COVER PAGE

Official Title:	A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis Via a Subcutaneous Route of Administration
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PROTOCOL TITLE: A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of Administration

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SPONSOR INFORMATION

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For urgent medical issues in which the study Medical Monitor should be contacted, please refer to contact information in the protocol attachment for complete contact information.

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

SPONSOR SIGNATURE PAGE

Protocol 101MS330 was approved by:

_____ _____

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[redacted]

Biogen

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1. KEY STUDY ELEMENTS

1.1. Synopsis

Protocol Title:	A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of Administration	
Protocol Number:	101MS330	
Version Number:	3.0	
Name of Study Treatment:	Research Name:	BG00002
	Generic Name:	Natalizumab
	Trade Name:	Tysabri
Study Phase:	3	
Study Indication:	Relapsing-Remitting Multiple Sclerosis	
Study Rationale:	The Sponsor has developed a pharmaceutical formulation for SC administration in a PFS that delivers natalizumab at a dose of 150 mg (in 1 mL), enabling a total dose of 300 mg to be delivered by 2 consecutive injections, Q4W. Studies in cohorts of participants with MS have shown that this product is similar to the IV formulation with respect to its PK and PD profile as well as its efficacy and safety (Studies 101MS102 and 101MS206). The SC route of administration may provide additional benefits to patients and physicians compared with IV infusion as noted in the benefit-risk analysis section that follows. This Phase 3 study will evaluate the efficacy, safety, PK, and PD of natalizumab 300 mg Q4W administered to Japanese participants with RRMS via a SC route of administration.	
Rationale for Dose and Schedule Selection:	The natalizumab SC dose selected for this study (300 mg Q4W) is the approved dose regimen in the EU for the treatment of patients with RMS and has been selected as the recommended dose in marketing applications to other health authorities.	

The results from modelling and simulation analysis of SC and IV natalizumab were consistent with the outcomes of the clinical studies 101MS102 and 101MS206 and demonstrated that administering natalizumab 300 mg SC Q4W would result in a similar C_{trough} value and PD response as administering the clinically approved 300 mg IV Q4W dose. The results from these studies support the use of the SC injection as an additional route of administration for natalizumab at the same dose level as the current commercial product.

Study Objectives and Endpoints

Primary Objective	Primary Endpoint
To evaluate the efficacy of natalizumab 300 mg SC Q4W administrations up to 24 weeks in Japanese participants with RRMS	Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans
Secondary Objectives	Secondary Endpoints
To evaluate other clinical and MRI measures of efficacy of natalizumab 300 mg SC Q4W administrations in Japanese participants with RRMS	• Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Change from baseline in number of gadolinium-enhancing lesions at Week 24 and Week 48

	• The number of nonenhancing new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 • The number of new T1 hypointense lesions at Week 24 and Week 48 • ARR at Week 24 • ARR at Week 48 • ARR at Week 52 • Proportion of relapse-free participants at Week 24 and Week 52 • VAS assessing the participant's global impression of their well-being at Week 24 and Week 48
To evaluate the safety, tolerability, and immunogenicity of natalizumab 300 mg SC Q4W administrations up to 48 weeks in Japanese participants with RRMS	• Incidence of treatment-emergent AEs and SAEs from Baseline to end of study • Anti-JCV antibody status as measured by anti-JCV antibodies • Incidence of injection site reactions and injection reactions • Immunogenicity as measured by incidence of anti-natalizumab antibodies • Change in EDSS score from Baseline to Week 24 • Change in EDSS score from Baseline to Week 48
To evaluate the PK and PD of natalizumab 300 mg SC Q4W administrations up to 24 weeks and for an additional 24 weeks in Japanese participants with RRMS	• Serum natalizumab concentrations (C_{trough}) at each visit until Week 48 • Serum natalizumab concentration between Day 6 and Day 8 • α4-integrin saturation and serum soluble VCAM-1 concentrations at each visit until

	Week 48 (excluding Week 1 [Day 6 to Day 8] visit)

[redacted]

Study Design:	This Phase 3, single-arm, open-label study will evaluate the efficacy, safety, PK, and PD of natalizumab SC in Japanese participants with RRMS.
Study Location:	Approximately 10 sites in Japan are planned.
Study Population:	This study will be conducted in adult male and female Japanese participants with RRMS. Detailed criteria are described in Section 6.
Number of Planned Participants:	Approximately 20 participants will be enrolled.
Treatment Groups:	Natalizumab 300 mg SC will be administered as a Q4W regimen over 48 weeks.
Sample Size Determination:	The study plans to enroll approximately 20 participants which was based on feasibility. Approximately 15 through 17 evaluable participants are deemed sufficient to characterize the efficacy profile of natalizumab SC. The margin in Study 101MS330 showing comparability of the natalizumab SC to IV is set at 2.32, which is one-third of the mean difference (1.53 and 8.49) between the natalizumab and placebo groups in new active lesions at Week 24 in Japanese natalizumab IV Study 101MS203. To demonstrate the comparability of natalizumab SC to IV, 15 evaluable participants allow at least 80% probability that the upper limit of the 95% CI for mean new active lesions at Week 24 in natalizumab SC is lower than 3.85 (i.e., 2.32 plus 1.53), assuming similar field MRI machines are used for Studies 101MS203 and 101MS330 and the true mean of new active lesions for the natalizumab SC is 1.53. In addition, assuming 70% of participants will have MRIs using 3T machines in Study 101MS330, compared to approximately 13% in Study 101MS203, and the true mean of new active lesions is 1.73, 17 evaluable participants allow 80% probability that observing the upper limit of 95% CI for new active lesions at Week 24 in natalizumab SC is lower than 3.85 [Shilane and Bean 2013].

Visit Schedule:	Participants will have up to 16 scheduled visits during the study and 2 safety follow-up phone calls. All visits should be performed ± 3 to 10 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the date of first dose). Study assessments conducted at each visit are listed in the Schedule of Activities (Table 1).
Duration of Study Participation:	Study duration for each participant will be approximately 76 weeks: • 4-week Screening Period • 24-week Treatment Period in Part 1 • 24-week Treatment Period in Part 2 • 4-week Safety Follow-Up Period • Follow-up safety phone calls 12 and 24 weeks after the last dose
Benefit-Risk Analysis:	With over 17 years of experience in the postmarketing setting, natalizumab IV 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 IV demonstrated a 67% reduction in ARR 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 who have 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 IV. Infusion and hypersensitivity reactions and anti-natalizumab antibody production are important safety concerns; however, they are manageable in routine clinical practice. Serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in MS patients receiving natalizumab. In postmarketing experience, there have been rare reports of clinically significant liver injury.

The most important AE affecting natalizumab benefit-risk assessment is the occurrence of 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-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.

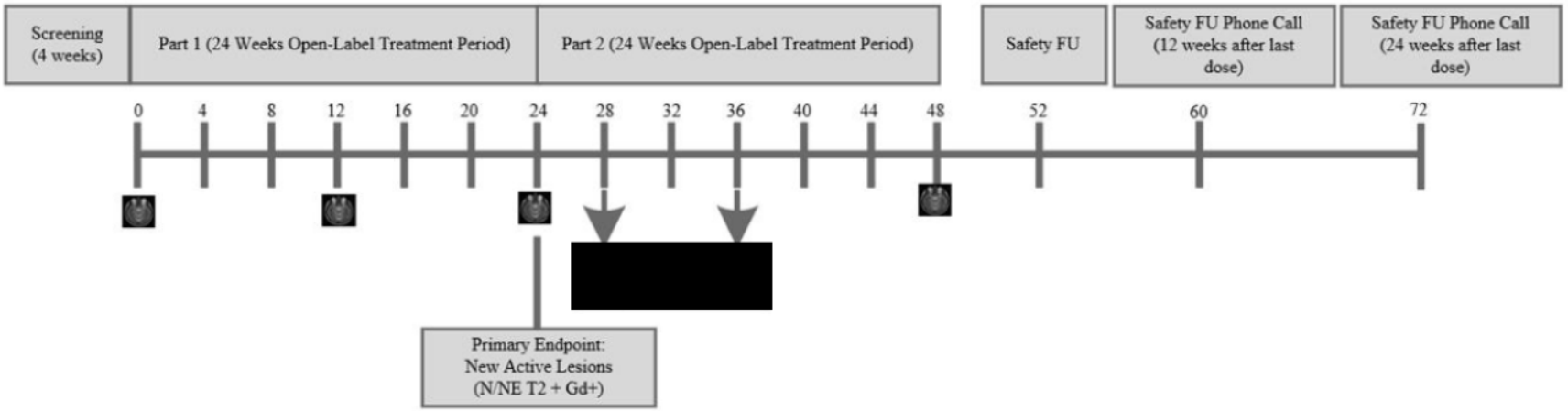
The SC route of administration may provide additional benefits to patients and physicians by offering a less invasive route of administration, lower complexity, and reduced time required at each treatment visit compared with IV infusion [Despiau 2017; Lopez-Vivanco 2017]. There is evidence from other medical conditions and indications that patients prefer SC to IV route of administration based on convenience and data from quality-of-life measurements [Falanga 2019; Pivot 2013; Santus 2019; Syrios 2018]. The economic and cost-saving benefits of SC versus IV route of administration in the hospital setting have been demonstrated [Farolfi 2017; Lopez-Vivanco 2017; Olsen 2018].

The safety profile observed for natalizumab administered SC was consistent with the known safety profile of natalizumab administered IV, with the exception of injection site pain. During the 2 SC clinical studies (Studies 101MS102 and 101MS206), injection site pain was reported in 4% (3 of 71) of participants receiving natalizumab 300 mg SC Q4W and no participants receiving natalizumab 300 mg IV Q4W reported injection site pain.

The potential risks related to participation in this study are justified by the anticipated benefit to participants.

1.2. Study Design Schematic

Figure 1: Study 101MS330 Schematic



Note: An additional visit will occur between Day 6 and Day 8 to collect a blood sample for C_{trough}.

1.3. Schedule of Activities

Table 1: Schedule of Activities

		Part 1: 24-Week Open-Label Treatment								Part 2: 24-Week Open-Label Treatment						Safety FU	Safety FU Phone Call[1]	Safety FU Phone Call[2]	Unscheduled	
	SCR	BL	W1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W60	W72	Neurological Worsening[3]	ET Visit[4]
Assessments	D -28 to D -1	D1	D6 to D8	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D225 (±3)	D253 (±3)	D281 (±3)	D309 (±3)	D337 (±3)	D365 (±7)	D421 (±10)	D505 (±10)		
Informed Consent	X																			
Inclusion/Exclusion Criteria	X	X																		
Medical History	X																			
Physical Examination[5]	X	X		X		X			X			X			X	X			X	X
Height	X																			
Vital Signs[6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
12-Lead ECG	X								X							X				X
FSH[7]	X																			
EDSS/Neurological Examination	X	X							X						X				X	X
Participant-Assessed Well-Being VAS		X							X						X					X
MRI (brain, with contrast)[8]	X[9]					X			X						X				X	X
C-SSRS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X
HIV/Hepatitis Screen	X																			
Alcohol and Drug Screen	X																			
Screening for TB (IGRA)	X																			

		Part 1: 24-Week Open-Label Treatment								Part 2: 24-Week Open-Label Treatment						Safety FU	Safety FU Phone Call[1]	Safety FU Phone Call[2]	Unscheduled	
	SCR	BL	W1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W60	W72	Neurological Worsening[3]	ET Visit[4]
Assessments	D -28 to D -1	D1	D6 to D8	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D225 (±3)	D253 (±3)	D281 (±3)	D309 (±3)	D337 (±3)	D365 (±7)	D421 (±10)	D505 (±10)		
Serum Pregnancy Test[10]	X																			
Urine Pregnancy Test[10,11]		X		X	X	X	X	X	X	X	X	X	X	X	X	X				X
Hematology	X	X		X		X			X	X		X			X	X				X
Blood Chemistry	X	X		X		X			X	X		X			X	X				X
Urinalysis	X	X		X		X			X	X		X			X	X				X
Blood Sampling for PK Assessments[12]		X	X[13]	X	X	X	X	X	X	X	X	X	X	X	X					X
Blood Sampling for PD Assessments[12]		X		X	X	X	X	X	X	X	X	X	X	X	X					X
Blood Sample for Anti-Natalizumab Antibody Assessments[12]	X					X			X			X			X				X	X
Anti-JCV Antibody	X								X						X				X	X
Anti-AQP4 Antibody	X[14]																			
Anti-MOG Antibody	X[14]																			
Study Treatment Administration[15,16]		X		X	X	X	X	X	X	X[17]	X	X[17]	X	X	X					
Relapse Assessment																			X	
Adverse Event Recording		----------X----------																		

		Part 1: 24-Week Open-Label Treatment								Part 2: 24-Week Open-Label Treatment						Safety FU	Safety FU Phone Call[1]	Safety FU Phone Call[2]	Unscheduled	
	SCR	BL	W1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W60	W72	Neurological Worsening[3]	ET Visit[4]
Assessments	D -28 to D -1	D1	D6 to D8	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D225 (±3)	D253 (±3)	D281 (±3)	D309 (±3)	D337 (±3)	D365 (±7)	D421 (±10)	D505 (±10)		
Serious Adverse Event Reporting	----------X----------																			
Concomitant Therapy and Procedures Recording	----------X----------																			

[1] Participants should have a follow-up safety phone call 12 weeks after their last dose of study treatment for AE/SAE recording and concomitant therapy and procedure recording.

[2] Participants should have a follow-up safety phone call 24 weeks after their last dose of study treatment for AE/SAE recording and concomitant therapy and procedure recording and to discuss if there has been 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.

[3] Participants who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to telephone the Investigator within 72 hours of the onset of symptoms. The participant 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.

[4] Participants are encouraged to undergo an ET Visit unless withdrawal is due to death or withdrawal of consent. The ET Visit in such participants should occur at 4 weeks (±7 days) after the last dose of study treatment and should be followed by safety phone calls at 12 weeks (±10 days) and 24 weeks (±10 days) after the last dose of study treatment.

[5] Participant weight measurement to be included as part of physical examination.

[6] Vital signs collected at each of the specified timepoints include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Participants must remain in the same body position (seated or supine) quietly for 5 minutes prior to pulse rate and blood pressure measurements; measurements must be performed within 1 hour prior to administration of study treatment.

[7] To be performed only in women who have had 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical reason; result must be > 40 mIU/mL to confirm postmenopausal status.

[8] Careful evaluation of MRI, including comparison with previous MRI scans. If, in the opinion of the Investigator, a participant'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.

[9] For inclusion criteria assessment, an MRI from the participant's medical record within 12 months of the Screening Visit can be used. For all enrolled participants, the screening MRI must have been performed within 4 weeks prior to the Baseline Visit.

[10] To be performed only in women of childbearing potential; results must be negative to continue participation in study.

[11] Samples for urine pregnancy test are to be analyzed locally.

[12]Blood sample will be collected before dosing.
[13]One blood sample will be collected between Day 6 and Day 8.
[14]If a participant was ever tested previously for anti-AQP4 and anti-MOG antibodies and the results were negative, the test does not have to be repeated at Screening. If not tested previously, the participant will need to be tested at Screening.
[15]Participants should be observed during both SC injections and for 1 hour after for signs and symptoms of injection site reactions and injection reactions including hypersensitivity. After the first 6 natalizumab doses, the 1-hour post-administration observation time for subsequent SC injections may be reduced or removed according to clinical judgement if the participants have not experienced any injection reactions including hypersensitivity.
[16]All prespecified evaluations must be performed prior to study treatment administration at each visit.

[redacted]

2. LIST OF ABBREVIATIONS

3T	3 Tesla
1.5T	1.5 Tesla
ADA	anti-drug antibody
AE	adverse event
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AQP4	aquaporin-4
ARR	annualized relapse rate
BL	baseline
[redacted]	[redacted]
CI	confidence interval
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSS	Clinical Site Support
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	trough concentration
CV	coefficient of variation
D	day
DHA	Directions for Handling and Administration
DMT	disease-modifying therapy
ECG	electrocardiogram
eCRF	electronic case report form
EDSS	Expanded Disability Status Scale
ET	early termination
EU	European Union
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
[redacted]	[redacted]
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IFN-β	interferon beta
IGRA	interferon-gamma release assays
IRT	interactive response technology
IV	intravenous(ly)
JCV	John Cunningham virus (human polyomavirus)

MedDRA	Medical Dictionary for Regulatory Activities
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
Q4W	every 4 weeks
RMS	relapsing multiple sclerosis
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SCR	screening
SOC	system organ class
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TSE	transmissible spongiform encephalopathy
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
W	week

3. INTRODUCTION

Natalizumab (Tysabri) is a recombinant, humanized, anti-α4-integrin monoclonal antibody currently approved as a DMT for the treatment of MS. From its original approval in the US in 2004 through 31 July 2020, worldwide 210,072 individuals have been treated with natalizumab, with a cumulative exposure of 833,874 person-years. Natalizumab 300 mg for IV injection was approved on 24 March 2014 in Japan. As of 07 August 2019, 866 Japanese patients have been treated with natalizumab.

3.1. Study Rationale

The safety, tolerability, and efficacy of IV natalizumab in Japanese participants with RRMS has been shown in a randomized, double-blind, placebo-controlled study (Study 101MS203) and a long-term extension study (Study 101MS204). The findings of these studies were consistent with the safety and efficacy profiles observed in cohorts of non-Japanese participants with RRMS.

Despite the availability of multiple DMTs for patients with MS, an unmet need exists for effective treatment that has more convenient means of administration for the benefit of patients and [redacted]. The SC route of administration may provide additional benefits to patients and physicians compared with the IV route (see additional details in Section 3.3).

The Sponsor has developed a pharmaceutical formulation for SC administration in a PFS that delivers natalizumab at a dose of 150 mg (in 1 mL), enabling a total dose of 300 mg to be delivered by 2 consecutive injections, Q4W. Studies in cohorts of participants with MS have shown that this product is similar to the IV formulation with respect to its PK and PD profile as well as its efficacy and safety (Studies 101MS102 and 101MS206).

This Phase 3 study will evaluate the efficacy, safety, PK, and PD of natalizumab 300 mg Q4W administered to Japanese participants with RRMS via a SC route of administration.

3.1.1. Rationale for Study Population

Although the complex and multifactorial pathogenesis of MS is considered to be generally similar across Caucasian and Asian populations, there are currently no safety, tolerability, or efficacy data of natalizumab SC in Japanese MS participants. Therefore, additional data are warranted in this population. This Phase 3 study is designed to collect data in Japanese participants with MS who are treated with natalizumab SC.

3.1.2. Rationale for Dosing Regimen

The natalizumab SC dose selected for this study (300 mg Q4W) is the approved dose regimen in the EU for the treatment of patients with RMS and has been selected as the recommended dose in marketing applications to other health authorities.

The results from modelling and simulation analysis of SC and IV natalizumab were consistent with the outcomes of the clinical studies 101MS102 and 101MS206 and demonstrated that

administering natalizumab 300 mg SC Q4W would result in a similar C_{trough} value and PD response as administering the clinically approved 300 mg IV Q4W dose. The results from these studies support the use of the SC injection as an additional route of administration for natalizumab at the same dose level as the current commercial product.

3.2. Background

3.2.1. Overview of Multiple Sclerosis

MS is a chronic autoimmune and neurodegenerative disorder of the central nervous system that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss; it most frequently presents as RRMS. It is one of the most common progressive neurological diseases in young adults worldwide [Collaborators 2019; GBD 2016 Multiple Sclerosis Collaborators 2019].

The total number of people living with MS worldwide is approximately 2.8 million individuals [Walton 2020]. The prevalence of MS varies by race and geography and is lower in Asia than in Europe and the US [Kira 2003; Rosati 2001]. MS is approximately twice as common in women as in men and predominantly affects adults aged 20 to 60 years.

Prevalence estimates of MS in the US range widely from 42.8 per 100,000 to 176.7 per 100,000 [Evans 2013]. The average prevalence in the total population for Europe is 93 per 100,000 [Kobelt and Kasteng 2009] and ranges from as low as 0.77 to 14.4 per 100,000 in East Asia. The MS prevalence in Japan is estimated to be between 7.7 and 14.4 per 100,000 [Kinoshita 2015; Makhani 2014], which is approximately 10% of that in Europe and the US [Horiuchi and Kira 2004]. Incidence in Japan has been reported as 0.79 and 0.78 per 100,000 [Lai and Tseng 2009; Makhani 2014]. Based on the real-world data from the Japan Medical Data Center Co., Ltd., the age-adjusted prevalence of MS increased from 0.015% to 0.019% between 2011 and 2015. [Ogino 2017].

See the Investigator's Brochure for additional information on MS pathophysiology and presentation.

3.2.2. Current Therapies for Multiple Sclerosis

The current standard of clinical care in the treatment of RMS employs 2 complementary approaches: (1) the use of immunomodulatory drugs to reduce the frequency and severity of relapses and accumulation of physical disability; and (2) the use of drugs that provide symptomatic treatment as needed for depression, bladder dysfunction, and walking impairment. Immunomodulatory drugs currently available for RMS include interferon-beta products (Avonex, Rebif, Betaseron, Betaferon, Extavia, and Plegridy), glatiramer acetate (Copaxone), teriflunomide* (Aubagio), dimethyl fumarate (Tecfidera), monomethyl fumarate* (Bafiertam), natalizumab (Tysabri), alemtuzumab* (Lemtrada), mitoxantrone* (Novantrone), cladribine* (Mavenclad), diroximel fumarate* (Vumerity), sphingosine-1-phosphate receptor modulators (fingolimod [Gilenya], siponimod [Mayzent], ozanimod [Zeposia], and ponesimod* [Ponvory]), and B-cell-depleting therapies (ocrelizumab* [Ocrevus] or ofatumumab [Kesimpta]).
[Note: Drugs marked with "" are not approved for MS treatment in Japan.]*

3.2.3. Profile of Previous Experience With Natalizumab

Natalizumab IV has been used extensively in RRMS, both in clinical studies as well as in the postmarketing setting.

The efficacy of natalizumab IV in participants 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 IV has a profound impact on disability worsening and relapse rate and markedly attenuates brain MRI measures of inflammation and tissue destruction in participants with relapsing forms of MS. Moreover, the data indicate that efficacy is realized early and persists throughout the Treatment Period.

The safety, tolerability, and efficacy of natalizumab IV in Japanese participants with RRMS has been shown in a randomized, double-blind, placebo-controlled study (Study 101MS203) and a long-term extension study (Study 101MS204). The findings of these studies were consistent with the safety and efficacy profiles observed in cohorts of non-Japanese participants with RRMS.

The results from Studies 101MS102 and 101MS206 suggest that the efficacy and safety profiles of natalizumab SC is similar to that of natalizumab IV.

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

3.3. Benefit-Risk Assessment

With over 17 years of experience in the postmarketing setting, natalizumab IV 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 IV demonstrated a 67% reduction in ARR 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 who have 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 IV. Infusion and hypersensitivity reactions and anti-natalizumab antibody production are important safety concerns; however, they are manageable in routine clinical practice. Serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in MS patients receiving natalizumab. In postmarketing experience, there have been rare reports of clinically significant liver injury.

The most important AE affecting natalizumab benefit-risk assessment is the occurrence of 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-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.

The SC route of administration may provide additional benefits to patients and physicians by offering a less invasive route of administration, lower complexity, and reduced time required at each treatment visit compared with IV infusion [Despiau 2017; Lopez-Vivanco 2017]. There is evidence from other medical conditions and indications that patients prefer SC to IV route of administration based on convenience and data from quality-of-life measurements [Falanga 2019; Pivot 2013; Santus 2019; Syrios 2018]. The economic and cost-saving benefits of SC versus IV route of administration in the hospital setting have been demonstrated [Farolfi 2017; Lopez-Vivanco 2017; Olsen 2018].

The safety profile observed for natalizumab administered SC was consistent with the known safety profile of natalizumab administered IV, with the exception of injection site pain. During the 2 SC clinical studies (Studies 101MS102 and 101MS206), injection site pain was reported in 4% (3 of 71) of participants receiving natalizumab 300 mg SC Q4W and no participants receiving natalizumab 300 mg IV Q4W reported injection site pain.

The potential risks related to participation in this study are justified by the anticipated benefit to participants.

Detailed information about the known and expected benefits and risks and reasonably expected AEs of natalizumab SC is provided in the Investigator's Brochure and ICF. A high-level summary of those benefits and risks known during study design is provided here.

4. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
To evaluate the efficacy of natalizumab 300 mg SC Q4W administrations up to 24 weeks in Japanese participants with RRMS	Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans
Secondary Objectives	**Secondary Endpoints**
To evaluate other clinical and MRI measures of efficacy of natalizumab 300 mg SC Q4W administrations in Japanese participants with RRMS	• Cumulative number of new active lesions (sum of gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans • Proportion of participants with any new active lesions (gadolinium-enhancing lesions or nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 48 (Part 2) brain MRI scans • Change from Baseline in number of gadolinium-enhancing lesions at Week 24 and Week 48 • The number of nonenhancing new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48 • The number of new T1 hypointense lesions at Week 24 and Week 48 • ARR at Week 24 • ARR at Week 48 • ARR at Week 52

	• Proportion of relapse-free participants at Week 24 and Week 52 • VAS assessing the participant's global impression of their well-being at Week 24 and Week 48
To evaluate the safety, tolerability, and immunogenicity of natalizumab 300 mg SC Q4W administrations up to 48 weeks in Japanese participants with RRMS	• Incidence of treatment-emergent AEs and SAEs from Baseline to end of study • Anti-JCV antibody status as measured by anti-JCV antibodies • Incidence of injection site reactions and injection reactions • Immunogenicity as measured by the incidence of anti-natalizumab antibodies • Change in EDSS score from Baseline to Week 24 • Change in EDSS score from Baseline to Week 48
To evaluate the PK and PD of natalizumab 300 mg SC Q4W administrations up to 24 weeks and for an additional 24 weeks in Japanese participants with RRMS	• Serum natalizumab concentrations (C_{trough}) at each visit until Week 48 • Serum natalizumab concentration between Day 6 and Day 8 • α4-integrin saturation and serum soluble VCAM-1 concentrations at each visit until Week 48 (excluding Week 1 [Day 6 to Day 8] visit)

5. STUDY DESIGN

5.1. Study Overview

This is a multicenter, open-label, single-arm Phase 3 study to evaluate the efficacy, safety, tolerability, PK, and PD of natalizumab SC formulation in Japanese participants with RRMS. The study will be conducted at approximately 10 sites in Japan. The study will have 2 parts and enroll approximately 20 participants, who will receive natalizumab 300 mg SC Q4W.

Part 1 is designed for a period of 24 weeks to include the efficacy, safety, tolerability, PK, and PD evaluation of natalizumab SC formulation.

Part 2 is designed for an additional period of 24 weeks to include efficacy and safety assessments. Additionally, similar assessments, including safety, PK, and PD, will be assessed after [redacted] in Part 2 to confirm the usability of a [redacted] of natalizumab SC.

At the completion of their 48-week Treatment Period, participants will have Safety Follow-Up Visit at Week 52 and will receive a follow-up safety phone call at Week 60 and Week 72 (i.e., 12 and 24 weeks after the last dose of study treatment on Week 48, respectively) before completing the study.

See Figure 1 for a schematic of the study design.

5.2. Study Duration for Participants

The total study duration for each participant will be up to 76 weeks:

- 4-week Screening Period
- 24-week Treatment Period in Part 1
- 24-week Treatment Period in Part 2
- 4-week Safety Follow-Up Period
- Follow-up safety phone calls 12 and 24 weeks after the last dose

Participants will have up to 16 scheduled visits during the study and 2 safety follow-up phone calls. All visits should be performed ± 3 to 10 days from the nominal visit day. Visit days are calculated with respect to Day 1 (the date of first dose).

The end of study date for a participant may be the last study visit, last follow-up telephone conversation, or last protocol-specified assessment, or if the participant has ongoing AEs that are being followed, the date may be the date of AE resolution or the date the AE becomes stable at discretion of the Investigator.

5.3. Study Stopping Rules

The Sponsor may terminate this study, after informing Investigators, at any time. The Sponsor will notify Investigators when the study is to be placed on hold, completed, or terminated.

If occurrence of any of the following at levels greater than expected for the approved dosing regimen (300 mg natalizumab IV QW4) is detected, study treatment dosing will be stopped:

- anti-natalizumab antibodies
- hypersensitivity reactions
- study treatment administration reactions
- MS disease activity

5.4. Unscheduled Visits and Treatment for MS Relapses

Data collected during unscheduled visits should be recorded on eCRFs only if the data support protocol objectives and/or are required for safety monitoring.

If an MS relapse is suspected during the study, the participants 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 participants' visit schedule. If a participant'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 after 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.

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. Treatment of a protocol-defined relapse may proceed at the discretion of the Investigator according to local standard of care and will not affect the participant'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).

5.5. End of Study

The end of study is last participant, last visit for final collection of data.

6. STUDY POPULATION

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Day 1 or at the timepoint specified in the individual eligibility criterion listed.

6.1. Inclusion Criteria

1. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.

2. Japanese men and women aged 18 to 65 years, inclusive, at the time of informed consent. For participants aged < 20 years*, written informed consent should be obtained from the participant and his or her legally acceptable representative.

   * Informed consent from a legally acceptable representative is not mandatory if the participant is classified as an adult based on the latest applicable local laws.

3. Must have had a diagnosis of RRMS, as defined by the revised 2017 McDonald's criteria [Lublin 2014; Thompson 2018]. All other possible neurologic diagnoses must have been reasonably excluded by means of laboratory and/or imaging studies, in the opinion of the Investigator.

4. Must have had an EDSS score between 0.0 and 5.5, inclusive.

5. Must have experienced at least 1 medically documented clinical exacerbation within 12 months of enrollment (Day 1).

6. Must have had screening MRI or documentation of an MRI within the participant's medical record within 12 months of the Screening Visit that revealed 3 or more T2 hyperintense lesions consistent with MS.

7. Must be willing to remain free from concomitant immunosuppressive or immunomodulatory treatment (including IFN-β and chronic systemic corticosteroids) while receiving study treatment and for at least 12 weeks after the last dose of study treatment. Treatment with natalizumab IV is allowed after Week 52.

8. All women of childbearing potential must practice contraception as described in Section 11.5.

9. Was born in Japan, and biological parents and grandparents were of Japanese origin.

6.2. Exclusion Criteria

Medical History and Current Health Status

1. Evidence of current SARS-CoV-2 infection within 14 days prior to Screening, between Screening and Baseline Visit, or at Baseline Visit, including but not limited to a fever (temperature > 37.5°C), new and persistent cough, breathlessness, or loss of taste and/or smell.

   Note: If a SARS-CoV-2 test (polymerase chain reaction or other regulatory approved method) is performed per the discretion of the Investigator in accordance with local site practice, the test result must be negative in order for the participant to be enrolled in the study.

2. Have close contact within 14 days prior to Day 1 with a SARS-CoV-2–positive individual. Close contact is defined as:
   a. face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;
   b. direct physical contact with a probable or confirmed case;
   c. direct care for a patient with probable or confirmed COVID-19 disease without the use of recommended personal protective equipment; or
   d. other situations as indicated by local risk assessments.
3. History or positive test result at Screening for HIV. The requirement for testing at Screening may be omitted if it is not permitted by local regulations.
4. Diagnosis of primary progressive MS or secondary progressive MS.
5. Diagnosis or history of neuromyelitis optica spectrum disorders, e.g., a long spinal lesion extending over 3 or more vertebral bodies was detected, or a history of positive tests for anti-AQP4 or anti-MOG antibodies.
6. An MS exacerbation (relapse) within 30 days prior to enrollment or, in the opinion of the Investigator, the participant not having stabilized from a previous relapse prior to enrollment (Day 1).
7. History of hepatitis C infection or positive test result at Screening for HCV antibody.
8. Current hepatitis B infection (defined as positive for HBsAg and/or total anti-HBc). Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs) or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.
9. Clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within the 30 days prior to enrollment (Day 1).

10. Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 14 days prior to Screening or during the screening period (Day -28 to Day -1). Participants with local fungal infection (e.g., candidiasis, tinea) are eligible to be rescreened after successful treatment of the infection.

11. History of hypersensitivity reaction to the excipients contained in the formulation and any diagnostic agents (including gadolinium) to be administered during the study.

12. History of, or ongoing, malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell carcinomas and squamous cell carcinomas that have been completely excised and considered cured at least 12 months prior to Day -1).

13. History of, or available abnormal laboratory results indicative of any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric (including major depression), renal, and/or any other major disease or known drug hypersensitivity that, in the opinion of the Investigator, would preclude the administration of a recombinant humanized antibody immunomodulating agent for the course of the study. The Investigator must review the participant's medical fitness for participation and consider any disease that would preclude treatment.

14. History of transplantation and anti-rejection therapy.

15. History of PML.

16. Systolic blood pressure > 150 mmHg or < 90 mmHg after remaining in the same body position (seated or supine) for 5 minutes at Screening or prior to administration of the first dose. If out of range, testing may be repeated once at Screening and once prior to dosing. Participant must not be dosed if the repeated value is still out of range.

17. Clinically significant (as determined by the Investigator) 12-lead ECG abnormalities.

18. Confirmed demonstration of corrected QT interval, using Fridericia's correction method, of > 450 ms for males and > 460 ms for females.

19. History of alcohol or substance abuse (as determined by the Investigator), a positive drug/alcohol test at Screening, alcohol use within 48 hours prior to enrollment (Day 1), or an unwillingness to refrain from alcohol, or illicit or recreational drugs, during the study.

20. A participant who is positive or uncertain of being positive for TB* within 30 days of Day 1.

    * Note: Participants with following IGRA test results will be excluded:

    T-spot TB test: positive or 2 successive borderline/invalid test results

QuantiFERON-TB Gold Plus test: positive or 2 successive indeterminate test results

21. The participant is considered by the Investigator to be immunocompromised (e.g., lymphopenic), based on medical history (e.g., opportunistic infections), physical examination, or laboratory testing (e.g., white blood cell).

22. The participant is unable to have a brain MRI scan (e.g., a participant with a metal clip to repair a cerebral aneurysm).

Medications

23. Previous exposure to natalizumab.

24. Previous treatment with any of the following: total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, hematopoietic stem cell therapy, or alemtuzumab.

25. Treatment with immunosuppressant medications, e.g., azathioprine, cyclophosphamide, and methotrexate within 6 months prior to enrollment (Day 1); mitoxantrone and cyclosporine within 12 months prior to enrollment (Day 1).

26. Treatment with any of the following medications or procedures within 6 months prior to enrollment (Day 1): IV immunoglobulin, plasmapheresis, or cytapheresis.

27. Treatment with any of the following medications within 30 days prior to enrollment (Day 1):
    a. IV corticosteroid treatment
    b. Systemic corticosteroid treatment
    c. 4-Aminopyridine or related products

28. Treatment with sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, or ozanimod) within 90 days prior to enrollment (Day 1).

29. Treatment with fumarates (Fumaderm, Tecfidera, or Vumerity) within 4 weeks prior to enrollment (Day 1).

30. B-cell-targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab, ofatumumab) within 12 months of Screening; greater than 12 months of Screening is permissible with evidence that the CD19 cells have returned to within normal range (per local laboratory reference range).

31. Treatment with immunomodulatory medications (including IFN-β and glatiramer acetate) within 2 weeks of enrollment (Day 1).

32. Administration of any live-attenuated vaccine given within 30 days prior to Day -1 or planned to be given during study participation.

Other

33. Blood donation (1 unit or more) within 90 days prior to Screening, plasma donation from 1 week prior to Screening, and platelet donation from 6 weeks prior to Screening.

34. Clinically significant abnormal laboratory test values, as determined by the Investigator, during the screening period (Day -28 to Day -1).

35. Abnormal screening liver function test results: alanine aminotransferase or aspartate aminotransferase > 2 × ULN or bilirubin > 1.5 × ULN during Screening.

36. Plans to undergo elective procedures or surgeries at any time after signing the ICF through the Safety Follow-Up Visit.

37. Participants who are pregnant or currently breastfeeding and those intending to become pregnant during the study.

38. 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 6 months prior to the Baseline Visit.

39. Inability to comply with study requirements.

40. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrollment.

6.3. Screening, Retesting, and Screen Failures

6.3.1. Screening

Once informed consent is obtained, screening assessments can occur. At this time, a unique identification number is assigned that will be used on study-related documents pertaining to the participant. Any identification numbers that are assigned will not be reused even if the participant does not receive treatment or continue in the study. Study sites are required to document all screened participants initially considered for inclusion in the study.

6.3.2. Retesting

Participants who fail screening criteria because of an out-of-range result that is not clinically significant can be retested once at the discretion of the Investigator. Participants who have clinically significant abnormal laboratory test values should not be retested. The Screening Period may be extended for eligible individuals who cannot complete the Day 1 Visit within 28 days of signing the ICF. Individuals who signed the ICF and subsequently do not meet concomitant medication criteria can have their Screening Period extended to ensure the requirements for concomitant medication stabilization have been met.

If a participant initially fails screening due to meeting any of the following exclusion criteria, the participant may be allowed to rescreen 1 time, at the Sponsor's discretion:

- Exclusion no. 1: Evidence of current SARS-CoV-2 infection within 14 days prior to Screening, between Screening and Baseline Visit, or at Baseline Visit, including but not limited to a fever (temperature > 37.5°C), new and persistent cough, breathlessness, or loss of taste and/or smell (Note: If a SARS-CoV-2 test [polymerase chain reaction or other regulatory approved method] is performed per the discretion of the Investigator in accordance with local site practice, the test result must be negative in order for the participant to be enrolled in the study).

- Exclusion no. 2: Have close contact within 14 days prior to Day 1 with a SARS-CoV-2 positive individual. Close contact is defined as:

  a. face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;
  b. direct physical contact with a probable or confirmed case;
  c. direct care for a patient with probable or confirmed COVID-19 disease without the use of recommended personal protective equipment; or
  d. other situations as indicated by local risk assessments.

- Exclusion no. 6: An MS exacerbation (relapse) within 30 days prior to enrollment or, in the opinion of the Investigator, the participant not having stabilized from a previous relapse prior to enrollment (Day 1).

- Exclusion no. 9: Clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within the 30 days prior to enrollment (Day 1).

- Exclusion no. 10: Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 14 days prior to Screening or during the screening period (Day -28 to Day -1). Participants with local fungal infection (e.g., candidiasis, tinea) are eligible to be rescreened after successful treatment of the infection.

- Exclusion no. 25: Treatment with immunosuppressant medications, e.g., azathioprine, cyclophosphamide, and methotrexate within 6 months prior to enrollment (Day 1); mitoxantrone and cyclosporine within 12 months prior to enrollment (Day 1).

- Exclusion no. 26: Treatment with any of the following medications or procedures within 6 months prior to enrollment (Day 1): IV immunoglobulin, plasmapheresis, or cytapheresis.

- Exclusion no. 27: Treatment with any of the following medications within 30 days prior to enrollment (Day 1):

  a. IV corticosteroid treatment
  b. Systemic corticosteroid treatment
  c. 4-Aminopyridine or related products

- Exclusion no. 28: Treatment with sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, or ozanimod) within 90 days prior to enrollment (Day 1).

- Exclusion no. 29: Treatment with fumarates (Fumaderm, Tecfidera, or Vumerity) within 4 weeks prior to enrollment (Day 1).

- Exclusion no. 30: B-cell-targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab, ofatumumab) within 12 months of Screening; greater than 12 months of Screening is permissible with evidence that the CD19 cells have returned to within normal range (per local laboratory reference range).

- Exclusion no. 31: Treatment with immunomodulatory medications (including IFN-β and glatiramer acetate) within 2 weeks of enrollment (Day 1).

- Exclusion no. 32: Administration of any live-attenuated vaccine given within 30 days prior to Day -1 or planned to be given during study participation.

- Exclusion no. 33: Blood donation (1 unit or more) within 90 days prior to Screening, plasma donation from 1 week prior to Screening, and platelet donation from 6 weeks prior to Screening.

In addition, participants with an 'indeterminate result' for HCV antibody during Screening may be allowed to retest and will be re-evaluated on a case-by-case basis, after discussion with the Medical Monitor and Sponsor Medical Study Director to determine eligibility.

Upon rescreening, and in consultation with the Medical Monitor and Sponsor Medical Study Director, the participant should sign the ICF again and repeat the screening assessments as per discussion with the Investigator and study team.

Rescreened participant will receive a new screening number, where the trailing alphanumeric character in the screening number will move forward sequentially, e.g., from XXXA to XXXB.

If the participant fails screening twice, they may not undergo further screening for this study.

6.3.3. Screen Failures

Screen failures are defined as participants who sign the ICF but are not subsequently dosed. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant'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.

7. STUDY TREATMENT

7.1. Regimen

Participants will receive natalizumab 300 mg SC Q4W for 48 weeks (2 PFS for SC injection 150 mg/mL [total of 300 mg/2 mL]).

Injections should be administered one after the other without significant delay. The second injection should be administered no later than 30 minutes after the first injection. Participants should be observed during both SC injections and for 1 hour after for signs and symptoms of injection site reactions and injection reactions including hypersensitivity. After the first 6 natalizumab doses, the 1-hour postadministration observation time for subsequent SC injections may be reduced or removed according to clinical judgement if the participants have not experienced any injection reactions including hypersensitivity.

The sites for SC injection should be the thigh, abdomen, or the posterior aspect of the upper arm. Do not inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way. When removing the syringe from the injection site, let go of the plunger while pulling the needle straight out. Letting go of the plunger will allow the needle guard to extend and cover the needle. The second injection should be at least 1 inch (2.5 cm) away from the first injection location.

[redacted]

Missed doses should be taken as soon as possible. Doses should not be doubled to make up for missed doses.

7.2. Modification of Dose and/or Treatment Schedule

The dosage or treatment schedule cannot be modified.

7.3. Study Treatment Management

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

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA aligns with all other references, including the protocol.

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment is for

one-time use only; do not use any study treatment remaining in the syringe for another participant.

7.3.1. Natalizumab

Natalizumab for SC injection is provided in a 1 mL PFS containing 150 mg natalizumab and excipient materials (sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, polysorbate 80, and water for injection at 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 is stored in the IRT system, and printable assignment reports are available to site staff. Study treatment should not be used after the expiry or use-by date.

Natalizumab is produced using fetal bovine serum that was used in cloning before master cell bank preparation and storage for the master cell bank and working cell bank. Also, natalizumab is produced using bovine blood-derived bovine serum albumin that was used in preparation for the master cell bank and working cell bank. This fetal bovine serum meets the criteria set forth by a public agency, the European Directorate for the Quality of Medicines, for the prevention of infection with TSE agents to humans. None of these bovine materials are contained in the final product. There is no report of TSE being transmitted from the final product to humans.

Human transferrin is used in the cell bank media used for the preparation of the master cell bank and the working cell bank for natalizumab. The manufacturing process for natalizumab does not use the human transferrin, and the final product does not contain human transferrin. Nucleic acid amplification test is not conducted for the source plasma of origin for human blood derivatives, but it is confirmed that the results of serological testing for viruses (antigen and/or antibody to viruses) is performed. In addition, there are several steps that can remove/inactivate viruses during the manufacturing process of natalizumab. Therefore, the risk of contamination with HBV, HCV, HIV-1, and HIV-2 is extremely low. There is no report of TSE being transmitted from natalizumab to humans, although human transferrin comes from human blood obtained in the US. Theoretical risk assessment for TSE demonstrated the safety level required to ensure that the risk of transmission of TSE by natalizumab is extremely low.

However, since the risk of TSE transmission cannot totally and theoretically be denied, this product must be used after careful consideration of the need for the product in the treatment of the disease, and this information must be provided to the patient prior to the administration of the product.

7.3.1.1. 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 syringes or study treatment, do not use the study treatment. The syringe in question should be saved at the study site and the problem immediately reported to the Sponsor.

Contact information for reporting a problem is provided in the study reference guide.

7.3.1.2. 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.

7.3.1.3. Handling and Disposal

The Investigator must return all used and unused syringes of natalizumab as instructed by the Sponsor unless approved for onsite destruction.

If any natalizumab supplies are to be destroyed at the study site, the institution or appropriate site staff must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor 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.

7.3.1.4. Accountability

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

Unless otherwise notified, all syringes both used and unused, must be saved for study treatment 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 the Sponsor. A written explanation must be provided for any discrepancies.

7.4. Blinding Procedures

Not applicable. This is an open-label study.

7.5. Precautions

Refer to the DHA for details on postdose observation requirements.

7.6. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Study treatment will be administered by the site staff at all visits except Week 28 and Week 36 Visits. [redacted]

7.7. Concomitant Therapy and Procedures

7.7.1. Concomitant Therapy

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

Participants should be instructed to contact their Investigators before taking any new medications (including nonprescription drugs and herbal preparations) or immunization/vaccination.

7.7.1.1. Allowed Concomitant Therapy

Concomitant treatment with any of the following is allowed so long as the exclusionary criteria described in Section 6.2 are observed:

- Medications necessary for the treatment of AEs.
- 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 5.4).
- Corticosteroids that are administered by nonsystemic routes (e.g., topical, inhaled).

7.7.1.2. Disallowed Concomitant Therapy

Concomitant treatment with any of the following is not allowed while receiving study treatment and for at least 12 weeks after the last dose of 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, alemtuzumab, cyclosporine, ofatumumab, 4-Aminopyridine or related products, or any therapeutic monoclonal antibody.

- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any steroid therapy for treatment of MS other than for acute relapse. Use of steroids for other purposes is to be considered on a case-by-case basis and must be discussed with the Medical Monitor. Protocol-defined treatments of relapses as described in Section 5.4 are allowed.
- Treatment with natalizumab IV is not allowed up to Week 52 but is allowed after Week 52.
- Treatment with > 800 µg/day of inhaled beclomethasone dipropionate for pressurized metered dose inhalers with extra fine particle hydrofluoroalkane propellant.
- COVID-19 vaccine within 7 days prior or 7 days postadministration of study treatment.

Participants who receive any of these restricted treatments will be reviewed by the study team and may be required to discontinue study treatment permanently and may be withdrawn from the study as outlined in Section 8.1.

7.7.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the participant's last study visit.

7.7.2.1. 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
- hematopoietic stem cell therapy

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 8.1.

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

7.8. Continuation of Treatment

No further provisions are made for access to the study treatment. If natalizumab SC is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

8. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

8.1. Discontinuation of Study Treatment

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

- The participant becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 11.4.1.
- The participant develops persistent anti-natalizumab antibodies (2 consecutive readings).
- The participant experiences hypersensitivity or suspected allergic reaction to study treatment.
- The participant develops PML or another serious opportunistic infection.
- The participant experiences an AE or SAE that necessitates permanent discontinuation of study treatment.
- The participant experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- At the discretion of the Investigator for medical reasons.
- The participant withdraws consent to continue study treatment.
- The participant is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor for noncompliance.

The primary reason for discontinuation of study treatment must be recorded in the participant's eCRF.

Participants who discontinue treatment may remain in the study and continue protocol-required tests and assessments. Thus, a participant may continue study visits every 4 weeks up to Week 52 and receive safety phone calls at Week 60 and Week 72.

8.2. Lost to Follow-Up

Participants 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 participant fails to return to the study site for a required study visit:

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

8.3. Withdrawal of Participants From the Study

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

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

The primary reason for the participant's withdrawal from the study must be recorded in the participant's eCRF.

Participants are encouraged to undergo an ET Visit unless withdrawal is due to death or withdrawal of consent. The ET Visit in such participants should occur at 4 weeks (±7 days) after the last dose of study treatment and should be followed by safety phone calls at 12 weeks (±10 days) and 24 weeks (±10 days) after the last dose of study treatment.

Participants who withdraw from the study may be replaced at the Sponsor's discretion.

9. EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

See Section 1.3 for the timing of all assessments.

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

9.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of natalizumab SC:

MRI Efficacy Assessments

- T2 hyperintense lesion number
- T1 hypointense lesion number
- Gadolinium-enhancing lesion number

The images will be captured according to the MRI Acquisition and Procedures Manual provided by the Sponsor.

All MRIs should be read by the central radiologist to evaluate only for the purpose of performing quantitative measurements of new active lesions. No incidental findings will be provided to the study site Investigator by the central radiologist. Local radiologists may provide any incidental findings on the MRI scans to the site Investigator as medically needed. Locally read MRIs will not be used for endpoint analyses.

Clinical Efficacy Assessments

- Relapses (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; see Section 5.4 for further details)
- Neurological examination
- VAS assessing the participant's global impression of their well-being

9.2. Pharmacokinetic Assessments

The serum natalizumab concentrations between Day 6 and Day 8 and at predose administration (C_{trough}) at each visit until Week 48 will be measured as the PK assessments.

9.3. Pharmacodynamic Assessments

The α4-integrin saturation and serum soluble VCAM-1 concentrations at predose administration at each visit until Week 48 will be measured as the PD assessments.

In addition to trough α4 integrin saturation, [redacted]

10. SAFETY ASSESSMENTS

See Section 1.3 for the timing of all safety assessments.

10.1. Clinical Safety Assessments

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

- AE and SAE recording
- Medical history
- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate. Participants must remain in the same body position (seated or supine) quietly for 5 minutes prior to pulse rate and blood pressure measurements; measurements must be performed within 1 hour prior to administration of study treatment.
- Weight measurements
- 12-Lead ECGs will be collected after the participant has been resting in a supine position for at least 5 minutes.
- EDSS
- C-SSRS: the baseline version of C-SSRS will be used at Screening (recall period is lifetime); the Since Last Visit C-SSRS version will be used thereafter. The C-SSRS will be conducted by a trained [redacted], and any findings of concern will be handled as appropriate.
- Concomitant therapy and procedure recording

10.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

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

- Hematology: complete blood count with differential and platelet count, and absolute neutrophil count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count

- Blood chemistry: sodium, potassium, chloride, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, gamma glutamyl transferase, glucose, calcium, phosphorus, blood urea nitrogen, creatinine, uric acid, bilirubin (total and direct), total protein, albumin, and bicarbonate

- Urinalysis: color, protein, blood, glucose, ketones, pH, specific gravity, and microscopic examination if abnormal.

10.3. Product-Specific Safety Assessments

The following assessments will be performed to determine the safety of natalizumab SC:

- Anti-natalizumab antibodies

- Anti-JCV antibody index

11. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

At the signing of the ICF, each participant and/or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of site staff for reporting SAEs, pregnancies, overdoses, and medical emergencies. Throughout the protocol, the Sponsor is named, but reporting may be done through a CRO.

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject (participant) 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 assessment such as an abnormal laboratory value), 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 assessment (e.g., laboratory value, vital sign, and ECG) 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 participant to receive specific corrective therapy.
- The result is considered by the Investigator to be clinically significant.

11.1.2. 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 participant 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 participant 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.)

11.1.3. Combination Product

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Natalizumab SC is an investigational combination product in Japan.

11.1.4. Product Complaints for Investigational Combination Products

For investigational combination product with a medical device component, complaints include but are not limited to any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the Sponsor.

11.1.5. 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 participant is hospitalized. The study site must document all 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 participant's consent to be 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 participant's consent to be 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 participant 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 11.1.2 is met.

11.2. Safety Classifications

11.2.1. 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 11.1.2.
- The relationship of the event to study treatment as defined in Section 11.2.2
- The severity of the event as defined in Section 11.2.3.

11.2.2. 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.

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

11.2.4. Expectedness of Events

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

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and follow-up safety phone call is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

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

The events of relapse will not be collected as AEs as they are considered part of the efficacy endpoints.

11.3.2. Adverse Events of Special Interest

An AE of special interest is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required. The following AEs will be considered AESIs: PML, injection site pain, opportunistic infections other than PML, herpes infection, drug-induced liver injury, hypersensitivity reactions, and malignancies.

11.3.3. Serious Adverse Events

Any SAE experienced by the participant between the time of the signing of the ICF and 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. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs must be reported to the Sponsor within 24 hours as described in Section 11.3.5. Follow-up information regarding an SAE also must be reported within 24 hours.

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

11.3.4. Product Complaints

All product complaints must be entered into Biogen's CSS portal according to the Clinical Product Complaints Training Guidelines.

Product complaints associated with a device malfunction that result in an SAE must be reported in Biogen's CSS portal within 24 hours of awareness.

11.3.5. 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 the Sponsor within 24 hours of the 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 the Sponsor regardless of the following: • Whether or not the participant has undergone study-related procedures • Whether or not the participant 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 or email a completed SAE form; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

11.3.5.1. Deaths

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

11.3.6. Suspected Unexpected Serious Adverse Reactions

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

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

11.4. Procedures for Handling Special Situations

11.4.1. Pregnancy

Participants should not become pregnant during the study and for 6 months after their last dose of study treatment. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant from first dose of study drug to 6 months after the last dose of study treatment by faxing or emailing the appropriate form to the Sponsor within 24 hours of the 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 site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE eCRF.

Congenital abnormalities and birth defects in the offspring of male or female participants should be reported as an SAE if conception occurred during the study treatment period or within 6 months from their last dose of study treatment.

11.4.2. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Sponsor 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 or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing eCRF.

11.4.3. Medical Emergency

In a medical emergency requiring immediate attention, site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Monitor. Refer to contact information in the protocol attachment for complete contact information.

11.5. Contraception Requirements

All women of childbearing potential must ensure that highly effective contraception is used during the study and for 6 months after their last dose of study treatment. In addition, participants should not donate eggs for the duration of the study and for at least 6 months after their last dose of study treatment.

For the purposes of this study, women of childbearing potential are defined as all women physiologically capable of becoming pregnant, UNLESS they meet one of the following conditions:

- Postmenopausal
  - 52 continuous weeks of natural (spontaneous) amenorrhea without an alternative medical cause and a serum FSH level > 40 mIU/mL
  - 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 use of 1 of the following:

For females:

- Established use of oral, intravaginal[1], or transdermal[1] combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected[1], or implanted[1] progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Barrier methods of contraception, if applicable according to local guidelines.
- Bilateral tubal occlusion.

True abstinence, when this is consistent with the preferred and usual lifestyle of the participant, 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 11.4.1.

[1] Intravaginal and transdermal combined hormonal methods of contraception and injected and implanted hormonal methods of contraception are not approved for use in Japan.

11.6. Safety Responsibilities

11.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the eCRF 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 participants and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the eCRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.
- Report any product complaints in Biogen's CSS Portal.
- Report product complaints associated with a device malfunction that result in an SAE in Biogen's CSS portal within 24 hours of awareness.

11.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any participants, the Medical Monitor is responsible for reviewing with site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 4.

The primary endpoint of the study will be cumulative number of new active lesions (sum of gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) on Week 24 (Part 1) brain MRI scans. The analysis of the primary endpoint will be performed after the last participant completes the Week 24 Visit. The final analysis of key functional outcomes will be performed after the last participant completes the Week 52 Visit. All participants will be followed up until Week 72 for further long-term evaluation of safety.

A summary of primary and secondary efficacy endpoints, PK, PD, safety endpoints, and immunogenicity data is provided in this section. Analyses of other supportive endpoints, including analyses of exposure-response relationships for clinical, imaging, and safety outcome measures, will be described in the SAP, which will contain the final details on the statistical methods used in this study. The analyses planned for the interim database lock after the last participant completes the Week 24 Visit and for the final database lock after the last participant completes the Week 52 Visit as well as for the long-term safety database lock for an addendum after the last participant completes the Week 72 Follow-Up Visit will be described in the SAP.

12.1. General Considerations

Efficacy and safety endpoints will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, 95% CI, median, minimum, and maximum) for continuous variables and frequency and percentage for categorical variables.

12.2. Analysis Sets

Full analysis set is defined as all participants who receive at least 1 dose of study treatment and have at least 1 postbaseline efficacy assessment.

The PK analysis set is defined as all participants who receive at least 1 dose of study treatment and have at least 1 measurable serum natalizumab concentration.

The PD analysis set is defined as all participants who receive at least 1 dose of study treatment and have at least 1 assessment for α4-integrin saturation, serum soluble VCAM-1 concentration, and [redacted]

The safety analysis set is defined as all participants who receive at least 1 dose of study treatment.

12.3. Methods of Analysis for Efficacy Endpoints

12.3.1. Analysis of the Primary Endpoint

The primary endpoint of cumulative number of new active lesions (gadolinium-enhancing lesions and nonenhancing new or newly enlarging T2 hyperintense lesions) at Week 24 (Part 1) will be calculated as the sum of the new active lesions over the postbaseline scans at Weeks 12 and 24 for all treated participants with at least 1 postbaseline efficacy assessment excluding persistent ADA or PML cases. The cumulative number will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, 95% CI, median, minimum, and maximum) and will be analyzed using negative binomial distribution.

Intercurrent events include start of rescue medication, early discontinuation of treatment due to safety and/or lack of efficacy and/or other reasons, start of persistent ADA, and start of PML. The proposed primary and [redacted] estimands will be based on a hypothetical strategy and/or the treatment policy strategy.

Missing gadolinium-enhancing or new or newly enlarging nonenhancing T2 hyperintense lesions at Week 12 or 24 will be imputed using last observation carried forward on-treatment.

12.3.2. Analysis of the Secondary Endpoints

The secondary endpoint of cumulative number of new active lesions at Week 48 (Part 2) will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, 95% CI, median, minimum, and maximum).

The change from Baseline in number of gadolinium-enhancing lesions at Week 24 and Week 48, the number of nonenhancing new or newly enlarging T2 hyperintense lesions at Week 24 and Week 48, and the number of new T1 hypointense lesions at Week 24 and Week 48 will be summarized descriptively as well.

Other secondary endpoints will also be summarized, including proportion of participants with any new active lesions at Weeks 24 and 48; ARR within the past 12 months, at Weeks 24, 48, and 52; proportion of relapse-free participants at Weeks 24 and 52; and VAS assessing the participant's global impression of their well-being at Weeks 24 and 48.

[redacted]

12.4. Methods of Analysis for Pharmacokinetic Endpoints

Serum natalizumab concentrations (C_{trough}) measured Q4W (just prior to dose administration) until Week 48 and 1 serum natalizumab concentration measured between Day 6 and Day 8 to

obtain absorption information for SC administration will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, geometric mean, 95% CIs of geometric mean, geometric CV%, median, minimum, and maximum) at each timepoint.

All measured serum natalizumab concentrations in this study will be combined with other natalizumab study data, and they will be used for population PK analysis to evaluate absorption profile after natalizumab SC administration. The analysis plan and reports will be prepared separately from this study.

12.5. Methods of Analysis for Pharmacodynamic Endpoints

α4-integrin saturation levels, soluble VCAM-1 serum concentrations, and [redacted] The data will be summarized using descriptive statistics (number of participants with data, mean, standard deviation, geometric mean, 95% CI of geometric mean, geometric CV%, median, minimum, and maximum) at each timepoint.

12.6. Methods of Analysis for Safety Endpoints

12.6.1. Adverse Events

AEs will be coded using the MedDRA.

Treatment-emergent AEs will be summarized and presented. A treatment-emergent AE is defined as any AE that has an onset date and time that is on or after the date and time of the first dose of study treatment, or that has worsened after the date and time of the first dose of study treatment through 84 days after the last dose of study treatment.

All AEs will be classified using the MedDRA. The incidence of AEs will be summarized as follows:

- by MedDRA preferred term
- by primary SOC
- by primary SOC and MedDRA preferred term
- by severity
- by relationship to study treatment

The incidence of SAEs and AEs leading to early termination, as well as hypersensitivity reactions, injection site reactions, injection reactions, infections, and malignancies will also be summarized.

12.6.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis. Laboratory evaluations will be evaluated to determine the incidence of abnormalities that emerge during the study. Laboratory abnormalities will be summarized in shift tables.

12.6.3. Vital Signs

Vital signs will be examined to determine the incidence of clinically relevant abnormalities. The definitions of these abnormalities are provided in Table 2.

Table 2: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	> 38°C and an increase from predosing of at least 1°C
Pulse rate	> 120 beats per minute and an increase from predosing of more than 20 beats per minute, or < 50 beats per minute and a decrease from predosing of more than 20 beats per minute
Systolic Blood Pressure	> 180 mmHg and an increase from predosing of more than 40 mmHg, or < 90 mmHg and a decrease from predosing of more than 30 mmHg
Diastolic Blood Pressure	> 105 mmHg and an increase from predosing of more than 30 mmHg, or < 50 mmHg and a decrease from predosing of more than 20 mmHg

For each vital sign, the number of participants evaluated and the number and percentage of participants with the defined abnormality at any time postbaseline will be presented.

12.6.4. 12-Lead ECG

A listing of participants with abnormal status will be presented. Changes from baseline will be summarized using shift tables.

12.6.5. C-SSRS

Incidence of potentially clinically significant criteria at any postbaseline visit and shifts from baseline in C-SSRS will be summarized using counts and percentages.

12.6.6. EDSS

Change in EDSS score from Baseline to Week 24 and Week 48 will be summarized descriptively (number of participants, mean, standard deviation, median, minimum, and maximum).

12.7. Methods of Analysis for Immunogenicity Data and Anti-JCV Antibodies

Immunogenicity is measured by the presence of anti-natalizumab antibodies. The incidence of anti-natalizumab antibodies and anti-JCV antibodies will be summarized descriptively.

12.8. Interim Analyses

An interim analysis, based on the primary endpoint of cumulative number of new active lesions, will be performed at Week 24. The interim efficacy data will be summarized descriptively and analyzed using negative binomial distribution. [redacted] The interim safety data will also be summarized.

12.9. Sample Size Considerations

The study plans to enroll approximately 20 participants which was based on feasibility. Approximately 15 through 17 evaluable participants are deemed sufficient to characterize the efficacy profile of natalizumab SC.

The margin in Study 101MS330 showing comparability of the natalizumab SC to IV is set at 2.32, which is one-third of the mean difference (1.53 and 8.49) between the natalizumab and placebo groups in new active lesions at Week 24 in Japanese natalizumab IV study 101MS203. To demonstrate the comparability of natalizumab SC to IV, 15 evaluable participants allow at least 80% probability that the upper limit of the 95% CI for mean new active lesions at Week 24 in natalizumab SC is lower than 3.85 (i.e., 2.32 plus 1.53), assuming similar field MRI machines are used for Studies 101MS203 and 101MS330 and the true mean of new active lesions for the natalizumab SC is 1.53. In addition, assuming 70% of participants will have MRIs using 3T machines in Study 101MS330, compared to approximately 13% in Study 101MS203, and the true mean of new active lesions is 1.73, 17 evaluable participants allow 80% probability that observing the upper limit of 95% CI for new active lesions at Week 24 in natalizumab SC is lower than 3.85 [Shilane and Bean 2013].

13. ETHICAL AND REGULATORY REQUIREMENTS

The Sponsor, any contracted third party, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable ICH and GCP guidelines and conduct the study according to local regulations.

The Investigators are responsible for demonstrating timely oversight of all clinical trial data from their site, including data external to the electronic data capture system, such as laboratory and imaging data. Investigators must approve all their data on completed eCRFs by signing electronically, at the participant, visit, or casebook level, at any time prior to an interim lock or database lock, as well as before any subsequent re-lock. The electronic data capture system does not prohibit Investigator approval or signing in any way.

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.

13.1. Declaration of Helsinki

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

13.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study. The Sponsor will submit documents on behalf of the study sites.

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

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

The Sponsor 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 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, where required, the study site must submit a close-out letter to the ethics committee and the Sponsor.

13.3. Changes to Final Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before 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, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a participant. 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 13.4).

13.4. Informed Consent

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

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

A copy of the signed and dated ICF must be given to the participant and/or the participant's legally authorized representative. 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 and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the participant's medical record.

When additional information that may affect participants' willingness to continue in the study becomes available, the Investigators will be notified in a timely manner, according to all local and applicable law. An updated ICF may be required.

13.5. Participant Data Protection

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

During the study, participants' 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. Because it is not always known whether the effects of the study treatment are influenced by race or ethnicity, this information will be of value in the analysis of efficacy and safety data.

Study reports will be used for research purposes only. The participant will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. The Sponsor, 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 participant's personal medical data confidential.

13.6. Compensation for Injury

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

13.7. Conflict of Interest

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

13.8. Study Report Signatory

The Sponsor 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 participant enrollment; or by other factors determined to be relevant by the Sponsor.

13.9. Registration of Study and Disclosure of Study Results

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

The Sponsor also will notify, when required, the regulatory authorities and ethics committees about the completion or termination of this study and send a copy of the study synopsis in accordance with necessary timelines.

13.10. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor 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 site.

14. KEY ROLES AND STUDY GOVERNANCE COMMITTEES

14.1. Site Staff

The Investigator of the site will designate the appropriate site personnel and their role in the study.

14.2. Vendors

The Sponsor 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.

14.2.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, management of SAE reports, monitoring, and data management.

14.2.2. Interactive Response Technology

IRT will be used in this study. Before participants 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.

14.2.3. Electronic Data Capture

Participant information will be captured and managed by study sites on eCRFs by a Web-based electronic data capture tool configured by the Sponsor and hosted by the electronic data capture vendor.

14.2.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to analyze the hematology, blood chemistry, antibody, and urine samples collected for this study. PK and PD samples will be analyzed at a laboratory selected by the Sponsor.

No duplicate samples will be taken; however, aliquots of the original samples will be stored as back-up in case the original samples are lost or not evaluable.

14.2.5. Central Facility for Other Assessments

A central facility has been selected by the Sponsor to read and interpret all MRI scans for this study.

14.2.6. Central Review of Raters

The Sponsor has selected a rater management group to establish rater qualifications, provide study-specific training about the rater process, and provide oversight. As part of the oversight

process, the rater management group will incorporate a central review of the raters to ensure that data are consistently rated across sites.

14.3. Study Committees

Not applicable.

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

The Investigator must not screen any participants prior to the Sponsor completing a study initiation visit. This initiation visit with the Investigator and other site staff, as appropriate, will include a detailed review of the protocol, study procedures, and study responsibilities.

15.2. 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 sites for clarification and resolution, as appropriate. The Investigator is responsible for endorsing all eCRF data prior to any interim or final database lock.

During and/or after completion of the study, quality assurance officers named by the Sponsor 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.

15.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the participants' 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 Medical 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 participant safety, data integrity, and critical data and processes.

During these visits, eCRFs, 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 the Sponsor 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 participant 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 investigational site and its facilities.

15.4. Study Funding

The Sponsor is responsible for setting up the funding for the study. All financial details are provided in the separate contracts between the institution, Investigator, and Sponsor organization.

15.5. Publications

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

16. REFERENCES

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17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of 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

_____

Investigator's Name (Print)

_____

Study Site (Print)

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

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

AMENDMENT SUMMARY

Biogen Protocol 101MS330

A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of Administration

Version 3.0

Date: 21 February 2022

Version 3.0 of the protocol has been prepared for this amendment, which supersedes Version 2.0.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 101MS330 was to include a safety phone call at Week 60.

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

Section 1.3, Schedule of Activities

Now reads:

		Part 1: 24-Week Open-Label Treatment								Part 2: 24-Week Open-Label Treatment						Safety FU	**Safety FU Phone Call[1]**	Safety FU Phone Call[1,2]	Unscheduled	
	SCR	BL	W1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	**W60**	W72	Neurological Worsening	ET Visit
Assessments	D -28 to D -1	D1	D6 to D8	D29 (±3)	D57 (±3)	D85 (±3)	D113 (±3)	D141 (±3)	D169 (±3)	D197 (±3)	D225 (±3)	D253 (±3)	D281 (±3)	D309 (±3)	D337 (±3)	D365 (±7)	**D421 (±10)**	D505 (±10)		
Adverse Event Recording		----------X----------																		
Serious Adverse Event Reporting	----------X----------																			
Concomitant Therapy and Procedures Recording	----------X----------																			

[1] **Participants should have a follow-up safety phone call 12 weeks after their last dose of study treatment for AE/SAE recording and concomitant therapy and procedure recording.**

[1,2] Participants should have a follow-up safety phone call 24 weeks after their last dose of study treatment for **AE/SAE recording and concomitant therapy and procedure recording and** 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: Treatment-emergent AE is defined as having an onset date on or after the first randomized injection date and up to 84 days after the last injection date. Considering this, a safety FU phone call was added at Week 60 to assess safety 12 weeks (i.e., 84 days) after the last dose of study treatment.

This change also affects Section 1.1, Synopsis, Section 1.2, Study Design Schematic, Section 5.1, Study Overview, and Section 5.2, Study Duration for Participants.

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~~.

Sponsor Information

Change: Changes were made to the Sponsor information to remove Biogen MA Inc.**Now reads:**

~~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	Biogen Japan Ltd. Nihonbashi 1-chome Mitsui Building 14F 4-1 Nihonbashi 1-chome Chuo-ku, Tokyo 103-0027 Japan

For urgent medical issues in which the study Medical Monitor should be contacted, please refer to contact information in the protocol attachment for complete contact information.

~~Biogen~~ **The Sponsor** may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, ~~Biogen~~ **the Sponsor** retains overall accountability for these activities.

Rationale: Biogen MA Inc. is not the Sponsor of the clinical trial in Japan.

This change also affects Section 14.2, Vendors; Section 14.2.3, Electronic Data Capture; and Section 15.4, Study Funding.

Section 6.1, Inclusion Criteria

Change: Inclusion criterion 2, regarding informed consent, was updated.

Now reads:

2. Japanese men and women aged 18 to 65 years, inclusive, at the time of informed consent. For participants aged < 20 years*****, written informed consent should be obtained from the participant and his or her legally acceptable representative.

***Informed consent from a legally acceptable representative is not mandatory if the participant is classified as an adult based on the latest applicable local laws.**

Rationale: This inclusion criterion was updated to clarify that it is not mandatory to obtain informed consent from a legally acceptable representative if a participant was considered an adult per the latest applicable local laws.

Section 6.2, Exclusion Criteria

Change: Exclusion criterion 20, regarding TB testing, was updated.

Now reads:

20. ~~A positive diagnostic TB test result within 30 days of Day 1, defined as a positive IGRA test result or 2 successive indeterminate IGRA test results~~

A participant who is positive or uncertain of being positive for TB* within 30 days of Day 1.

*** Note: Participant with following IGRA test results will be excluded:**

T-spot TB test: positive or 2 successive borderline/invalid test results

QuantiFERON-TB Gold Plus test: positive or 2 successive indeterminate test results

Rationale: This exclusion criterion was updated to clarify that a participant with 2 successive borderline/invalid test results based on a T-spot TB test or 2 successive indeterminate test results based on a QuantiFERON-TB Gold Plus test will be excluded because such results indicate uncertainty of being positive for TB.

Section 6.3.2, Retesting

Change: This section was updated to include rescreening details.

Now reads:

Participants who fail screening criteria because of an out-of-range result that is not clinically significant can be retested once at the discretion of the Investigator. **Participants who have clinically significant abnormal laboratory test values should not be retested.** The Screening Period may be extended for eligible individuals who cannot complete the Day 1 Visit within 28 days of signing the ICF. Individuals who signed the ICF and subsequently do not meet concomitant medication criteria can have their Screening Period extended to ensure the requirements for concomitant medication stabilization have been met.

~~Participants who have clinically significant abnormal laboratory test values should not be retested.~~

If a participant initially fails screening due to meeting any of the following exclusion criteria, the participant may be allowed to rescreen 1 time, at the Sponsor's discretion:

- **Exclusion no. 1: Evidence of current SARS-CoV-2 infection within 14 days prior to Screening, between Screening and Baseline Visit, or at Baseline Visit, including but not limited to a fever (temperature > 37.5°C), new and persistent cough, breathlessness, or loss of taste and/or smell (Note: If a SARS-CoV-2 test**

[polymerase chain reaction or other regulatory approved method] is performed per the discretion of the Investigator in accordance with local site practice, the test result must be negative in order for the participant to be enrolled in the study)

- **Exclusion no. 2: Have close contact within 14 days prior to Day 1 with a SARS-CoV-2 positive individual. Close contact is defined as:**

  a. face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;

  b. direct physical contact with a probable or confirmed case;

  c. direct care for a patient with probable or confirmed COVID-19 disease without the use of recommended personal protective equipment; or

  d. other situations as indicated by local risk assessments.

- **Exclusion no. 6: An MS exacerbation (relapse) within 30 days prior to enrollment or, in the opinion of the Investigator, the participant not having stabilized from a previous relapse prior to enrollment (Day 1).**

- **Exclusion no. 9: Clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia) within the 30 days prior to enrollment (Day 1).**

- **Exclusion no. 10: Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 14 days prior to Screening or during the screening period (Day -28 to Day -1). Participants with local fungal infection (e.g., candidiasis, tinea) are eligible to be rescreened after successful treatment of the infection.**

- **Exclusion no. 25: Treatment with immunosuppressant medications, e.g., azathioprine, cyclophosphamide, and methotrexate within 6 months prior to enrollment (Day 1); mitoxantrone and cyclosporine within 12 months prior to enrollment (Day 1).**

- **Exclusion no. 26: Treatment with any of the following medications or procedures within 6 months prior to enrollment (Day 1): IV immunoglobulin, plasmapheresis, or cytapheresis.**

- **Exclusion no. 27: Treatment with any of the following medications within 30 days prior to enrollment (Day 1):**

  a. IV corticosteroid treatment
  b. Systemic corticosteroid treatment
  c. 4-Aminopyridine or related products

- **Exclusion no. 28: Treatment with sphingosine 1-phosphate receptor modulators (fingolimod, siponimod, or ozanimod) within 90 days prior to enrollment (Day 1).**

- **Exclusion no. 29: Treatment with fumarates (Fumaderm, Tecfidera, or Vumerity) within 4 weeks prior to enrollment (Day 1).**

- **Exclusion no. 30: B-cell-targeted therapies for the treatment of MS (e.g., ocrelizumab, rituximab, ofatumumab) within 12 months of Screening; greater than 12 months of Screening is permissible with evidence that the CD19 cells have returned to within normal range (per local laboratory reference range).**

- **Exclusion no. 31: Treatment with immunomodulatory medications (including IFN-β and glatiramer acetate) within 2 weeks of enrollment (Day 1).**

- **Exclusion no. 32: Administration of any live-attenuated vaccine given within 30 days prior to Day -1 or planned to be given during study participation.**

- **Exclusion no. 33: Blood donation (1 unit or more) within 90 days prior to Screening, plasma donation from 1 week prior to Screening, and platelet donation from 6 weeks prior to Screening.**

In addition, participants with an 'indeterminate result' for HCV antibody during Screening may be allowed to retest and will be re-evaluated on a case-by-case basis, after discussion with the Medical Monitor and Sponsor Medical Study Director to determine eligibility.

Upon rescreening, and in consultation with the Medical Monitor and Sponsor Medical Study Director, the participant should sign the ICF again and repeat the screening assessments as per discussion with the Investigator and study team.

Rescreened participant will receive a new screening number, where the trailing alphanumeric character in the screening number will move forward sequentially, e.g., from XXXA to XXXB.

If the participant fails screening twice, they may not undergo further screening for this study.

Rationale:

Rescreening: Rescreening details were added to allow rescreening if the participant did not meet specific time-bound exclusion criteria.

Case-by-case retesting allowing for HCV antibody tests of 'indeterminate result': DAA for hepatitis C infection are available in Japan. As per the Japan Society of Hepatology guidelines for the management of hepatitis C virus infection: 2019 update, DAA are recommended for

initial antiviral therapy in hepatitis C infection under certain conditions. These medications have high cure rates. If participants have been treated for HCV infection with other drugs prior to a first-time DAA, it does not rule out the possibility of pre-existing liver damage versus participants who were treated for HCV infection for the first time with DAA very early in their disease trajectory. It would be risky to allow previously treated participants (treated prior to DAA) to enroll in the study because there have been rare reports of clinically significant liver injury, including cases that recurred upon rechallenge with Tysabri (note: some cases occurred in patients with pre-existing liver disease or in the presence of other drugs that have been associated with hepatic injury). Hence, an indeterminate result on the HCV antibody test will be evaluated on a case-by-case basis but will exclude 'previously treated' participants (e.g., participants treated with IFN prior to treatment with DAA) and participants with cirrhosis/chronic liver damage, even if there is no evidence of current hepatitis C infection.

Section 11.3.2, Adverse Events of Special Interest

Change: List of AESIs was updated.

Now reads: An AE of special interest is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required. The following AEs will be considered AESIs: PML, injection site pain, opportunistic infections other than PML, **herpes infection**, drug-induced liver injury, hypersensitivity reactions, and malignancies.

Rationale: Herpes infection was added to the list of AESIs because it is an important identified risk for Tysabri.

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.
- In Section 1.3, Schedule of Activities, the footnote given to 'Week 72 Safety FU Phone Call' was updated with the addition of AE/SAE recording and concomitant therapy and procedure recording according to other sections of the protocol.
- In Section 1.3, Schedule of Activities, the footnote given to 'Study Treatment Administration' was elaborated as 'After the first 6 natalizumab doses, the 1-hour postadministration observation time for subsequent SC injections may be reduced or removed according to clinical judgement if the participants have not experienced any injection reactions including hypersensitivity' for better clarity. This change also affects Section 7.1, Regimen.
- [redacted] This change also affects Section 9.3, Pharmacodynamic Assessments and Section 12.2, Analysis Sets.
- In Section 6.2, Exclusion Criterion 10 (regarding bacterial, fungal, or viral infection), the phrase "between Screening and Day -1" was changed to "during the screening period (Day -28 to Day -1)" for a clearer understanding.
- In Section 6.2, Exclusion Criterion 32 (regarding live-attenuated vaccine), the phrase "live or attenuated immunization or vaccination" was changed to "live-attenuated vaccine" for better clarity.
- In Section 6.2, Exclusion Criterion 34 (regarding clinically significant abnormal laboratory test values), the phrase "at Screening or Day -1" was changed to "during the screening period (Day -28 to Day -1)" for a clearer understanding.
- In Section 7.3.1, Natalizumab, the list of excipients was updated to mention salts of sodium phosphate (i.e., monobasic monohydrate and dibasic heptahydrate) and water for injection.

- In Section 8.1, Discontinuation of Study Treatment, a sentence was added to clarify that a participant who discontinues treatment may continue for study visits every 4 weeks up to Week 52 and receive safety phone calls at Week 60 and Week 72.

- In Section 8.3, Withdrawal of Participants From the Study, a sentence was added to clarify that participants are encouraged to undergo an ET Visit unless withdrawal is due to death or withdrawal of consent. The ET Visit in such participants should occur at 4 weeks (±7 days) after the last dose of study treatment and should be followed by safety phone calls at 12 weeks (±10 days) and 24 weeks (±10 days) after the last dose of study treatment. This change also affects Section 1.3, Schedule of Activities.

- In Section 12.4, Methods of Analysis for Pharmacokinetic Endpoints, and Section 12.5, Methods of Analysis for Pharmacodynamic Endpoints, 95% CV of geometric mean was changed to geometric CV%.

- In Section 12.5, Methods of Analysis for Pharmacodynamic Endpoints, text was updated as 'α4-integrin saturation levels, soluble VCAM-1 serum concentrations, and [redacted]

- In Section 12.7, Methods of Analysis for Immunogenicity Data, the phrase 'Anti-JCV Antibodies' was added to the title for better clarity because immunogenicity data (ADA) and anti-JCV antibody data are different.

- Section 14.2.4, Central Laboratories for Laboratory Assessments, was updated for simplification and to clarify that a central laboratory has been selected by the Sponsor to analyze the hematology, blood chemistry, antibody, and urine samples collected for this study. PK and PD samples will be analyzed at a laboratory selected by the Sponsor.

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CV	coefficient of variation
DAA	direct-acting antivirals
ET	early termination
FU	follow-up
HCV	hepatitis C virus
ICF	informed consent form
IFN	interferon
IGRA	interferon-gamma release assays
IV	intravenous(ly)
JCV	John Cunningham virus (human polyomavirus)
MS	multiple sclerosis
PML	progressive multifocal leukoencephalopathy
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
TB	tuberculosis

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AMENDMENT SUMMARY

Biogen Protocol 101MS330

A Single-Arm, Open-Label, Phase 3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of Natalizumab (BG00002) Administered to Japanese Participants With Relapsing-Remitting Multiple Sclerosis via a Subcutaneous Route of Administration

Version 2.0

Date: 04 November 2021

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 101MS330 is to add language to the relevant section of the protocol, in response to a PMDA query, to clarify that while all of the raw materials used do not conform to the standards for biological ingredients, the theoretical risk to participants for contamination or TSE transmission is extremely low.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 7.3.1, Natalizumab

Change: Addition of text to the relevant section of the protocol, in response to a PMDA query, to clarify that while all of the raw materials used do not conform to the standards for biological ingredients, the theoretical risk to participants for contamination or TSE transmission by the raw materials is extremely low.

Now reads:

…

Natalizumab is produced using fetal bovine serum that was used in cloning before master cell bank preparation and storage for the master cell bank and working cell bank. Also, natalizumab is produced using bovine blood-derived bovine serum albumin that was used in preparation for the master cell bank and working cell bank. This fetal bovine serum meets the criteria set forth by a public agency, the European Directorate for the Quality of Medicines, for the prevention of infection with TSE agents to humans. None of these bovine materials are contained in the final product. There is no report of TSE being transmitted from the final product to humans.

Human transferrin is used in the cell bank media used for the preparation of the master cell bank and the working cell bank for natalizumab. The manufacturing process for natalizumab does not use the human transferrin, and the final product does not contain human transferrin. Nucleic acid amplification test is not conducted for the source plasma of origin for human blood derivatives, but it is confirmed that the results of serological testing for viruses (antigen and/or antibody to viruses) is performed. In addition, there are several steps that can remove/inactivate viruses during the manufacturing process of natalizumab. Therefore, the risk of contamination with HBV, HCV, HIV-1, and HIV-2 is extremely low. There is no report of TSE being transmitted from natalizumab to humans, although human transferrin comes from human blood obtained in the US. Theoretical risk assessment for TSE demonstrated the safety level required to ensure that the risk of transmission of TSE by natalizumab is extremely low.

However, since the risk of TSE transmission cannot totally and theoretically be denied, this product must be used after careful consideration of the need for the product in the treatment of the disease, and this information must be provided to the patient prior to the administration of the product.

Rationale: The text was added in response to a PMDA query, to clarify while all of the raw materials used do not conform to the standards for biological ingredients, the theoretical risk to participants for contamination or TSE transmission by the raw materials is extremely low.

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.
- Section 2, List of Abbreviations, was updated.

LIST OF ABBREVIATIONS

HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
PMDA	Pharmaceuticals and Medical Devices Agency
TSE	transmissible spongiform encephalopathy
US	United States