	-	1260 (±10)
Informed Consent Form for Part 2[5]	---- X ----																	
Eligibility Criteria Check for Part 2[5]	---- X ----																	
Randomization						X												
Vital signs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[1]		X				X				X				X	X	X	X	
Body Weight[1]		X				X				X				X				
C-SSRS[1,7]		X																
[redacted]																		
TSQM						X				X				X				
[redacted]																		
EDSS		X				X				X				X		X	X	

Study Week	78	84[1]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[2]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[3]	Follow-Up Safety Phone Call 180[4]
Study Day	546 (-2/ +5)	588 (-2/ +5)	630 (-2/ +5)	672 (-2/ +5)	714 (-2/ +5)	756 (-2/ +5)	798 (-2/ +5)	840 (-2/ +5)	882 (-2/ +5)	924 (-2/ +5)	966 (-2/ +5)	1008 (-2/ +5)	1050 (-2/ +5)	1092 (-2/ +5)	1176 (±10)	-	-	1260 (±10)
Neurological Examination (MS Signs & Symptoms)		X				X				X				X		X	X	
Blood Hematology[8]		X				X				X				X	X	X	X	
Blood Chemistry[9]		X													X	X	X	
Urine Pregnancy Test[10]																		
PD Assessments (whole blood)[8]				X		X	X	X	X	X	X	X	X	X				
PK Natalizumab Concentration (serum)[8]				X		X	X	X	X	X	X	X	X	X				
Anti-natalizumab Antibodies[8]						X		X		X		X		X			X	
[redacted]																		
Brain MRI[11]						X				X				X		X		
Natalizumab EID IV infusion	X	X	X	X	X									X				

Study Week	78	84[1]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[2]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[3]	Follow-Up Safety Phone Call 180[4]
Study Day	546 (-2/ +5)	588 (-2/ +5)	630 (-2/ +5)	672 (-2/ +5)	714 (-2/ +5)	756 (-2/ +5)	798 (-2/ +5)	840 (-2/ +5)	882 (-2/ +5)	924 (-2/ +5)	966 (-2/ +5)	1008 (-2/ +5)	1050 (-2/ +5)	1092 (-2/ +5)	1176 (±10)	-	-	1260 (±10)
Natalizumab EID SC-IV Crossover[12]						X	X	X	X	X	X	X	X	X[13]				
PPQ[14]											X		X			X		
Safety (AEs, SAEs)	Record as per Section 15.3 of the protocol																	
Concomitant Therapy and Procedures	Record as per Section 11.5 of the protocol																	X

AE = adverse event; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; EDSS = Expanded Disability Status Scale; EID = extended interval dosing; EOS = end of study; [redacted]; ET = early termination; Gd = gadolinium; IV=intravenous; [redacted]; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; SAE = serious adverse event; SC = subcutaneous; TSQM = Treatment Satisfaction Questionnaire for Medication.

1 **The Part 1 and Part 2 assessments at Week 84 are the same and should be performed only once.**

2 **If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12 weeks (± 10 days) and the safety follow-up phone call at 24 weeks after the last dose of study treatment.**

3 **Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of the symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit).**

4 **Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.**

5 **The Part 2 informed consent and eligibility assessment should be performed during Week 72 of Part 1 if possible. In the event that this cannot be performed at that time, informed consent and eligibility assessment should be conducted prior to the subject starting Part 2 at the Week 78 or Week 84 visit. Randomization to crossover study treatment should be done at the Week 108 visit to confirm crossover treatment allocation. After Week 84, subjects are not eligible for enrollment in Part 2 of the study.**

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

[7] **The Part 1 "baseline/screening" C-SSRS must be completed at the Part 1 screening Visit; at all other visits, the "since last visit" C-SSRS must be used.**

[8] **Sample to be collected prior to dosing.**

[9] **If a subject experiences signs and symptoms suggestive of liver failure (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.**

[10] **Follow-up testing for women of childbearing potential throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (more than 1 month between menstrual periods), a urine pregnancy test should be performed.**

[11] **All postbaseline MRIs are to be completed within a 7-day window of the dosing visit. If a subject's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early termination for a pregnancy, a Gd-enhancing MRI should not be conducted.**

[12] **The time required for drug preparation and drug administration should be recorded in detail for each occasion of treatment administration during the crossover period. Subjects must be observed for 1 hour after completion of the SC injection or IV infusion.**

[13] **Subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at the Week 156 visit with the route of administration being the subject’s choice.**

[14] **PPQ assessments at Week 138 and Week 150 must be collected after study treatment administration.**

Table 2: Part 2 Schedule of Activities – EID SC vs. IV OLE for New Subjects

Tests and assessments are listed in the recommended order. At each visit, assessments should be performed as follows: [redacted], 2) clinical and neurological assessments, 3) PK/PD [redacted] collection, and 4) dose administration. It is not required that all screening tests and assessments be completed during 1 visit. This Schedule of Activities is identical to the Schedule in Table 3 after the Week 84 visit.

Nominal Study Week	Screen[1]	Baseline Visit 72	78	84[2]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[3]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[4]	Follow-Up Safety Phone Call[5] 180
Nominal Study Day	-41 to -1	504 (-2/+5)	546 (-2/+5)	588 (-2/+5)	630 (-2/+5)	672 (-2/+5)	714 (-2/+5)	756 (-2/+5)	798 (-2/+5)	840 (-2/+5)	882 (-2/+5)	924 (-2/+5)	966 (-2/+5)	1008 (-2/+5)	1050 (-2/+5)	1092 (-2/+5)	1176 (±10)	-	-	1260 (±10)
Informed Consent Form for Part 2[1]	X																			
Eligibility Criteria Check for Part 2[1]	X	X																		
Randomization								X												
Medical History[1]	X																			
Physical Examination[1]	X	X		X				X				X				X	X	X	X	
Body Weight[1]	X	X		X				X				X				X				
Vital signs[6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, Hep B, and Hep C Testing	X																			
TSQM		X						X				X				X				
[redacted]																				

Nominal Study Week	Screen[1]	Baseline Visit 72	78	84[2]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[3]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[4]	Follow-Up Safety Phone Call[5] 180
Nominal Study Day	-41 to -1	504 (-2/+5)	546 (-2/+5)	588 (-2/+5)	630 (-2/+5)	672 (-2/+5)	714 (-2/+5)	756 (-2/+5)	798 (-2/+5)	840 (-2/+5)	882 (-2/+5)	924 (-2/+5)	966 (-2/+5)	1008 (-2/+5)	1050 (-2/+5)	1092 (-2/+5)	1176 (±10)	-	-	1260 (±10)
[redacted]																				
EDSS	X			X				X				X				X		X	X	
Neurological Examination (MS Signs & Symptoms)	X			X				X				X				X		X	X	
Blood Hematology[7]	X			X				X				X				X	X	X	X	
Blood Chemistry[8]	X			X													X	X	X	
Serum Pregnancy Test[9]	X																			
Serum FSH[10]	X																			
Urine Pregnancy Test[11]		X																		
PD Assessments (whole blood)[7]		X				X		X	X	X	X	X	X	X	X	X				
PK Natalizumab Concentration (serum)[7]		X				X		X	X	X	X	X	X	X	X	X				
Anti-natalizumab Antibodies[7]	X							X		X		X		X		X			X	

Nominal Study Week	Screen[1]	Baseline Visit 72	78	84[2]	90	96	102	108	114	120	126	132	138	144	150	156	Follow-Up EOS Visit 168	ET Visit[3]	Unscheduled Visit (Neurological Worsening and Relapse Assessment)[4]	Follow-Up Safety Phone Call[5] 180
Nominal Study Day	-41 to -1	504 (-2/+5)	546 (-2/+5)	588 (-2/+5)	630 (-2/+5)	672 (-2/+5)	714 (-2/+5)	756 (-2/+5)	798 (-2/+5)	840 (-2/+5)	882 (-2/+5)	924 (-2/+5)	966 (-2/+5)	1008 (-2/+5)	1050 (-2/+5)	1092 (-2/+5)	1176 (±10)	-	-	1260 (±10)
[redacted]																				
Brain MRI[12]	X							X				X				X		X		
Natalizumab EID IV infusion		X	X	X	X	X	X									X				
Natalizumab EID SC-IV Crossover[13]								X	X	X	X	X	X	X	X	X[14]				
PPQ[14]													X		X			X		
Safety (AEs, SAEs)		Record as per Section 15.3 of the protocol																		
Concomitant Therapy and Procedures			Record as per Section 11.5 of the protocol																	X
Assessment of New Neurological Symptoms[15]																				X

AE = adverse event; CRF = case report form; EDSS = Expanded Disability Status Scale; EID = extended interval dosing; EOS = end of study; [redacted] ET = early termination; FSH = follicle stimulating hormone; Gd = gadolinium; Hep = hepatitis; HIV = human immunodeficiency virus; IV=intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; [redacted]; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; PPQ = Patient Preference Questionnaire; SAE = serious adverse event; SC = subcutaneous; Sg = Screening; TSQM = Treatment Satisfaction Questionnaire for Medication.

[1] **The Part 2 Screening, informed consent, and eligibility assessment for new subjects should be performed within 6 weeks of the Baseline Visit. Randomization to crossover study treatment should be done at the Week 108 visit to confirm crossover treatment allocation.**

[2] **The Part 1 and Part 2 assessments at Week 84 are the same and should be performed only once.**

[3] **If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit at 12 weeks (± 10 days) and the safety follow-up phone call at 24 weeks after the last dose of study treatment.**

[4] **Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit).**

[5] **Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.**

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

[7] **Sample to be collected prior to dosing.**

[8] **If a subject experiences signs and symptoms suggestive of liver failure (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.**

[9] **Required for women of childbearing potential. Results must be known prior to Baseline.**

[10] **For postmenopausal subjects only.**

[11] **Follow-up testing for women of childbearing potential throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (more than 1 month between menstrual periods), a urine pregnancy test should be performed.**

[12] **The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs are to be completed within a 7-day window of the dosing visit. If a subject's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET Visit if the last MRI was performed within the previous 4 weeks. In the event of an early termination for a pregnancy, a Gd-enhancing MRI should not be conducted.**

[13] **The time required for drug preparation and drug administration should be recorded in detail for each occasion of treatment administration during the crossover period. Subjects must be observed for 1 hour after completion of the IV infusion or the SC injection.**

[14] **Subjects in Part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at the Week 156 visit with the route of administration being the subject's choice.**

[15] **PPQ assessments at Week 138 and Week 150 must be collected after study treatment administration.**

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

Rationale: In Section 5 in the previous version of the protocol, now Section 5.1, the timing of the Baseline Visit and [redacted] assessments had been incorrectly identified. Footnote 2 was added to define the transition of subjects completing treatment in Part 1 and enrolling in Part 2. Footnotes 4 and 15 were revised to provide further detail regarding post-treatment safety considerations. In the new Section 5.2, the tables and associated text were added to summarize the treatment and assessment of subjects who complete treatment in Part 1 of the study and choose to enroll in Part 2 (Table 3) and of new subjects who choose to enroll in Part 2 but did not participate in Part 1 (Table 4).

Section 6, Study Objectives and Endpoints

Change: Section 6 was revised to comprise Section 6.1, Part 1 Objectives and Endpoints, and Section 6.2, Part 2 Objectives and Endpoints. In Section 6.1, the original objectives and endpoints of the study are retained; in Section 6.2, the objectives and endpoints of Part 2 of the study are described.

Now reads:

6.2. Part 2 Objectives and Endpoints

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

To evaluate the efficacy of SC versus IV routes of natalizumab administration.	**All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period.** • **Number of new or newly enlarging T2 hyperintense lesions** • **Time to first relapse** • **Annualized relapse rate** • **Change in EDSS score** • **Number of new Gd-enhancing lesions** • **Number of new T1 hypointense lesions** • **PBVC and change in cortical and thalamic brain region volume**
To characterize PK and PD of SC versus IV routes of natalizumab administration.	**All endpoints will be assessed between 6 months of SC and 6 months IV in the randomized, crossover period.** • **C_{trough}** • **Trough α4 integrin saturation**
[redacted]	

Rationale: The objective of the OLE is to evaluate subject preference for, and satisfaction, with SC injection and IV infusion of natalizumab under EID, and to develop long-term efficacy and safety data with regard to natalizumab administration in general under the EID regimen.

This change also *substantially* affects Section 13, Efficacy, Pharmacokinetic, and Pharmacodynamic Assessments; and Section 16, Statistical Methods and Determination of Sample Size.

Section 7.1, Study Duration for Subjects

Change: Section 7 was revised to comprise Section 7.1.1, Study Duration for Subjects Enrolled Only in Part 1, and Section 7.1.2, Study Duration for Subjects Enrolled in Part 1 and Part 2.

Now reads:

7.1.1. Study Duration for Subjects Enrolled Only in Part 1

The total duration of study participation **in Part 1** for ~~each~~ subject**s who do not participate in Part 2** will be up to 102 weeks~~;~~**. t****T**his ~~consists of~~ **comprises** a screening period of up to 6 weeks~~,~~**;** a treatment period of 72 weeks~~,~~**;** ~~and~~ **a** follow-up period of 12 weeks**; and** ~~. A~~**a** follow-up safety phone call ~~will be performed~~ ~~24~~**12** weeks after **the follow-up period (i.e., 24 weeks after** the last dose of study treatment**)**.

The end of study (EOS) date for a subject **in Part 1** may be the last study visit, ~~last~~ **the** follow-up **safety** phone ~~conversation~~**call**, or last protocol-specified assessment~~,~~**;** ~~or~~ if the subject has ongoing AEs that are being followed ~~up~~, then the date may be the date of AE resolution.

7.1.2 Study Duration for Subjects Enrolled in Part 1 and Part 2

The total duration of study participation in Part 1 for subjects who also participate in Part 2 will be up to 78 weeks, comprising a screening period of up to 6 weeks and the randomized SID or EID treatment period of 72 weeks.

The total duration of study participation in Part 2 for these subjects will be approximately 108 weeks. This comprises EID IV treatment for 36 weeks; a randomized EID SC vs. IV crossover-treatment period of 48 weeks; a follow-up period of 12 weeks; and a follow-up safety phone call 12 weeks after the follow-up period (i.e., 24 weeks after the last dose of study treatment). The total duration of study participation for subjects who participate in both Part 1 and Part 2 will be approximately 186 weeks.

The EOS date for subjects participating in Part 1 and Part 2 may be the last study visit, the follow-up safety phone call, or last protocol-specified assessment; if the subject has ongoing AEs that are being followed, then the date may be the date of AE resolution.

Rationale: Revision of this section was required to differentiate the duration of study for subjects who participate in Part 1 only, in both Part 1 and Part 2, as well as for new subjects who participate in Part 2 of the study without having participated in Part 1.

This change also *substantially* affects Section 7.3, Unscheduled Visits and Treatment for MS Relapses; Section 7.5, End of Study; Section 9, Screening and Randomization; Section 10, Discontinuation of Study Treatment and Withdrawal of Subjects from the Study; and Section 11, Study Treatment Use.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The title, version number, and date were updated throughout the protocol.
- Section 2, List of Abbreviations, was updated.
- In Section 4.2, current therapies for multiple sclerosis were updated.
- Typographical errors and formatting were corrected.

LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough serum concentration of natalizumab
DNA	deoxyribonucleic acid
EDSS	Expanded Disability Status Scale
EID	extended interval dosing
EOS	end of study
[redacted]	[redacted]
ET	early termination
FSH	follicle stimulating hormone
Gd	gadolinium
Hep	hepatitis
HIV	human immunodeficiency virus
IV	intravenous(ly)
JCV	John Cunningham virus
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PBVC	percentage of brain volume change
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPQ	Patient Preference Questionnaire
PRO	patient-reported outcome
Q4W	every 4 weeks
Q6W	every 6 weeks
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event

SC	subcutaneous
[redacted]	[redacted]
SID	standard interval dosing
[redacted]	[redacted]
TSQM	Treatment Satisfaction Questionnaire for Medication
USA	United States
VCAM-1	vascular cell adhesion molecule 1

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AMENDMENT SUMMARY

Biogen Protocol 101MS329

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

Version 2.0

Date: 28 February 2019

EUDRA CT Number: 2018-002145-11

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 101MS329 was to incorporate scientific advice received from the EMA, including 1) to change the timing of the primary efficacy endpoint to Week 72, 2) to prioritize time to EDSS worsening as a secondary endpoint, and 3) to further specify and clarify the study's statistical analysis plan within the protocol.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 6, Study Objectives and Endpoints

Now reads:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment, with the goal of estimating the difference between SID and EID, with high precision ~~with~~**and** a narrow 95% confidence interval (CI), ~~and adequate power~~ to ~~detect small but clinically relevant differences~~ **support the treatment decision based on individualized benefit/risk assessments**.	The number of new or newly enlarging T2 hyperintense lesions at Week ~~48~~**72**
Secondary Objectives	**Secondary Endpoints**
To evaluate additional relapse-based clinical efficacy measures of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	• Time to first relapse (relapses will be adjudicated by an Independent Neurology Evaluation Committee [INEC]) • Annualized relapse rate at Week ~~48 and Week~~ 72
To evaluate disability worsening of natalizumab EID in subjects who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	• **Time to Expanded Disability Status Scale (EDSS) worsening (confirmed after at least 24 weeks)**
To evaluate additional MRI-lesion efficacy measures of natalizumab EID in subjects	• Number of new or newly enlarging T2 hyperintense lesions at Week 24

who have previously been treated with natalizumab SID for at least 12 months, in relation to continued SID treatment.	and Week ~~72~~**48** • Number of new gadolinium (Gd)-enhancing and new T1 hypointense lesions at Weeks 24, 48, and 72
…	…

[redacted]

Rationale: The timing of the primary efficacy endpoint was changed to Week 72 to allow the collection of efficacy data over a 48-week period after stable trough concentrations have been

reached and as per request by the EMA. With the primary endpoint changed to Week 72, the corresponding secondary endpoint timing was changed to Week 48 and there will no longer be an efficacy analysis performed at Week 48; [redacted]

The primary endpoint "new or newly enlarging T2 lesions" might not entirely cover disease activity in this heavily pretreated population, and the EMA requested that disability worsening be assessed as a secondary endpoint; therefore, time to EDSS worsening was prioritized as a secondary endpoint [redacted]. Language was added to further define that EDSS worsening requires EDSS to be confirmed after at least 24 weeks, consistent with the definitions used as primary and secondary endpoints in prior multiple sclerosis clinical trials.

Section 16, Statistical Methods and Determination of Sample Size

Now reads:

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Efficacy

~~The primary endpoint, the number of new or newly enlarging T2 hyperintense lesions at Week 48, will be analyzed using negative binomial regression models with treatment as the classification variable and body weight (≤90 kg versus >90 kg), EDSS, and region as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value. The treatment will be considered different if the p-value (2-sided) is less than 0.05. The possibility of a 2-fold increase in the mean lesion number in the EID group as compared with the SID group will be considered ruled out if the upper limit of 95% CI is less than 2. The proportion of subjects with no new or newly enlarging T2 hyperintense lesions will be analyzed using logistic regression models with the same covariates as those described above. New or newly enlarging T2 hyperintense lesions at other timepoints as well as Gd-enhancing lesions will be analyzed similarly. Key secondary endpoints of relapse will also be analyzed using negative binomial regression models. Time-to-event endpoints will be analyzed using the Cox regression model as well as Kaplan-Meier (KM) estimates. Performance test outcomes [redacted] will be analyzed using the mixed model of repeated measures (MMRM). The relationship between PK concentration and efficacy endpoints (MRI lesions and relapse) as well as between [redacted] and efficacy endpoints will be assessed using negative binomial regression or logistic regression models. Treatment differences in subgroups defined by PK concentration categories and α4 integrin saturation level categories will also be assessed.~~

~~The incidence of AEs during the randomized treatment period will be tabulated by treatment group, severity, and relationship to study treatment. The tabular summaries will include incidence by system organ class and by preferred term. AEs and SAEs resulting in study~~

~~withdrawal will be summarized by treatment group. Clinically relevant abnormalities for laboratory parameters will be identified by treatment group.~~

16.1.1. Analysis Population

The modified intent-to-treat population, defined as all randomized subjects who receive at least 1 dose of study treatment and have at least 1 postbaseline efficacy assessment, will be used for all efficacy analyses. Subjects will be analyzed in the groups to which they are randomized.

16.1.2. Methods of Analysis

16.1.2.1. Analysis of the Primary Endpoint

The primary endpoint, the number of new or newly enlarging T2 hyperintense lesions at Week ~~48~~**72**, will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤~~90~~ **80** kg versus >~~90~~ **80** kg), ~~EDSS,~~**duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years),** and region **(North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)** as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value. The treatment will be considered different if the ~~p-value (2-sided) is less than 0.05. The~~**lower limit of the 95% CI is above 1. As a secondary inference, the** possibility of a 2-fold increase in the mean lesion number in the EID group as compared with the SID group will be considered ruled out if the upper limit of 95% CI is ~~less~~**no greater** than 2. The proportion of subjects with no new or newly enlarging T2 hyperintense lesions will be analyzed using logistic regression models with the same covariates as those described above.

~~For subjects who withdraw or receive rescue SID natalizumab prior to Week 48, the Week 48 number of lesions may be imputed using the MMRM.~~

16.1.2.2. Primary and Secondary Estimands and Handling of Intercurrent Events

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

The proposed primary estimand will be based on a treatment policy strategy, in which the study is intended to estimate the difference of a potential treatment decision of switching subjects from SID to EID compared with keeping subjects on SID over the next 72 weeks in

a realistic clinical setting, where switching to a different dosing regimen or different medication may occur depending on disease activity. Therefore, the primary analysis will utilize all measurements regardless of whether subjects remain on randomized treatment. For subjects who withdraw from the study for reasons related to efficacy or an AE or who have a "possibly related" withdrawal, as described above, the missing values will be imputed by the worst observed value of the subjects on study treatment at the given timepoint. For withdrawals classified as "no information", the missing values will be treated as missing at random and will be addressed using multiple imputation. The number and proportion of subjects with intercurrent events and the time to intercurrent event will also be tabulated and compared between randomized groups. Sensitivity analysis may be conducted using tipping point analysis. Supplementary analyses by imputing all missing values by treating all as missing at random using multiple imputation will also be conducted.

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

~~16.1.2.2~~**16.1.2.3**. Analysis of the Secondary Endpoints

…

Annualized Relapse Rate

The annualized relapse rate at Week ~~48 and Week~~ 72 will be analyzed ~~at each timepoint~~ using negative binomial regression models with treatment as the classification variable and baseline body weight (≤~~90~~ **80** kg versus >~~90~~ **80** kg), ~~EDSS,~~**duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years),** and region **(North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)** as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI and associated p-value.

EDSS Worsening

Confirmed EDSS worsening is defined as an increase of at least 1.0 point from a baseline EDSS score ≥ 1.0 or an increase of at least 1.5 points from a baseline EDSS score of 0 that is confirmed after at least 24 weeks. Time to EDSS worsening will be analyzed using KM estimates and Cox regression models similar to the method described above for time to first relapse.

Secondary MRI Endpoints

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

[redacted]

…

[redacted]

…

16.1.2.5. Subgroup Analyses

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

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

In addition, subgroup analysis of the primary and key secondary endpoints will be evaluated in subgroups defined by prior disease activity, the number and type of therapies prior to natalizumab, quartiles of the trough PK concentrations, and α-integrin saturation levels at Weeks 24, 48 and 72.

…

16.7. Interim Analyses

An interim futility analysis, based on the number of new or newly enlarging T2 hyperintense lesions at 24 weeks, will be conducted when 50% of subjects have at least 6 months of randomized treatment. ~~The interim futility analysis is designed to ensure that if clinically meaningful loss of efficacy is occurring in the EID group, the study can be stopped early to prevent unnecessary risk to the study participants of uncontrolled MS disease activity as a result of potential efficacy failure on EID~~**The interim data will be analyzed using negative binomial regression models with treatment as the classification variable and baseline body weight (≤ 80 kg versus > 80 kg), duration of natalizumab exposure at baseline (≤ 3 years versus > 3 years), and region (North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia) as covariates. The ratio of mean lesion numbers of EID versus SID (EID/SID) will be derived from the model with a 95% CI. The study may be stopped for futility if the lower limit of the 95% CI is > 2 and a 2-fold increase in mean lesion numbers in the EID group can be concluded with 97.5% confidence**.

16.8. Sample Size Considerations

~~To detect an increase in the mean number of new or newly enlarging T2 hyperintense lesions over 48 weeks at the alpha level of 0.05 (2-sided), a sample size of 400 subjects (200 subjects per arm) will provide the following:~~

- ~~>80% power to detect an increase from a mean of 0.3 (expected efficacy of SID dosing arm in this population) to 0.5.~~
- ~~≥90% power to detect an increase from a mean of 0.3 to 0.6.~~

~~Historical data on MS treatments, including meta-analyses on the relationship between new or newly enlarging T2 hyperintense lesions and relapses, suggest little or no clinical relevance of a difference smaller than 0.2 in mean new or newly enlarging T2 hyperintense lesions over 48 weeks.~~**Historical data on MS treatments, including a meta-analysis on the relationship between new or newly enlarging T2 lesions and relapses, suggest little or no clinical relevance of a difference of 0.2 to 0.3 in mean lesion numbers over 72 weeks [Sormani and Bruzzi 2013]. With the planned sample size of N = 200/group, the precision of the estimated mean lesion numbers is sufficient to allow > 80% probability to observe the lower limit of the 95% CI for the ratio of EID to SID in the estimated mean lesion number above 1 if the true mean is 0.5 and 0.3 in the EID and SID group, respectively. If the true mean is 0.6 and 0.3 in the EID and SID group, respectively, the probability will be approximately 90%. In the other direction, the sample size provides a precision that allows approximately 90% probability to observe the upper limit of the 95% CI to be ≤ 2 if the true mean lesion numbers in both groups are 0.3.** Approximately 480 subjects will be enrolled to account for a drop-out rate of approximately 17%.

Rationale: The text describing the overview of statistical analysis for efficacy in Section 16.1 was revised per regulatory advice, and detailed rationales for each section are provided below.

The timing of the primary efficacy endpoint was changed to Week 72 to allow the collection of efficacy data over a 48-week period after stable trough concentrations have been reached. Stratification on the factor "country/region" was clarified per EMA request because it was not clear whether stratification would be based on regions, countries, or a mixture of the two. A lower cutoff for body weight (i.e., 80 kg) was used because at weight > 80 kg, a decrease in efficacy was suggested based on the PK/PD modelling data and per EMA request. Duration of natalizumab exposure was added as a covariate in place of EDSS per EMA request and guidance that any factor utilized in randomization stratification should also be utilized as a model covariate. Detailed inference criteria for the primary analysis were edited to avoid the potential misinterpretation that the study was designed to test the superiority of EID over SID and to better reflect the study goal of estimating the difference between SID and EID, with high precision and a narrow 95% confidence interval (CI), to support the treatment decision based on individualized benefit/risk assessments, as discussed and agreed upon with the EMA.

The analysis plan was revised to include primary and secondary estimands based on International Council for Harmonisation E9 (R1) Draft Addendum on estimands EMA/CHMP/ICH/436221/2017 and per request from the EMA that these statistical details be included in the protocol rather than only in the study statistical analysis plan.

With the primary endpoint changed to Week 72, the corresponding secondary endpoint timing was changed to Week 48 and there will no longer be an efficacy analysis performed at Week 48; [redacted]. EDSS worsening was further defined, consistent with the reprioritization of EDSS worsening as a secondary endpoint.

Time to EDSS worsening was prioritized as a secondary endpoint; [redacted]

Subgroup analyses are useful for assessing heterogeneity and might further stress or refute the need for individualized benefit/risk assessments. The EMA requested that information on prespecified subgroup analyses be included in the protocol rather than only in the statistical analysis plan.

Interim analysis text was updated to clarify that the study may be stopped for a degree of inferior efficacy that would discourage the use of EID in all settings. Consultation with leading neurologists treating MS led to an empirical consensus view that a change from 0.3 with SID to 0.6 (a 2-fold increase) with EID at a population level would represent an unacceptable disease activity for considering EID as a reasonable PML risk mitigation strategy. The EMA requested that details of the analysis planned for assessment of futility be included in the protocol rather than only in the statistical analysis plan.

Sample size considerations were revised to avoid the potential misinterpretation that the study was designed to test superiority of EID over SID and to better reflect the study goal of estimating

the difference between SID and EID, with high precision and a narrow 95% CI, to support the treatment decision based on individualized benefit/risk assessments, as discussed and agreed upon with the EMA. Text was added to address the sample size appropriateness for both the primary and secondary analyses discussed with the EMA, i.e., to check if there is a difference between EID and SID and to exclude the worsening of efficacy with EID at a level that would discourage the use of EID in most clinical settings.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The Synopsis was revised to reflect changes made throughout the protocol.

Section 5, Schedule of Activities

Change: The screening period was extended to Days -42 to -1, and a new footnote (Footnote 1) was added to clarify the screening timing.

Week 84 EDSS and neurological examination assessments as well as Week 60 assessments for anti-natalizumab antibodies were added.

Footnote 9 of Table 1 was added to include language on liver function testing in the event of a subject experiencing signs and symptoms suggestive of liver injury.

Footnote 12 of Table 1 was updated to include language on delayed menstrual period and pregnancy testing.

Now reads:

Table 1: Schedule of Activities – SID

Study Week	**Screening Visit ~~-4~~[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[12] 96**	**ET Visit[23]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[34]**
Study Day	**~~-28~~42 to -1**	**1**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
Informed Consent Form	X																							
Eligibility Criteria Check	X	X																						
Randomization		X																						
Medical History	X																							
Physical Examination	X	X[45]						X						X						X	X		X	X
Body Weight	X	X[45]						X						X						X	X		X	X
Vital Signs[56]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
HIV, Hep B, and Hep C Testing	X																							
[redacted]																								

Study Week	**Screening Visit ~~-4~~[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[12] 96**	**ET Visit[23]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[34]**
Study Day	**~~-28~~42 to -1**	**1**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																								
C-SSRS[67]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
[redacted]																								
EDSS	X							X						X						X	**X**		X	X
Neurological Examination	X							X						X						X	**X**		X	X
Blood Hematology[78]	X							X						X						X	X			X
Blood Chemistry[9]	X																				X			X
Serum Pregnancy Test[810]	X																							
Serum FSH[911]	X																							
Urine Pregnancy Test[1012]		X																						
[redacted]																								

Study Week	**Screening Visit ~~-4~~[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[12] 96**	**ET Visit[23]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[34]**
Study Day	**~~-28~~42 to -1**	**1**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
[redacted]																								
Brain MRI[~~12~~14]	X							X						X						X			X	X
Natalizumab Administration (SID)[~~13~~15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
AEs		Record as per Section 15.3 of the protocol																						
SAEs	Record as per Section 15.3 of the protocol																							
Concomitant Therapy and Procedures		Record as per Section 11.5 of the protocol																						

Study Week	**Screening Visit -4[1] -6 to -1**	**Baseline Visit 0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**Follow Up EOS Visit 84**	**Follow Up Safety Phone Call[12] 96**	**ET Visit[23]**	**Unscheduled Visit (Neurological Worsening and Relapse Assessment)[34]**
Study Day	~~-28~~42 to -1	**1**	**28 (-2/ +5)**	**56 (-2/ +5)**	**84 (-2/ +5)**	**112 (-2/ +5)**	**140 (-2/ +5)**	**168 (-2/ +5)**	**196 (-2/ +5)**	**224 (-2/ +5)**	**252 (-2/ +5)**	**280 (-2/ +5)**	**308 (-2/ +5)**	**336 (-2/ +5)**	**364 (-2/ +5)**	**392 (-2/ +5)**	**420 (-2/ +5)**	**448 (-2/ +5)**	**476 (-2/ +5)**	**504 (-2/ +5)**	**588 (±10)**	**672 (±10)**		
Assessment of New Neurological Symptoms[1416]																								X

[redacted], AE = adverse event; [redacted]; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]; EDSS = Expanded Disability Status Scale; EOS = end of study; [redacted]; ET = early termination; FSH = follicle-stimulating hormone; Hep = hepatitis; HIV = human immunodeficiency virus; [redacted]; MRI = magnetic resonance imaging; [redacted]; PML = progressive multifocal leukoencephalopathy; [redacted]; SAE = serious adverse event; [redacted]; SID = standard interval dosing; [redacted].

[1] **Informed consent can be obtained anytime between Day -42 and the day of the last prestudy dose of natalizumab. The last prestudy dose of natalizumab must occur between Days -33 and -26 from the baseline visit. Some screening assessments must be performed immediately prior to the last prestudy dose of natalizumab (see Footnote 8). All other screening assessments can occur anytime between the day of last prestudy natalizumab dose and baseline.**

[12] Subjects should have a follow-up safety phone call 24 weeks after their last dose of study treatment.

[23] If a subject chooses to withdraw from the study, an ET Visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS Visit 12 weeks (±10 days) after the final dose of study treatment.

[34] Subjects who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of the symptoms. The subject is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis are 2 (1 for each unscheduled visit). The samples will be named NW1 and NW2.

[45] If a screening test is performed within 7 days of the Baseline Visit, the assessment does not need to be repeated at Baseline.

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

[67] The "baseline/screening" C-SSRS must be completed at the Screening Visit; at all other visits, the "since last visit" C-SSRS must be used.

[78] Sample to be collected prior to dosing.

[8][9] **If a subject experiences signs and symptoms suggestive of liver injury (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis.**

[9][10] Required for women of childbearing potential. Results must be known prior to Day 1/Baseline.

[9][11] For postmenopausal subjects only.

[10][12] Required for women of childbearing potential. Follow-up testing throughout the study will be done at the discretion of the Investigator or as required by local law. **In each case of delayed menstrual period (over 1 month between menstruations), a urine pregnancy test should be performed.**

[redacted]

[12][14] The screening MRI must be performed at least 2 weeks prior to the Baseline Visit to confirm eligibility. All postbaseline MRIs, with the exception of the one conducted at the Neurological Worsening and Relapse Assessment, are to be completed within a 7-day window of the dosing visit. MRIs conducted at the Neurological Worsening and Relapse Assessment must be completed prior to dosing with rescue therapy, but can be completed on the same day. If a subject's MRI is scheduled to occur ~~less than~~< 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment.

[13][15] Subjects must be observed for 1 hour after completion of infusion.

[14][16] Subjects should be contacted by phone 24 weeks after the last dose of study treatment to discuss if there has been any new development of any new neurological symptoms. PML or new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days) must be immediately reported as an SAE.

Rationale: The screening period was extended to Days -42 to -1 to improve logistics for sites in the collection of informed consents.

EDSS and neurological examination assessments were added at Week 84 to confirm the Week 72 secondary endpoint. Anti-natalizumab antibodies assessment at Week 60 was added to make the schedule consistent with the existing text in the protocol and the ICF.

Footnote 9 of Table 1 was added to include information on the monitoring of liver function to make the global protocol consistent with the local protocol amendment required in France.

Footnote 12 of Table 1 was updated to include pregnancy testing consistent with Heads of Medicines Agencies Clinical Trial Facilitation Group guidance and to make the global protocol consistent with the local protocol amendment required in the UK.

This change also affects Table 2, Schedule of Activities – EID, Figure 1, Study Design, and Section 7.1, Study Duration for Subjects.

Section 7, Study Design

Change: Text was updated to clarify stratification on the factor "country/region" and to use a lower cut-off for body weight.

Now reads: Randomization will be stratified by country/region **(North America [includes USA and Canada], United Kingdom, Europe and Israel [includes Belgium, France, Germany, Israel, Italy, Netherlands, and Spain], and Australia)**, body weight (≤~~90~~ **80** kg versus >~~90~~ **80** kg), and duration of natalizumab exposure (≤ 3 years versus > 3 years). Subjects will receive open-label natalizumab at their assigned frequency throughout the 72 weeks of the study.

Rationale: Clarified stratification on the factor "country/region" because it was not clear whether stratification would be based on regions, countries, or a mixture of the two. A lower cut-off for body weight (i.e., 80 kg) was used because at weight > 80 kg, a decrease in efficacy was suggested based on the PK/PD modelling data and per the request of the EMA.

This change also affects Section 9.2, Randomization, Section 16.1.2.1, Analysis of the Primary Endpoint, and Section 16.1.2.3, Analysis of the Secondary Endpoints.

Section 11.6, Continuation of Treatment

Change: Text related to continuation of treatment after 72-week randomized treatment period was clarified.

Now reads: There is no provision to provide study treatment after the study. Natalizumab is available commercially and subjects/Investigators can continue Tysabri treatment via a commercial source. **Once subjects have completed the randomized 72-week treatment**

period in the study, it is up to the treating physician and subject as to what the most appropriate treatment plan is for that subject per local practice.

Rationale: Text was revised added to clarify that it is up to the treating physician and subject to decide the most appropriate treatment plan after the 72-week randomized treatment period.

Section 9.1, Screening

Change: Text revised to clarify the screening assessments' timing.

Now reads: It is not required that all screening tests and assessments be completed during 1 pretreatment visit**; however, some tests and assessments must be completed immediately prior to subjects receiving their last prestudy dose of natalizumab. Other assessments can occur anytime between the subjects receiving their last prestudy dose of natalizumab and baseline (see Section 5)**.

Rationale: Text was edited to clarify the original study protocol instructions that some screening assessments must be performed immediately prior to dosing, whereas others have more flexible timing. This change is to address the confusion expressed by sites at the study investigator meeting.

Section 13.5, Future Scientific Research Assessments

Change: Section describing future scientific research assessments was deleted.

Now reads: [redacted]

~~The samples collected may be utilized to identify or verify putative, prognostic, and predictive markers associated with disease and markers of therapeutic response to treatment, and/or to develop diagnostic and analytical tests. Background and dynamic clinical disease characteristics~~ [redacted] ~~may be utilized to predict subsequent disease worsening (severity), identify high-risk patient subgroups, and identify predictors of response to treatment.~~

Rationale: This section was deleted because it was repetitive with the assessments described elsewhere in the protocol as part of this study

Section 15.2.4, Expectedness of Events

Change: Text was revised to clarify the source document used for the determination of the expectedness of all adverse events.

Now reads: Expectedness of all AEs will be determined by Biogen according to the ~~local label~~ **natalizumab Investigator's Brochure**.

Rationale: This change was made for consistency in using the reference safety information contained in the Investigator's Brochure to determine the expectedness of all adverse events.

Section 15.4.2, Pregnancy

Change: Text related to reporting of pregnancy events was updated.

Now reads: The Investigator must report a pregnancy occurring in a female subject **between the first dose of study treatment and 3 months after the last dose of study treatment** by faxing the appropriate form to Biogen within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded in the AE CRF.

Rationale: Text was revised to specify the pregnancy events collection period.

Section 15.5, Contraception Requirements

Change: Text related to contraception for males and the donation of eggs/sperm for all subjects was removed.

Now reads: All women of childbearing potential ~~and all men~~ must ensure that highly effective contraception is used during the study and for at least 3 months after their last dose of study treatment. ~~In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 3 months after their last dose of study treatment.~~

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as contraception that achieves a failure rate of ~~less than~~< 1% when used consistently and correctly, and includes the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

~~For males:~~

- ~~Vasectomy with negative semen analysis at follow-up.~~
- ~~Sex with a woman who uses the methods described for females if she is of childbearing potential.~~

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.2.

Rationale: The deletions make this section consistent with the inclusion/exclusion criteria.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Typographical errors and formatting were corrected.