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TRACKING NUMBER: **205MS305/NCT02881567**

PHASE OF DEVELOPMENT: 3b

TITLE: A Phase 3b, 12-month, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BIIB019, Daclizumab, in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) Switching from Natalizumab (SUSTAIN)

EUDRA CT NO: 2016-002820-10

DATE: 06 July 2016
Version 1.0
FINAL

SPONSOR SIGNATURE PAGE

Protocol 205MS305 was approved by:

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27 Jul 2016
Date

Biogen MA Inc.

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1. SPONSOR INFORMATION

Biogen is responsible for conducting the study.

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

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
ARR	annualized relapse rate
AST	aspartate transaminase
BPM	beats per minute
CBC	complete blood count
CD25	α subunit of interlukin-2
CD122	β subunit of interlukin-2
CD132	γ subunit of interlukin-2
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CRF	case report form
CRO	contract research organization
DMF	Dimethyl Fumarate
DHA	Directions for Handling and Administration
DMT	disease-modifying therapy
DSMB	Data Safety Monitoring Board
EC	ethics committee
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
GA	glatiramer acetate
Gd	gadolinium
Gd+	gadolinium enhanced
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-β	interferon β
IL-2	interleukin 2
IL-2R	interleukin 2 receptor
IM	intramuscular
IS	immunosuppressant
IRB	Institutional Review Boark
ITT	intent-to-treat
IV	intravenous
JCV	John Cunningham Virus

LFT	liver function tests
MRI	magnetic resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
NEDA	no evidence of disease activity
[redacted]	[redacted]
NK	natural killer T cells
PD	pharmacodynamic
PHI	protected health information
PML	progressive multifocal leukoencephalopathy
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SABR	safety and benefit-risk
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit normal
US	United States
[redacted]	[redacted]

3. SYNOPSIS

Tracking number:	205MS305
Protocol Title:	A Phase 3b, 12-month, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BIIB019, Daclizumab, in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) Switching from Natalizumab (SUSTAIN)
Version Number:	1.0
Name of Study Treatment:	Daclizumab (high yield formulation)
Study Indication:	Relapsing-Remitting Multiple Sclerosis (RRMS)
Phase of Development:	3b
Rationale for the Study:	The purpose of this study is to evaluate the efficacy and safety of daclizumab (high yield formulation) in subjects switching from natalizumab due to safety concerns. There is a need for clearer evidence-based guidelines on alternative therapy and management of subjects during and post-transition from natalizumab. With a well-established safety and efficacy profile, daclizumab can be considered a good therapeutic option for RRMS subjects treated with natalizumab, who decide to change therapy.
Study Objectives and Endpoints:	**Primary Objective** The primary objective of the study is to evaluate the effects of treatment with daclizumab on proportion of subjects relapse-free at 6 months, in RRMS subjects who switched from treatment with natalizumab to daclizumab due to safety concerns. **Primary Endpoint** The primary endpoint in relation to this objective is the proportion of subjects relapse-free at Month 6, in RRMS subjects treated with daclizumab who switched from treatment with natalizumab.

Secondary Objectives

The secondary objectives of this study in this study population are to evaluate the effects of daclizumab on the following:

- Multiple Sclerosis (MS) relapse activity including annualized relapse rate (ARR) and the proportion of subjects experiencing relapses requiring hospitalization and/or steroid treatment.
- MS-related outcomes measured using magnetic resonance imaging (MRI).
- Safety and tolerability in subjects previously treated with natalizumab.

Secondary Endpoints

The secondary endpoints of this study are the following:

- The proportion of subjects relapse-free at Month 12.
- The proportion of subjects experiencing relapse requiring hospitalization and/or steroid treatment at Month 12.
- The ARR at Month 12.
- The number of new gadolinium enhanced (Gd+) and T1 hypointense lesions at Month 6 and Month 12 on MRI.
- The number of new or newly enlarged T2 hyperintense lesions at Month 6 and Month 12 on MRI.
- The permanent discontinuation rate of daclizumab at Month 12.
- The incidence of adverse events (AEs) and serious adverse events (SAEs) including clinically relevant shifts in clinical laboratory assessments.

Exploratory Objectives

The exploratory objectives of this study in this study population are to evaluate the effects of daclizumab on the following:

- [redacted]

- [redacted]
- [redacted]
- [redacted]

Exploratory Endpoints

The exploratory endpoints of the study include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

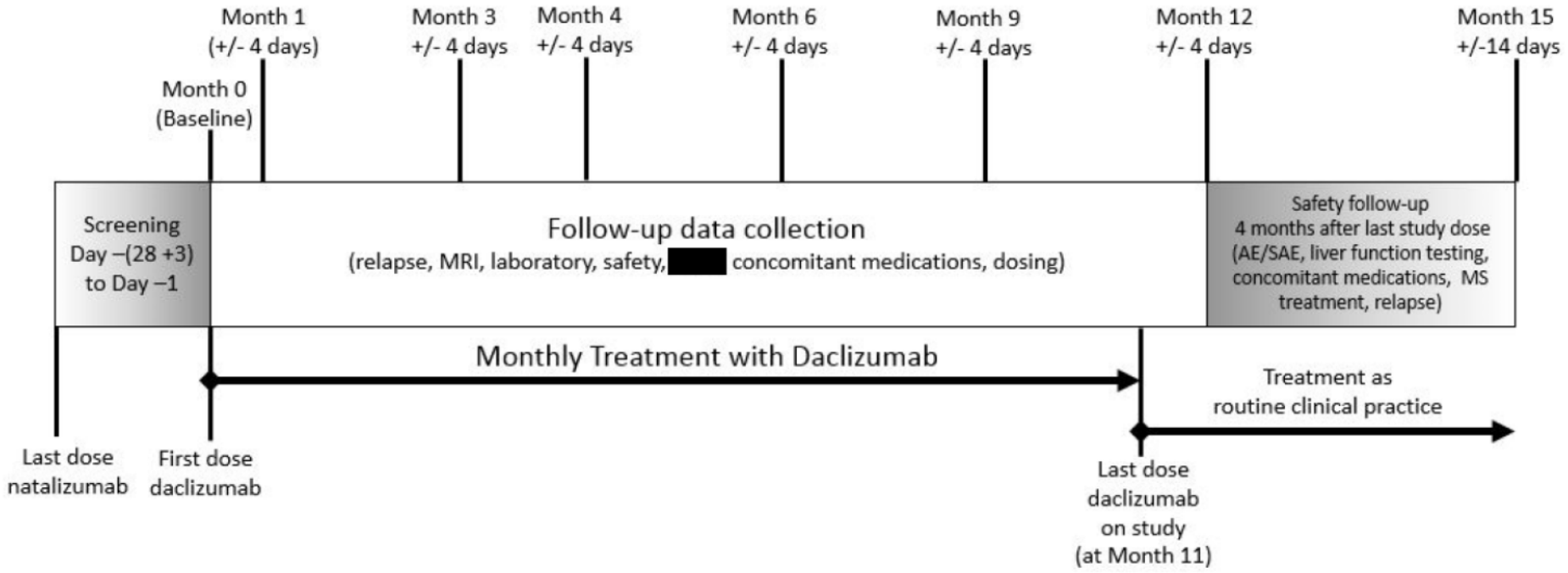
Study Design:	This is a multicenter, open-label study of daclizumab monotherapy in subjects with RRMS who were previously treated with natalizumab for at least 12 months. Subjects will be enrolled over an approximately 12-month period. Subjects discontinuing from natalizumab treatment due to safety concerns will commence treatment with daclizumab following consent and evaluation of eligibility. Subjects will initiate treatment with daclizumab at 28 (+3) days following the last infusion of natalizumab. Assessments will be completed at enrollment, baseline, Month 1, Month 3, Month 4, Month 6, Month 9 and Month 12.
Study Location and Number of Sites:	Approximately 40 sites in the United States (US) and rest of world.
Number of Planned Subjects:	Approximately 100 subjects.
Study Population:	The study will enroll RRMS subjects aged 18 to 55 years who discontinued treatment with natalizumab due to safety concerns. Subjects must enroll into the study within 28 (+3) days after discontinuation, and have been treated with natalizumab for at least 12 months prior to screening. Subjects must not have missed 2 or more consecutive scheduled doses.
Treatment Groups	Daclizumab monotherapy administered using a pre-filled pen, also known as an autoinjector.
Duration of Treatment and Follow-up:	The duration of subject participation will be up to 16 months, including a 28 (+3) day screening period, treatment with daclizumab for up to 12 months, and an additional safety follow-up visit performed remotely 4 months after last study treatment dose. Subjects having tentative disability progression near the end of the core study (e.g., Month 12) will attend additional follow-up visits 12 and 24 weeks later to confirm progression.
Data Monitoring	An independent Data Safety Monitoring Board (DSMB) will monitor the benefit/risk throughout the trial.

4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES

4.1. Study Design

Figure 1: Study Design below provides a schematic for study 205MS305.

Figure 1: Study Design



Abbreviations: AE: adverse event; [redacted]; MRI: magnetic resonance imaging; MS: Multiple Sclerosis; SAE: serious adverse event.

4.2. Schedule of Assessments

The schedule of assessments is presented in Table 1. Assessment time points include an enrollment visit, a baseline visit, and follow-up visits at Months 1, 3, 4, 6, 9 and 12. An additional safety assessment will be performed remotely 4 months after the last study treatment dose. Subjects who discontinue treatment early will still be evaluated during the safety follow-up visit (i.e., 4 months after treatment and study discontinuation). Subjects having tentative disability progression identified near the end of the core study (e.g., Month 12) will attend additional follow-up visits 12 and 24 weeks later to confirm progression.

Magnetic resonance imaging (MRI) scans will be performed at the enrollment visit (no later than 7 days prior to the first dose of daclizumab), and at Months 1, 4, 6 and 12. MRI scans will be performed under the supervision of a trained radiologist. Ad-hoc MRI scans may be performed as needed, such as in the event of a MS relapse, in order to rule out a progressive multifocal leukoencephalopathy (PML) diagnosis.

Blood chemistry and hematology assessments will be performed at baseline and at Months 1, 3, 6, 9 and 12. Hematology assessments will include a complete blood count (CBC). Liver function tests (LFT) [alanine transaminase (ALT)/ aspartate transaminase (AST)] will be done at enrollment and monthly visits. Bilirubin testing must be done together with the first AST/ALT test at the enrollment visit. Bilirubin testing must also be done if ALT/SGPT (serum glutamic pyruvate transaminase), or AST/SGOT (serum glutamic oxaloacetic transaminase) >3*upper limit of normal (ULN), since treatment must be permanently discontinued with the concomitant elevation of total bilirubin >2*ULN.

At the end of the study, liver monitoring will be done per routine clinical practice.

A safety follow-up visit at 4 months after the last dose of daclizumab provided by the study will be conducted remotely to evaluate potential delayed safety outcomes. The assessments during the additional safety follow-up period will include all safety endpoints described in Table 1. Liver function tests (LFT) will be performed only if the subject is continuing daclizumab or if the subject is within 4 months since study treatment discontinuation, and monitoring is deemed appropriate by the Investigator.

Table 1: Study Schedule of Assessments

Study Period	Screening		Study Follow-up							
Visit Number	1	2	3	4	5	6	7	8	9	10
Title	Enrollment (Day - [28+3] to -1)	Baseline (Day 0)	Month 1 (± 4 days)	Month 3 (± 4 days)	Month 4 (± 4 days)	Month 6 (± 4 days)	Month 9 (± 4 days)	Month 12 (± 4 days)	Month 15 Safety follow-up[13] (± 14 days)	Early discontinuation[14]
Informed consent[1]	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Disease and medical history	X									
MS treatment history	X									
MRI[2]	X		X		X	X		X		
Pregnancy testing[3]			Monitor and record throughout the study							
Liver function testing (AST/ALT)[4]	X		X	X	X	X	X	X	X[5]	X
Concomitant medications and non-drug therapies			Monitor and record throughout the study							
[redacted]	X	X		X		X	X	X		X
Vital signs	X	X	X	X		X	X	X		X
Physical examination	X	X	X	X		X	X	X		X
[redacted]	X	X	X	X		X				
MS relapse assessment		X	X	X		X	X	X	X	X
Daclizumab dispensation/ administration[8]		X	X	X	X	X	X			

Study Period	Screening		Study Follow-up							
Visit Number	1	2	3	4	5	6	7	8	9	10
Title	Enrollment (Day - [28+3] to -1)	Baseline (Day 0)	Month 1 (± 4 days)	Month 3 (± 4 days)	Month 4 (± 4 days)	Month 6 (± 4 days)	Month 9 (± 4 days)	Month 12 (± 4 days)	Month 15 Safety follow-up[13] (± 14 days)	Early discontinuation[14]
Daclizumab dosing diary[9]						X	X			
Daclizumab accountability			Monitor and record throughout the study							
Hematology (CBC)[7]		X	X	X		X	X	X		X
Blood chemistry[7,10]		X	X	X		X	X	X		X
[redacted]		X	X	X		X	X	X		
[redacted]		X				X		X		
[redacted]		X	X	X		X	X	X		
AEs/SAEs			Monitor and record throughout the study							

Abbreviations: MS: Multiple Sclerosis; MRI: magnetic resonance imaging; [redacted]; CBC: complete blood count; ALT: alanine transaminase; AST: aspartate transaminase; NK: natural killer T-cells; [redacted]; AE: adverse event; SAE: serious adverse event.

1. Written informed consent must be obtained prior to start of the study.
2. Screening MRI should occur no later than 7 days prior to the first dose of daclizumab. For subsequent visits, MRI scan can be performed up to 4 days prior to the visit. Ad-hoc MRIs may be conducted as needed, such as in the event of a relapse to rule out PML diagnosis.
3. This is required only for females of child-bearing potential. A urine pregnancy test will be performed monthly.
4. Liver function tests (LFTs) are required to be performed monthly (either on-site or via home visits at Month 7, 8, 10 and 11, if applicable), and samples will be analyzed centrally for the purposes of this study. Results from either local or central LFT tests can be used for medical management of the patient and to determine whether dosing should continue or be suspended at the monthly dosing timepoint. In cases where local LFTs were performed, samples must also be collected for central analysis.
5. Liver function tests (LFTs) during the safety follow-up will be performed only if the subject is continuing daclizumab or if the subject is within 4 months since study treatment discontinuation, and monitoring is deemed appropriate by the Investigator; Abnormal AST/ALT values as described in the product label will lead to treatment suspension or discontinuation.
6. [redacted]
7. Samples will be analyzed centrally.
8. Daclizumab dosing will start at baseline and occur monthly until Month 11. Doses at baseline and Months 1, 2, 3, 4, 5, 6 and 9 will be administered in the clinic, and doses at Months 7, 8, 10 and 11 can be administered at home or in the clinic. Daclizumab dosing will not begin until a minimum of 28 days have passed since last natalizumab dose. Before a monthly dose of daclizumab is given, LFT results from a prior test performed within the previous 28 (+3) days must be reviewed by the Study Neurologist or their backup.
9. Subjects will be provided a dosing diary at the Month 6 and Month 9 visits to record observations for home dosing only; home dosing is possible for Month 7, 8, 10, and 11. A window of ± 4 days applies to daclizumab dose even if it is done at home; subjects should be appropriately instructed on daclizumab self-administration using the autoinjector.
10. Blood chemistry assessments will include bilirubin testing at baseline. Bilirubin testing must also be done if ALT/SGPT, or AST/SGOT >3*ULN, since treatment must be permanently discontinued with the concomitant elevation of total bilirubin >2*ULN.
11. [redacted]
12. [redacted]
13. Safety assessment follow-up at 4 months after last study treatment dose.
14. Early study discontinuation is discontinuing study participation at any time after baseline.

5. INTRODUCTION

5.1. Background

5.1.1. Overview of Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting approximately 400,000 individuals in the United States (US) and over 2 million persons worldwide [Campbell 2014; Flachenecker and Stuke 2008; Hanson 2014]. Disease incidence is approximately 5–6 per 100,000 persons per year in northern parts of North America and Europe where it is most common, and it typically presents in individuals aged 15 to 45 years [Goodin 2014]. Although the etiology of MS is uncertain, evidence suggests that it begins as an inflammatory immune-mediated disorder characterized by autoreactive lymphocytes [Roach 2004; Weiner 2004]. Patients typically first present with clinically isolated syndrome (CIS), a stage in which characteristics of inflammatory demyelination that could be MS are present (e.g., optic neuritis, brainstem syndromes, or transverse myelitis), but McDonald criteria of dissemination in time have yet to be fulfilled [Lublin 2014; McDonald 2001]. A second neurologic exacerbation consistent with demyelination and separated both in time and location is required for a clinically definitive diagnosis [Poser 1983]. However, use of the 2010 revisions to the McDonald diagnostic criteria allows for fewer than 2 neurologic attacks when there is supportive para-clinical evidence based on MRI or cerebrospinal fluid results [Polman 2011].

The core MS phenotypes include relapsing and progressive disease and are further categorized by the following clinical subtypes: CIS, Relapsing-Remitting Multiple Sclerosis (RRMS), secondary progressive MS, and primary progressive MS [Lublin 2014]. About 70–90% of patients with MS start out with RRMS, a clinical course characterized by relapses of neurologic dysfunction, which occur over many years [Sumelahti 2014]. Symptoms of such relapses may include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and/or bladder dysfunction. Early in the course of this phase of the disease, symptoms may subside completely after each attack. Over time, there tends to be incomplete recovery from such attacks and gradual progressive deterioration of neurologic function. Most patients develop progressive disability, with or without occasional relapses, minor remissions, and plateaus. Without effective treatment, approximately half of all patients with MS are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989].

5.1.2. Current Therapies for Multiple Sclerosis

Several commercially available treatment options exist for patients with relapsing multiple sclerosis (RMS), including interferon beta (IFN-β) preparations, glatiramer acetate (GA), natalizumab, alemtuzumab, dimethyl fumarate (DMF), teriflunomide, and fingolimod [Goodin 2002; Miller 2012; National Collaborating Centre for Chronic Conditions 2004; Perumal and Khan 2012; Tullman 2013]. The choice of the specific therapeutic agent is individualized to the patient according to disease activity and patient values and preferences.

The IFN-β therapies and GA have well-established safety and efficacy profiles, but many patients continue to experience significant MS disease activity while on treatment. These therapies are also associated with known side effects, including flu-like symptoms for the IFN-β therapies and lipoatrophy and other injection site pathologies for GA, which can be a significant burden for some patients. Furthermore, available data suggest that approximately 40% of MS patients may not adhere to prescribed injectable therapies for MS out of fear of or the inconvenience associated with such frequent injections [Devonshire 2011; Kobelt 2006a; Kobelt 2006b; Treadaway 2009].

Alemtuzumab is a monoclonal antibody that has shown superior efficacy to IFN β-1a in patients with RMS but entails risks of life-threatening autoimmune disorders, including fatal thrombocytopenia and nephropathies; additionally, autoimmune thyroid disease is common during treatment with alemtuzumab.

DMF, fingolimod, and teriflunomide are oral disease-modifying therapies (DMTs) approved for the treatment of RMS. While these therapies offer an improved route of administration for some patients, they require daily administration, and some patients may not tolerate them or may continue to experience disease activity while on treatment. Oral therapies have also been associated with side effects, such as lymphopenia in DMF-treated patients [Fox 2012; Gold 2012]; bradycardia, atrioventricular block, and macular edema in fingolimod-treated patients [Kawasaki 2010; Khatri 2011]; and hepatotoxicity and lymphopenia in teriflunomide-treated patients [Confavreux 2012]. In addition, cases of PML have been reported in patients treated with DMF and with fingolimod [GILENYA USPI 2016; National Multiple Sclerosis Society 2015; Nieuwkamp 2015; Rosenkranz 2015; TECFIDERA™ USPI 2014]. PML is a severe demyelinating disease of the CNS caused by reactivation of JCV, a polyomavirus that is pathogenic only in humans. These risks require specialized monitoring both prior to initiation and during therapy and may necessitate exclusion of vulnerable patients.

Natalizumab is a DMT available for the treatment of RMS that is known to be highly effective. In the pivotal 2-year, placebo-controlled, phase 3 AFFIRM trial, natalizumab was shown to reduce 12-week confirmed disability progression by 42%, annualized relapse rate (ARR) by 68%, and formation of MRI lesions by 92% (gadolinium-enhancing [Gd+]) and 83% (T2-hyperintense) compared to placebo [Polman 2006]. Natalizumab was also the first RMS therapy for which no evidence of disease activity (NEDA; no relapses, no disability progression, no Gd+ or new/enlarging T2-hyperintense lesions) was demonstrated, with 37% of natalizumab patients in AFFIRM achieving NEDA over 2 years compared to 7% of placebo patients [Havrdova 2009]. From a safety perspective, the most critical concern for natalizumab is an increased risk of PML, and as such natalizumab carries a boxed warning for PML and is contraindicated in patients with a history of PML and in patients with increased risk for opportunistic infections, including immunocompromised patients [Tysabri® Prescribing Information 2013/SmPC ; Tysabri® USPI 2013]. Natalizumab is also contraindicated in patients who have had a hypersensitivity reaction to natalizumab.

Three factors associated with an increased risk of natalizumab-associated PML have been identified: 1) the presence of anti-JCV antibodies; 2) prior exposure to an immunosuppressant (IS; e.g., mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil);

and 3) natalizumab treatment duration ≥2 years [Bloomgren 2012; Fox and Rudick 2012; Kappos 2011; Tysabri® USPI 2013].

In a 2012 review of natalizumab-associated PML and related risk factors, data from 3 clinical trials and a registry of patients with MS were evaluated to estimate the risk of PML while on natalizumab treatment [Bloomgren 2012]. For patients who were seronegative for anti-JCV antibodies, the estimated risk of natalizumab-associated PML was ≤0.09 per 1000 (≈1/10,000). The estimated risk of natalizumab-associated PML among patients who were seropositive for anti-JCV antibodies but without prior exposure to IS treatment was 0.56 per 1000 (5.6/10,000) for those treated with natalizumab for 1 to 24 months and 4.6 per 1000 (46/10,000) for those treated for 25 to 48 months. The estimated risk of natalizumab-associated PML among patients who had prior IS treatment was 0.88 per 1000 (8.8/10,000) for those treated for 1 to 24 months and 6.1 per 1000 (61/10,000) for those treated for 25 to 48 months. For patients who were seropositive for anti-JCV antibodies with prior IS treatment, the risk of natalizumab-associated PML was 1.6 per 1000 (16/10,000) for those treated for 1 to 24 months and 11.1 per 1000 (111/10,000) for those treated for 25 to 48 months.

For natalizumab-treated patients who have no prior IS use and a positive test for anti-JCV antibodies, the anti-JCV antibody index may further differentiate patients at higher and lower risk of PML. The anti-JCV antibody index is calculated using an antibody ELISA test and is a corollary to anti-JCV antibody titer [Lee 2013; Plavina 2014]. In natalizumab-treated patients with no prior IS use, anti-JCV antibody index values have been shown to be significantly higher in patients with PML compared to patients without PML (median = 2.4 vs 1.4; $P<0.0001$). In contrast, index distribution was shown to be similar for PML and non-PML patients with prior IS use (median = 1.6 for both groups; $P=0.82$). Recently, the European Medicines Agency (EMA) conducted a review of the available data on the risk of natalizumab-associated PML and provided recommendations for identifying patients at higher risk of developing PML [European Medicines Agency 2016]. These recommendations for higher risk patients are as follows:

- Have tested positive for JCV, and
- Have been treated with natalizumab for more than 2 years, and
- Either have used an IS before starting natalizumab, or have not used an IS and have a high JCV antibody index (>1.5).

Revised management strategies for patients on natalizumab treatment were also part of the EMA recommendations because early detection and treatment of PML when the disease is asymptomatic (i.e., still in the initial stages and showing no symptoms) may improve patients' outcomes. All patients on natalizumab should undergo full MRI scans at least once a year, but on the basis of new data, the EMA now recommends that for patients at higher risk of PML more frequent MRI scans (e.g., every 3 to 6 months) performed using simplified protocols (e.g., fluid attenuated inversion recovery, T2-weighted, and diffusion weighted) should be considered. If lesions suggestive of PML are discovered, the MRI protocol should be extended to include 'contrast-enhanced T1-weighted MRI', and testing the patient's spinal fluid for the presence of JCV should be considered. Patients should also be monitored at regular intervals for signs and symptoms of new neurological dysfunction [European Medicines Agency 2016].

Given that duration of natalizumab treatment is a risk factor for PML, many patients who are seropositive for anti-JCV antibodies choose to discontinue natalizumab after 2 years of treatment. Additionally, patients who were seronegative for anti-JCV antibodies when starting treatment may become seropositive, and, as a consequence, choose to discontinue natalizumab due to an increased risk of PML. Because of these circumstances, it is becoming increasingly important to develop follow-on treatment strategies for patients who discontinue natalizumab [Butzkueven 2014; Sangalli 2014].

5.1.3. Daclizumab

Interleukin-2 (IL-2) is a cytokine signaling molecule that regulates the activities of lymphocytes responsible for conferring immunity. Effects of IL-2 are mediated by the IL-2 receptor (IL-2R), which has 3 forms that differ in affinity for IL-2, and in their expression patterns. Three protein chains make up the various forms of the receptor: α (alpha or CD25), β (beta, or CD122), and γ (gamma, or CD132). CD25 alone binds to IL-2 with low affinity, CD122 and CD132 together form a complex found on memory T cells and NK cells which binds to IL-2 with intermediate affinity, and the 3 chains together form a complex on activated T cells and regulatory T cells which binds to IL-2 with high affinity [Gaffen and Liu 2004]. The intermediate affinity IL-2R is highly expressed by $CD56^{bright}$ NK T cells, a subset of NK cells that can directly kill activated T cells [Poli 2009].

Daclizumab High Yield Process, referred to as "daclizumab" throughout this protocol, is a humanized monoclonal antibody that binds to CD25 and blocks the high affinity IL-2R, but does not affect intermediate affinity IL-2R mediated signaling. As such, this high yield formulation of daclizumab blocks proliferation of pro-inflammatory T cells and drives expansion of $CD56^{bright}$ NK cells, which in turn can kill pro-inflammatory T cells [Bielekova 2006]. This expansion is highly correlated with a profound treatment response of reduction in brain inflammatory activity as demonstrated by substantial reduction in the number of MRI Gd+ lesions [Elkins 2015]. However, trial data depict the experience of subjects treated with daclizumab who respond favorably with lower levels of expansion of $CD56^{bright}$ NK cells [Elkins 2015].

5.1.4. Profile of Previous Experience with Daclizumab

The efficacy and safety of the high yield formulation of daclizumab for the treatment of RRMS has been evaluated in 2 pivotal studies. In the first, a multicenter double blind, placebo-controlled Phase 2b study (SELECT, Study 205MS201), the efficacy of daclizumab was examined in over 600 adults with RRMS [Gold 2013]. Subjects were randomized to 1 of 3 groups: (1) subcutaneous (SC) placebo, (2) 150 mg daclizumab every 4 weeks for 52 weeks, or (3) 300 mg daclizumab every 4 weeks for 52 weeks. One year results showed that the ARR was significantly lower in groups assigned to daclizumab 150 mg and daclizumab 300 mg than placebo (0.21 and 0.23, versus 0.46 for placebo), corresponding to reductions of 54% and 50%, respectively. Additionally, subjects in the daclizumab 150 mg and 300 mg groups had reductions in the risk of disability progression versus placebo (hazard ratios 0.43 and 0.57, p=0.021 and p=0.091, respectively) at Week 52; the reduction for daclizumab 150 mg versus placebo is statistically significant. Daclizumab reduced new lesion activity in all subjects, with longitudinal analysis showing that Gd+ lesion activity was greater in the 150 mg group than in the 300 mg group during weeks 4–24, but was similar at Week 52.

Daclizumab was generally well tolerated among subjects in SELECT with adverse events (AEs) occurring in a similar proportion of subjects across all study groups. More subjects in the daclizumab groups had cutaneous events (e.g., injection site irritation and rash) than in the placebo groups. Additionally, more subjects in the daclizumab groups had hepatic enzyme elevations >5 times the ULN. Four malignancies were detected during the trial, including 2 cases of cervical carcinoma (1 in the placebo group and 1 in the daclizumab 150 mg group), and 2 cases of melanoma in the daclizumab 300 mg group. One subject given daclizumab, who was recovering from a serious rash, died because of local complication of a psoas abscess. The number of Tregs counts was reduced during treatment with daclizumab, but this was not associated with clinical/MRI outcomes or AEs [Milo 2014; Selmaj 2013]. $CD56^{bright}$ NK cells increased in subjects given daclizumab from a median of 8 cells per µL (0.6% of lymphocytes) at baseline to 40 cells per µL (3.6% of lymphocytes) at the end of treatment. Increases in $CD56^{bright}$ NK cells were apparent shortly after baseline (week 4) in both daclizumab groups versus placebo ($p<0.0001$). CD4+ and CD8+ T-cell counts modestly decreased by about 7–10% at week 52 in subjects given daclizumab, and the CD4+/CD8+ ratio remained constant. Neutralizing antibodies to daclizumab were detected in 2% of subjects in the daclizumab groups at week 24, but in <1% at week 52. While there were moderate reductions in the number of circulating CD4+ and CD8+ cells, the results of the study were consistent with previous findings that showed the potential for preservation of T-cell effector responses in the absence of high-affinity IL-2 signaling [Gold 2013]. No increase in infections associated with deficits in T-cell mediated immunity were noted.

Investigators conducted a multicenter, double blind, 1-year extension study (SELECTION, Study 205MS202) sponsored by Biogen to assess the safety and immunogenicity of daclizumab, as well as the durability of daclizumab treatment effect on disease activity [Giovannoni 2014]. Subjects who received placebo in SELECT were randomly assigned (1:1) to receive 150 mg or 300 mg SC daclizumab every 4 weeks for 52 weeks (treatment initiation group); while subjects who had received daclizumab were randomly assigned (1:1) to continue their present dose with (washout and re-initiation group) or without (continuous treatment group) a washout period of 20 weeks. In the continuous treatment group, the ARR was similar in year 1 (SELECT) and year 2 (SELECTION). The numbers of new Gd+ lesions in this group were also consistent between years 1 and 2. However, the number of new or newly enlarging T2 hyperintense lesions that formed during year 2 was lower than in year 1, as was the volume of new T1 hypointense lesions. The proportion of subjects who had confirmed disability progression was similar in year 1 and year 2 in this group. In the treatment initiation group, the ARR (0.434 in year 1, compared to 0.179 in year 2), proportion of subjects who relapsed (0.362 in year 1, compared to 0.176 in year 2), and proportion of subjects with confirmed disability progression (11% in year 1, compared to 5% in year 2) were reduced significantly in year 2. Similarly, the numbers of new Gd+ lesions (1.4 in year 1, compared to 0.2 in year 2) and new or newly enlarging T2 lesions (8.0 in year 1, compared to 2.1 in year 2) were reduced in year 2. Significant reductions were also recorded for the percentage change in volume of total T2 lesions and the volume of new T1 hypointense lesions.

In the washout and re-initiation group, serum concentration of daclizumab and number of $CD56^{bright}$ NK cells returned to pre-treatment values during the 24-week washout period. The mean number of new Gd+ lesions were similar at baseline (pooled 150 mg and 300 mg treatment groups, mean number 1.6 [SD 3.5]) and at the end of washout (1.1 [2.3]; figure 3B). During the

washout period, the ARR (0.437) was similar to that in the placebo group in SELECT (0.434). Overall, the ARR in the washout and re-initiation group was not significantly higher in year 2 than in year 1. At week 104, the number of new Gd+ lesions in this group was similar to the number at the end of year 1, as well as to the numbers in subjects in the continuous and treatment initiation groups. Additionally, the numbers of $CD56^{bright}$ NK cells at week 104 (daclizumab 150 mg: median 49.8 cells/mm^3 [interquartile range (IQR) 32.3–70.9]; 300 mg: median 47.2 [26.5–64.5]) were similar to those in subjects who had remained on continuous treatment for 2 years (daclizumab 150 mg: median 53.4 cells/mm^3 [38.3–68.8]; 300 mg: median 57.7 [39.8–85.7]). In total, 6 subjects (1%) had serious cutaneous events. In the 150 mg treatment initiation group, 1 subject had drug eruption and 1 had eczema; in the 150 mg washout and re-initiation group, 1 subject had pityriasis rubra pilaris; and in the 300 mg continuous treatment group, 1 subject had drug eruption and eczema, 1 had exfoliative dermatitis, and 1 had urticaria. One subject in the 300 mg treatment initiation group developed breast cancer, which was not considered to be related to treatment. Elevation in liver enzyme concentrations of more than 5 times the ULN occurred in 11 subjects (2%), with similar frequencies in each group. Ten of these subjects resumed daclizumab without recurrence during the study and one subject did not restart medication. The increases of more than five times the ULN resolved in a median time of 84.5 days (IQR 29.0–108.0).

One subject in the washout and re-initiation group died due to autoimmune hepatitis after re-initiation of 300 mg daclizumab. Alanine aminotransferase had increased to [redacted] U/L approximately 8 weeks after daclizumab re-initiation and continued to rise in the following 3 months to [redacted] U/L in conjunction with an increase in serum bilirubin concentration to [redacted] to [redacted] times greater than the ULN before clinical symptoms of liver failure developed. A contributory role of daclizumab could not be excluded.

Over the course of the study, 7 subjects tested positive for neutralizing antidrug antibodies. One of the 128 subjects (1%) with available data in the treatment initiation group tested positive (this subject also tested positive at baseline), 4 subjects (2%) in the continuous treatment group tested positive, and 2 of the 129 subjects (2%) in the washout and re-initiation group tested positive. Overall, AEs and immunogenicity were not increased in the second year of continuous treatment with daclizumab or during treatment washout and re-initiation, and clinical effects of treatment were sustained.

In the second pivotal trial (DECIDE, Study 205MS301), a double blind, active-controlled study, more than 1800 subjects with RRMS were randomized to receive either SC daclizumab (150 mg every 4 weeks) or intramuscular (IM) IFNβ-1a (30 mcg once a week) for at least 96 and up to 144 weeks [Kappos 2015c]. Subjects assigned to daclizumab had a significantly lower ARR compared with those assigned to IFNβ-1a (0.22 versus 0.39), corresponding to a 45% reduction ($p<0.001$). When evaluated at 6-month and yearly intervals, ARR was significantly lower for subjects in the daclizumab group compared to those in the IFN β-1a group for all specified time periods. Subjects in the daclizumab group also had a significantly lower number of new or newly enlarged brain lesions on T2-weighted MRI (4.3 versus 9.4) at 96 weeks compared with subjects treated with IFN β-1a ($p<0.001$). The volume of new or newly enlarged hyperintense lesions on T2-weighted MRI was significantly lower in the daclizumab group compared to the IFN β-1a group (225.7 mm^3 versus 556.8 mm^3) at 96 weeks ($p<0.001$). Regarding Gd+ lesions, subjects treated with daclizumab had a lower mean number of lesions compared to those in the

IFN β-1a group at both 24 weeks (0.5 versus 0.8, p<0.001) and 96 weeks (0.4 versus 1.0, p<0.001). The mean number of new hypointense lesions on T1-weighted MRI was also lower in the daclizumab group over a period of 96 weeks compared to the IFN β-1a group (2.13 versus 4.43, p<0.001). At 96 weeks, the changes in volume of hypointense lesions on T1-weighted MRI and hyperintense lesions on T2-weighted MRI were both significantly greater in subjects treated with IFN β-1a compared to subjects treated with daclizumab (p<0.001). From baseline to 96 weeks, subjects treated with daclizumab had a lower mean annualized percentage of brain volume loss than subjects treated with IFN β-1a (-0.559 versus -0.585, p<0.001).

In subjects who had disability progression, as measured by the Expanded Disability Status Scale (EDSS), that was confirmed at 12 weeks, the estimated rate of sustained disability progression at Week 144 was lower in the daclizumab group than in the IFN β-1a group (16% versus 20%, p=0.16). Similarly, in subjects with confirmed disability progression at 24 weeks, the estimated rate of sustained disability progression at Week 144 was 13% in the daclizumab group and 18% in the IFN β-1a group (p=0.03). Prespecified analyses to assess the sensitivity of assumptions made about disability progression at 12 weeks in censored subjects showed a statistically significant benefit of daclizumab over IFN β-1a. The outcomes of prespecified analyses of disability progression at 24 weeks were also significant in favor of daclizumab, except for when it was assumed that disability progression did not occur in any subject who was censored after a tentative disability progression (i.e., after documented worsening in the EDSS score but before a confirmatory visit). At 144 weeks, the percentage of subjects who were free from relapse was higher at 67% in the daclizumab group, compared to 51% of subjects free from relapse in the IFN β-1a group. Clinically meaningful worsening (defined as an increase of ≥7.5 points) in the subject-reported physical effect of MS, as assessed with the multiple sclerosis (MS) impact scale (MSIS-29) physical subscale, was observed in 19% of the subjects in the daclizumab group and 23% of those in the IFN β-1a group. In the daclizumab group, a higher percentage of subjects showed no evidence of disease activity (NEDA) over 96 weeks (22%) compared with subjects in the IFN β-1a group (13%).

The MS functional composite (MSFC) was used to measure ambulation, arm function, and cognition in subjects enrolled into the study. Negative changes from baseline in MSFC score and component Z scores indicate worsening in disability, and positive changes indicate improvement in disability [Polman and Rudick 2010]. The median change in MFSC score from baseline to weeks 48 and 96 was lower in the IFN β-1a group. The median change in score from baseline to week 48 was 0.058 for subjects in the IFN β-1a group, compared to 0.071 in the daclizumab group (p=0.05). The median change in score from baseline to week 96 was 0.055 in the IFN β-1a group, compared to 0.091 in the daclizumab (p<0.001). Changes in component Z-scores varied by test. IFN β-1a treated subjects showed worsening on the 25-foot walk test, which measures ambulation, from baseline to week 96, while daclizumab treated subjects showed no change (p=0.006). Both groups improved on the 9-hole peg test, which measures arm function, with the median change from baseline being significantly greater for the daclizumab group versus the IFN β-1a group at 48 weeks (p=0.08) and 96 weeks (p=0.002). Subjects in both the daclizumab and IFN β-1a groups improved equally on the 3-second paced auditory serial addition test, which measures cognition, with equal median changes in score from baseline to weeks 48 and 96.

Investigators used the symbol digit modalities test (SDMT) to measure changes in cognitive impairment over time in subjects enrolled into the study. Scores for the SDMT range from 0 to 110 with higher scores indicative of faster cognitive processing speed [Bever 1995]. Mean change in SDMT scores from baseline were significantly different across groups at week 96 (p=0.03). Subjects in the IFN β-1a group increased by an average of 2.9±12.7 points while subjects in the daclizumab group increased by an average of 4.1±12.4 points.

Serious adverse events (SAEs) were more common in the daclizumab group compared with the IFNβ-1a group (15% versus 10%), including rates of infection (4% versus 2%). The most frequent infections were urinary tract infections, reported in 8 subjects treated with daclizumab and 2 subjects treated with IFN β-1a. This was followed by pneumonia, which occurred in 5 subjects and 2 subjects in the daclizumab and IFN β-1a groups, respectively. Cutaneous AEs (including rash and eczema as the most common) were reported in 37% of daclizumab subjects and 19% of IFN β-1a subjects, leading to treatment discontinuation in 5% and 1% of daclizumab and IFN β-1a subjects, respectively. Cutaneous SAEs occurred in 2% of subjects in the daclizumab group and <1% of subjects in the INF β-1a group, including dermatitis and angioedema as the SAEs reported in more than 1 subject. A higher percentage of subjects in the daclizumab group were observed to have elevations in liver aminotransferase levels that were >5 times the ULN (6% versus 3% of subjects in the IFN β-1a group) [Kappos 2015c].

5.2. Overall Rationale

The clinical development program for daclizumab to date has demonstrated that the therapy is highly efficacious in the treatment of RMS, is well tolerated, has a safety profile that is manageable with appropriate monitoring and routine clinical care, and offers convenient once-monthly self-administered SC injection dosing [Kappos 2015c; Selmaj 2013]. In the 2 to 3 year, comparator-controlled, phase 3 DECIDE trial, daclizumab (150 mg) treatment resulted in several statistically significant effects compared to once-weekly IM IFNβ-1a including reduction in ARR by 45%, reduction in 24-week confirmed disability progression by 27%, and reduction in the formation of MRI lesions by 65% (Gd+), 54% (new/newly enlarging T2-hyperintense), and 52% (new T1-hypointense lesions) [Kappos 2015a; Kappos 2015b]. Additional findings from DECIDE indicated that daclizumab resulted in clinically meaningful cognitive improvement (as assessed by the SDMT) compared to IM IFNβ-1a, and fewer subjects receiving daclizumab experienced cognitive decline [Benedict 2015].

From a safety perspective, clinical data to date indicate no risk of opportunistic infections with daclizumab and, importantly, no risk of PML. The risks associated with daclizumab (e.g., infections, rash, dermatitis, hepatic enzyme abnormalities) have been shown to be manageable with standard monitoring and medical interventions [Gold 2013; Kappos 2015a; Kappos 2015c].

Although evidence demonstrates that natalizumab is a highly effective treatment for RMS, a number of patients who are effectively responding to therapy ultimately discontinue treatment due to concerns regarding the risk of PML or the occurrence of AEs [Butzkueven 2014; Polman 2006]. Multiple DMTs have been investigated as post-natalizumab treatment options, including fingolimod, DMF, IFNβ, GA, and pulsed steroids, but the results have been mixed, with some patients exhibiting MS disease activity despite alternative treatment [Centonze 2012; Clerico 2014; Cohan 2015; Cohen 2014; Faissner 2015; Fox 2014; Kappos 2015b; Rossi 2013]. In

multiple studies investigating the efficacy of fingolimod following discontinuation of natalizumab, upwards of 25% of subjects experienced a clinical relapse within the first 6 months of starting fingolimod [Comi 2015; Comi 2013; Kappos 2015c]. In a retrospective, observational study investigating the efficacy of DMF following discontinuation of natalizumab (STRATEGY), overall ARR increased from 0.114 on natalizumab to 0.248 after 1 year of DMF treatment [Cohan 2015]. Therefore, there remains an unmet medical need for new alternative high-efficacy treatment options for the often difficult to treat population of RMS patients who find it necessary to discontinue a therapy that otherwise may be effectively managing their disease.

Considering that daclizumab is a highly efficacious treatment for RMS with a manageable safety profile and no increased risk of PML to date, it could be a compelling option for patients switching off natalizumab. Therefore, the SUSTAIN study aims to establish whether daclizumab is a suitable DMT for RMS patients discontinuing natalizumab.

5.2.1. Rationale for Duration between Therapies

As part of the study design, subjects must receive their first dose of daclizumab at 28 (+ 3) days following discontinuation of natalizumab. The rationale for this requirement is to minimize the washout period between daclizumab and natalizumab. Clinical research studies in patients switching from natalizumab to an alternative treatment option have shown that disease activity can occur within the first 6 months of discontinuing natalizumab. However, in several of these studies, the risk of disease recurrence was shown to be mitigated with a shorter washout period between treatments [Cohan 2015; Kappos 2015c]. In a randomized trial evaluating the effects of natalizumab treatment interruption (RESTORE), it was shown that natalizumab concentrations reach undetectable levels 8 weeks after discontinuation [Cree 2013]. Pharmacodynamic (PD) studies with daclizumab demonstrated increases in $CD56^{bright}$ NK cells and serum IL-2 levels within the first 4 weeks of treatment [Amaravadi 2015] and effects on disease activity, as evidenced by reductions in Gd+ lesion activity, were apparent within 8 to 12 weeks (SELECT; Biogen, data on file). These data indicate that a 28-day gap between the discontinuation of natalizumab and the initiation of daclizumab would maximize the PD overlap of these 2 therapies and thus minimize the amount of time patients are not protected by a highly efficacious therapy.

With respect to the time interval between natalizumab discontinuation and daclizumab initiation, it is also important to consider how these therapies are thought to function in the body and the possibility of additive immunosuppressive effects. Daclizumab and natalizumab impact the pathophysiology of MS in distinct and reversible ways. Daclizumab is a humanized monoclonal antibody that targets CD25 and reversibly modulates IL-2 signaling. These effects result in 1) selective antagonism of pro-inflammatory activated T cell function and 2) expansion of immunoregulatory $CD56^{bright}$ NK cells [Bielekova 2013; Pfender and Martin 2014; Wiendl and Gross 2013]. Natalizumab is a selective adhesion molecule inhibitor that binds to the α4-subunit of human integrins, disrupting their interaction with ligands such as vascular cell adhesion molecule-1. This action reduces the ability of immune cells to cross the blood-brain barrier and enter the CNS [Polman 2006; Tysabri® Prescribing Information 2013/SmPC]. Presently, no biological evidence suggests a risk of AEs resulting from the additive biological effects of these 2 therapies; the SUSTAIN study is expected to address this paucity of data. Ultimately, a

natalizumab washout period of 28 days is thought to represent an effective balance between efficacy and safety, and findings from this study are anticipated to help address the important unmet medical need of successful treatment post-natalizumab.

5.2.2. Rationale for Dose and Schedule Selection

Single-use, disposable pre-filled pens, also known as autoinjectors, will be provided to simplify the injection process and thereby reduce the burden of administering a long-term therapy such as daclizumab in the clinic or at home. The dose and frequency of daclizumab used in this study is the same used in other phase 3 studies of daclizumab (DECIDE, Study 205MS301; OBSERVE, Study 205MS302; EXTEND, Study 205MS303).

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective and Endpoints

The primary objective of the study is to evaluate the effects of treatment with daclizumab on the proportion of subjects relapse-free at 6 months in RRMS subjects, who switched from treatment with natalizumab to daclizumab due to safety concerns.

The primary endpoint is the proportion of subjects relapse-free at Month 6 in RRMS subjects treated with daclizumab, who switched from treatment with natalizumab.

See Section 11 for the definition of relapse.

6.1.2. Secondary Objectives and Endpoints

The secondary objectives of this study in this study population are to evaluate the effects of daclizumab on the following:

- MS relapse activity including the ARR and the proportion of subjects experiencing relapses requiring hospitalization and/or steroid treatment.
- MS-related outcomes measured using MRI.
- Safety and tolerability in subjects previously treated with natalizumab.

The secondary endpoints that relate to these objectives are the following:

- The proportion of subjects relapse-free at Month 12.
- The proportion of subjects experiencing relapse requiring hospitalization and/or steroid treatment at Month 12.
- The ARR at Month 12.
- The number of new Gd+ enhanced and T1 hypointense lesions at Month 6 and Month 12 on MRI.
- The number of new or newly enlarged T2 hyperintense lesions at Month 6 and Month 12 on MRI.
- The permanent discontinuation rate of daclizumab at Month 12.
- The incidence of AEs and SAEs including clinically relevant shifts in clinical laboratory assessments.

6.1.3. Exploratory Objectives and Endpoints

The exploratory objectives of this study in this study population are to evaluate the effects of daclizumab on:

- [redacted].

- [redacted]
- [redacted].
- [redacted].

The endpoints associated with the exploratory objectives are the following:

- [redacted]
- [redacted].
- [redacted]
- [redacted]
- [redacted].
- [redacted]
- [redacted]
- [redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a multicenter, open-label study of daclizumab monotherapy in subjects with RRMS who were previously treated with natalizumab for at least 12 months. Approximately 100 subjects will be enrolled from approximately 40 sites in the US and rest of world over a 12-month period.

Following consent and evaluation of eligibility, subjects will discontinue natalizumab and commence treatment with daclizumab. Subjects will initiate treatment with daclizumab at 28 (+3) days following the last infusion of natalizumab. A detailed description of study assessments is provided in Section 9.2.

The assessment schematic provides an overview of the study assessment schedule (Table 1). Assessments will be performed at enrollment, baseline, Month 1, Month 3, Month 4, Month 6, Month 9 and Month 12. The additional safety follow-up visit will be conducted remotely.

7.2. Overall Study Duration and Follow-Up

The study will consist of a 28-day (+3 days) screening period for each subject, a 12-month treatment period, and a 4-month remote safety follow-up visit after the subject's last treatment injection. The end of the study for each subject will be the last study visit or the visit at which the subject discontinues from the study (before the 12-month visit). Each follow-up visit will include a 4-day window before and after the visit for completion of all assessments. The follow-up period will include efficacy and safety following treatment initiation of daclizumab. The end of the study overall will be defined as the end of the 12-month study follow-up period for the last patient. The 4-month safety follow-up visit will be conducted remotely after the 12-month study follow-up visits have been completed.

Subjects having tentative disability progression identified near the end of the core study (e.g., Month 12) will attend additional follow-up visits 12 and 24 weeks later to confirm progression.

Subjects may discontinue treatment at any time during the study, and they will be followed for an additional 4 months to collect data on safety, LFT, MS treatment, relapses, and the use of concomitant medications.

7.3. Early Termination of Study

Biogen may terminate this study at any time, after informing the Investigator(s). Biogen will notify the Investigators if the study is placed on hold, completed, or closed.

8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria during the screening period (28 days [+3 days] following the last dose of natalizumab):

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Aged 18 to 55 years old, inclusive, at the time of informed consent.
3. Must have documented diagnosis of RRMS (McDonald 2010 Criteria) at screening [Polman 2011].
4. Must have been treated with natalizumab for at least the 12 months prior to screening and have not missed 2 or more consecutive scheduled doses.
5. Must be naïve to daclizumab and other forms of daclizumab such as Zenapax® prior to enrollment.
6. Must have a confirmed EDSS score of 0 to 5.5, inclusive, at screening.
7. Female subjects of childbearing potential must practice effective contraception from Day -1 and be willing and able to continue contraception for duration of the study.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist during the screening period (28 days [+3 days] following the last dose of natalizumab):

1. Inability to comply with study requirements or, at the discretion of the Investigator, is deemed unsuitable for study participation.
2. Current participation in another investigational study.
3. Diagnosis of primary progressive, secondary progressive, or progressive relapsing MS (as defined by Lublin and Reingold) [Lublin 2014].
4. Females breastfeeding, pregnant, or planning to become pregnant; or women who have a positive pregnancy test result during screening.
5. History of drug or alcohol abuse (as defined by the Investigator) within 1 year prior to screening.
6. History of severe opportunistic infections (including PML) or any clinically significant, cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic (other than MS), dermatologic, psychiatric, and renal, or other major disease, as determined by the Investigator.
7. Discontinued natalizumab due to suspicion of PML.

8. Known active malignancies (subjects with cutaneous basal cell carcinoma that has been completely excised prior to study entry remain eligible).
9. Clinically significant lab abnormalities revealed by blood tests at screening apart from those known to be associated with natalizumab (e.g., lymphocytosis).
10. Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN (normal range for AST: 8 to 48 units per liter and for ALT: 7 to 55 units per liter). The normal range for liver enzyme levels may vary slightly by laboratory.
11. A history of autoimmune hepatitis or other autoimmune condition involving the liver.
12. The subject is using another MS therapy concomitantly.
13. Known history of human immunodeficiency virus (HIV).
14. Positive test result for Hepatitis C virus (test for hepatitis C virus antibody [HCV Ab]) or hepatitis B virus (test for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). History of transplantation or any anti-rejection therapy.
15. Have had evidence of disease activity within the 6 months prior to screening visit defined as the following:
    - MS relapse, or
    - Gd+ enhancing lesions, or new or enlarging T2 lesions over the last 6 months, or
    - Disease progression (any increase of EDSS in the past 6 months).
16. The subject is considered by the Investigator to be immunocompromised based on medical history, physical examination, or laboratory testing.
17. The subject has been treated with immunosuppressive or immunomodulating treatments including mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil.

9. STUDY PROCEDURES

Once the investigational site is activated for study participation, subjects may be enrolled if they have met the inclusion criteria in Section 8.1 and have not been excluded based on the exclusion criteria in Section 8.2.

9.1. Screening, Enrollment and Randomization

Subjects must be consented before any screening tests or assessments are performed. At the time of consent, the subject will be enrolled into the study.

Subjects will be initiated on daclizumab after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to registration and assignment of a unique subject identification number. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment. If an eligible subject was approached and did not participate in the study, the reason for nonparticipation will be documented in the screening log

9.2. Follow-Up

Subjects will be followed-up for 12 months with assessments at Months 1, 3, 4, 6, 9, and 12. There will be a 4-month safety visit conducted remotely. The follow-up study assessments are described in Section 11.2.

Subjects having tentative disability progression identified near the end of the core study (e.g., Month 12) will attend additional follow-up visits 12 and 24 weeks later to confirm progression.

Subjects who do not receive a treatment dose for 2 or more consecutive months will continue to be followed for data collection.

9.3. Withdrawal of Subjects from the Study

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

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- The Investigator withdraws the subject from the study for medical reasons.

The reason for the subject's withdrawal from the study must be recorded in the subject's case report form (CRF).

Subjects who withdraw from the study will not be replaced.

10. STUDY TREATMENT

Biogen MA Inc. will provide daclizumab to sites in the US. Biogen Idec Research Limited will provide daclizumab to sites in all other countries. Daclizumab must be administered on-site during the first 6 months, and at the Month 9 visit. Sites have the option to allow subjects to administer the drug at home for doses at Month 7, 8, 10, and 11.

10.1. Dosing Regimen and Administration

Refer to and follow the prevailing local labeling, directions for handling and administration (DHA) and Investigator Brochure.

Daclizumab is supplied as a sterile, preservative-free, colorless to slightly yellow, and clear to slightly opalescent liquid. The drug product is supplied in a single-use pre-filled pen, also known as an autoinjector, in this study. Daclizumab is supplied as 150 mg of daclizumab per 1.0 mL and is administered SC once a month.

As shown in the study schematic, doses at Months 7, 8, 10 and 11 can be administered either at home or supervised at the site. Therefore, at Months 6 and 9, subjects choosing to self-administer at home will be provided with 2 kits to take home along with cool bags and sharp bins.

Subjects should be trained in the proper technique and storage for self-administering SC injection using the autoinjector. The usual sites for SC injection include the thigh, abdomen, and back of the upper arm.

Each daclizumab autoinjector is provided with the needle pre-attached. Autoinjectors contain a single dose only and should be discarded after use. Once removed from the refrigerator daclizumab should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm daclizumab. The daclizumab autoinjector must not be used if the liquid is cloudy or contains floating particles. The liquid must be colorless to slightly yellow.

10.2. Treatment Compliance

Compliance with at-home treatment dosing is to be monitored and recorded by subjects. Beginning with the Month 7 visit when at-home, self-administered treatment can be initiated, self-reported subject adherence to treatment along with MS treatment information will be captured using a dosing diary, for subjects who self-administer. The dosing diaries will be provided at the Month 6 and Month 9 visits, and will be reviewed periodically by study site staff and the Clinical Monitor. The provided drug kits will be individually numbered in order to help with tracking of any compliance differences between doses administered at home and in the clinic.

In the event that a dose is missed and less than 2 weeks have passed since the date the missed dose was originally scheduled, subjects should be instructed to inject their missed dose as soon as it is remembered and remain on their original monthly dosing schedule. If a dose is missed and more than 2 weeks have passed from the date the missed dose was originally scheduled,

subjects should skip the missed dose, wait to dose again until their next scheduled dose, and then remain on their original monthly dosing schedule. Only 1 dose should be administered at a time.

10.3. Daclizumab Stability and Storage

Daclizumab will be supplied as a solution for injection, in the autoinjector. In addition to the active ingredient daclizumab, the solution includes the following excipients: sodium succinate anhydrous (5.94 mg), succinic acid (0.35 mg), sodium chloride (5.84 mg), polysorbate 80 (0.30 mg), water for injection, and 0.14 mmol sodium per dose.

The label includes conditions for storage, lot number, and other pertinent information such as Sponsor and caution statement.

Study treatment must be stored in a secure location. Accountability for study treatment is the responsibility of the Investigator. More details concerning this responsibility are included in Section 10.4.

Study treatment must only be dispensed by a Pharmacist or appropriately trained staff. Study treatment is to be dispensed only to subjects enrolled in this study.

Study site staff should refer to the Investigator Brochure and/or Product Leaflet for specific instructions on the handling, preparation, administration, and disposal of the study treatment

10.3.1. Daclizumab Preparation

The individual administering daclizumab should first carefully review instructions provided in the prevailing local labeling, DHA, and Information for Patients (if subjects are self-administering) or Investigator's Brochure (for Investigators administering treatment). If kit packaging is damaged, or if there is anything unusual about the appearance or attributes of the pen device, it should not be used. The kit or pen in question should be saved at the study site, and the problem immediately reported to Biogen.

Daclizumab is to be stored in controlled refrigeration between 2°C to 8°C (36°F to 46°F) in the closed original carton to protect from light. If needed, daclizumab may be stored without refrigeration up to 30°C (up to 86°F) for up to 30 days. The daclizumab pen should not be placed back into the refrigerator after warming to room temperature. It should not be frozen or exposed to high temperatures. For the most up-to-date storage requirements, follow the instructions provided in the approved package insert

10.3.2. Daclizumab Handling and Disposal

The Investigator must destroy all unused pens of daclizumab as instructed by Biogen.

10.4. Daclizumab 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 (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all type of packaging both used and unused must be saved for study treatment accountability. Subjects self-administering daclizumab at home will be provided with sharps bins for disposal of packaging. Subjects must bring sharps bins with them to clinic visits for accountability. At the end of the study, reconciliation must be made between the amount of daclizumab supplied, dispensed, and subsequently destroyed or returned to Biogen. A written explanation must be provided for any discrepancies.

If any study treatment supplies are to be destroyed at the site, the Principle Investigator(s) must obtain prior approval by Biogen. The Principle Investigator(s) must notify Biogen, in writing, of the method, date, and location of the destruction.

10.5. Treatment Schedule Modification

Subjects who experience a significant change in their medical status (e.g., neurological worsening/suspected MS relapse, possible injection-site reaction, infection, cutaneous event, fever, abdominal pain, persistent diarrhea, jaundice, nausea, vomiting, pruritus) must contact the Study Neurologist as soon as possible and no more than 48 hours after symptom onset. The subject should then be evaluated by the Study Neurologist within no more than 72 hours for physical and neurological assessments and further treatment recommendations if appropriate. These subjects should not administer additional daclizumab until they have been evaluated by the Study Neurologist or their backup

10.5.1. Elevated Liver Function Tests

LFT procedures are described in Section 11.3.2. Prior to starting treatment with daclizumab, serum transaminases (ALT and AST) and bilirubin levels must be obtained. Serum transaminases must be monitored monthly during treatment and up to 4 months after the last study dose of daclizumab (see Section 4.2, for timing).

Study treatment must be temporarily suspended if a subject develops any of the following:

- ALT/SGPT, or AST/SGOT >3*ULN.
- ALT or AST have not exceeded 5 times the ULN; daclizumab may be resumed when ALT or AST have reached <2 times the ULN.
- Any other clinically significant hepatic condition in the opinion of the Investigator including jaundice.

Note: For subjects who present with jaundice, an LFT must be performed as soon as possible. After a suspension, dosing of daclizumab may be resumed when ALT/SGPT and AST/SGOT are <2*ULN provided that the criteria for permanent discontinuation have not been met.

Study treatment must be permanently discontinued if a subject develops any of the following:

- Confirmed ALT or AST of >5 times the ULN ALT/SGPT or AST/SGOT >3*ULN with concomitant elevation of total bilirubin >2*ULN.
- If a subject has treatment suspended for an LFT elevation and has also had a prior treatment suspension for an LFT elevation during daclizumab use, daclizumab must be permanently discontinued unless an alternative explanation for the LFT elevation unrelated to daclizumab use is clearly identified by the Investigator.

11. DATA COLLECTION

A written, signed Informed Consent Form (ICF) and all authorizations required by local law (e.g., PHI in North America) must be obtained prior to performing any tests or assessments under this protocol.

11.1. Site Personnel

For each subject, the Principal Investigator will designate the following study site personnel:

- A primary Study Neurologist and backup neurologist.
- A primary and backup Nurse (or Study Coordinator).
- A primary and backup Examining Technician.
- An MRI Technician.
- A Pharmacist (or authorized designee).

The Study Neurologists may designate another neurologist at the center who meets the same qualifications to perform the [redacted] assessments and other neurologic assessment during the trial.

The primary Study Neurologist will be responsible for the following:

- Management of the routine neurological care of the subject.
- Assessment (including assignment of causality) and treatment of AEs and MS relapses.
- Obtaining an [redacted] score.
- Review of selected hematology and all blood chemistry results from the central laboratory.
- Assessment of LFT results, as detailed in Section 11.3.2.
- Monitoring and follow-up of any abnormal hepatic tests.

Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The primary Nurse or Study Coordinator will be responsible for the following:

- Assisting the Study Neurologist in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications.
- Monitoring the [redacted] scores.
- Collection of blood samples and obtaining vital signs.
- Study treatment administration/dispensation/accountability.

The MRI Technician will be responsible for the following:

- Performing a brain MRI scan with and without Gd at all protocol-required timepoints. Study-specific MRI scan procedures and protocols, which will be provided prior to study start, must be followed.

The Pharmacist (or authorized designee) will be responsible for the following:

- Storage, distribution, and accountability of study treatment.

11.2. Assessments

11.2.1. Assessments at Screening

The following variables will be collected during screening at the enrollment visit:

- Date of signed ICF.
- Confirmation of eligibility criteria.
- Demographic information: age at screening (years), sex.
- MS disease history (type of MS, date of initial MS diagnosis, relapse history).
- Relevant medical history and co-morbidities including: assessment of clinically significant medical and surgical history and concomitant diseases, and known cardiovascular risk factors. Of interest are: smoking; alcohol consumption; subject and family history of high cholesterol; high blood pressure; cardiac disease; peripheral artery disease; arrhythmia; cerebrovascular disease; diabetes mellitus; HIV; hepatitis C virus (test for HCV Ab) or hepatitis B virus (test for HBsAg and/or HBcAb); history of transplantation or any anti-rejection therapy.
- Prior use and duration of natalizumab (e.g., start and stop dates, initial dose, dose reductions or escalations, dosing frequency).
- Prior use and duration of other therapies for MS (if any) (e.g., start and stop dates, initial dose, dose reductions or escalations, prescribed dosing frequency, reason for discontinuation, prior use of immunosuppresants).
- Vital signs.
- Physical examination.

Refer to Section 4 for the timing of assessments.

11.2.2. Assessments at Baseline and Follow-up

11.2.2.1. MS Treatments and Concomitant Medications

MS treatments and concomitant medications will be recorded as follows:

- Daclizumab dose and dates of administration on-site.
- Daclizumab self-administered dose, and dates of administration recorded by subject in dosing diary (beginning at Month 7, where applicable).

- Current use (i.e., at screening) of immunomodulatory, immunosuppressive (including corticosteroids), anti-neoplastic agents, and other approved MS therapies (if any).
- Current use (i.e., at screening) of non-MS therapy medications (if any).

Refer to Section 4 for the timing of assessments.

11.2.2.2. Laboratory Assessments

As per Section 11.3.2, a central laboratory will perform laboratory analyses and provide reference ranges for each test.

Laboratory assessments will include the following:

- CBC including hemoglobin, hematocrit, platelet count, red blood cell count and white blood cell count (with differential).
- Blood chemistry including sodium, potassium, chloride, total bilirubin, alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transferase, blood urea nitrogen, creatinine, and bicarbonate and bilirubin.
- [redacted]
- [redacted].
- [redacted].
- [redacted].
- LFT including ALT/SGPT, AST/SGOT, and bilirubin:
  - LFT is to be conducted monthly in a blood draw conducted.
  - LFT will be performed only if the subject is continuing daclizumab or if less than 4 months have passed since the subject discontinued treatment and monitoring is deemed appropriate by the Investigator.

Refer to Section 4 for the timing of assessments.

11.2.2.2.1. [redacted]

[redacted]

11.2.2.3. Safety

Safety assessments will include the following:

- SAEs.
- AEs, including laboratory abnormalities.
- Vital Signs.
- Physical Assessment (i.e., normal or abnormal).

An additional safety follow-up visit at 4 months after the last study injection will be conducted remotely to evaluate potential delayed safety outcomes.

Refer to Section 4 for the timing of assessments.

11.2.2.4. Efficacy

Efficacy assessments will include the following:

- MS relapse information including date of onset, date of visit, neurologic examination, duration, new and/or recurrent neurologic symptoms, hospitalization, and treatments including steroids. For the purposes of this study relapse is defined as new or recurrent neurologic symptoms not associated with fever, lasting at least 24 hours. New or recurrent neurologic symptoms that evolve gradually over months are to be considered disease progression, not an acute relapse. New or recurrent neurological symptoms that occur fewer than 30 days following the onset of a relapse as defined above are to be considered part of the same relapse.
- [redacted].
- Brain MRI scan including number and volume of Gd+ lesions, T1 hypointense lesions, and T2 hyperintense lesions.

Refer to Section 4 for the timing of assessments.

11.3. Special Instructions for Tests and Assessments

11.3.1. Rescreening

Subjects who are not eligible for participation at baseline due to a temporary condition (e.g., acute infection) are allowed to be rescreened once the condition has resolved.

11.3.2. Liver Function Test Assessments Prior to Daclizumab Dosing

Before a monthly dose of daclizumab is given, LFT results from prior testing performed within the previous 28 (+3) days must be reviewed by the Study Neurologist or their backup, and must be within protocol-required limits as described in Section 10.5.1.

LFTs can be performed as follows:

- Samples for LFTs must be drawn monthly and will be analyzed centrally for the purposes of this study. This includes any timepoints where there is not a scheduled

study visit and for samples which might be collected outside of the clinic (e.g., by visiting nurses). Accommodations will be made for LFT sampling and central testing for subjects choosing at-home dosing at Month 7, 8, 10 and 11.

- Results from either local or central LFT tests can be used for the medical management of the patient and to determine whether dosing should continue or be suspended at the monthly dosing timepoint (see Section 10).
- In any cases where LFTs are tested locally (e.g., at a local laboratory), samples must also be collected for central analysis for the purposes of this study.
- If the subject is administering daclizumab injections at home, site personnel must contact the subject after review of prior LFT results performed within 28 (+3) days to authorize the monthly injection, or if LFT results warrant, to instruct the subject to withhold their injection.
- LFTs following a treatment suspension must be performed through the central laboratory until the LFT abnormality has resolved. In cases where LFTs cannot be performed via central laboratory, repeat LFT results from local laboratory can be used for confirmation.

11.3.3. MRI Scans

MRI scan results will be assessed by a central reading center and will **not** be entered into the electronic data capture (EDC) tool. Please refer to the MRI Acquisition and Procedures Manual for a detailed list of results from the central reading center.

11.3.4. Other Assessments

Vital signs include systolic and diastolic blood pressure, pulse, and body temperature, measured pre-dose. The subject must rest quietly for 5 minutes prior to blood pressure and pulse measurements.

12. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

At the signing of the ICF, each subject or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

12.1. Definitions

12.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the Investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for as SAE.
- A laboratory test result that requires the subject to receive specific corrective therapy.
- A laboratory abnormality that the Investigator considers to be clinically significant.

12.1.2. Serious Adverse Event

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

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

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes

listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

12.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
- If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless 1 of the requirements in Section 12.1.2 is met.

12.2. Safety Classifications

12.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria of an SAE as defined in Section 12.1.2.
- The relationship of the event to study treatment as defined in Section 12.2.2.
- The severity of the event as defined in Section 12.2.3.

12.2.2. 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 commercial drug	
Not related	An AE is considered "not related" to the use of the investigational drug if there is not a 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 drug and the event, the presence of a biologically implausible relationship between the product and the AE (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.
Related	An AE is considered "related" to the use of the investigational drug if there is a 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 re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

12.2.3. Severity of Events

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

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

12.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen Safety and Benefit-Risk (SABR) according to the approved local label.

12.3. Monitoring and Recording Events

12.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and End of Study or Early Termination is to be recorded on the subject's CRF, regardless of the severity of the event or its relationship to study treatment.

12.3.2. Serious Adverse Events

Any SAE experienced by a subject after the subject signs the ICF and before End of Study or Early Termination, is to be recorded on an SAE Form, regardless of the event relationship to daclizumab. For reporting timelines and procedures, see Section 12.3.3.

Subjects will be followed for all SAEs until the end of the 4 month safety follow-up. Thereafter, the event should be reported to Biogen SABR or designee only if the Investigator considers the SAE to be related to study treatment.

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

12.3.3. Immediate Reporting of Serious Adverse Events

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

Reporting Information for SAEs

Any Serious Event that occurs between the time that the subject has signed informed consent and End of Study or Early Termination Visit must be reported to Biogen SABR or designee within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to Biogen SABR or designee regardless of the relationship to daclizumab or the severity of the event.

To report initial or follow-up information on a Serious Event, fax or email a completed SAE form to the following:

Fax: see Study Reference Manual

Email: [redacted] mailto:

12.3.4. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR or designee.

12.3.5. Suspected Unexpected Serious Adverse Reactions

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

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

12.4. Procedures for Handling Special Situations

12.4.1. Reporting Pregnancy

The Investigator should refer to the approved local label for guidance if female subjects become pregnant or are considering becoming pregnant during the study.

At each routine visit, female subjects of childbearing potential will be asked about their pregnancy status and possible pregnancies/spontaneous abortions since the last visit or contact. Spontaneous abortions are considered to be SAEs and must be reported as such.

If the partner of a male subject receiving daclizumab becomes pregnant at any time during the study, the Investigator should follow the pregnancy outcome and report any congenital anomaly or birth defect as an SAE to Biogen or designee.

12.4.2. Overdose

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Form and faxed to Biogen SABR or designee within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded in the CRF; dosing information is recorded on a CRF.

12.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care.

12.5. Investigator Responsibilities

The Investigator's responsibilities include the following (refer to Section 12.1):

- Review all AEs to determine seriousness and fulfillment of collection criteria.
- Monitor and record all SAEs, regardless of the relationship to daclizumab.
- Determine the relationship of each SAE to daclizumab.
- Determine the onset and resolution dates of each SAE.
- Record all pregnancies.
- Complete the appropriate form for each SAE, pregnancy and overdose and fax or email it to Biogen SABR or designee within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR or designee within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the subjects' medical records.

- Report SAEs to local institutional review board (IRB)/ethics committees (ECs), as required by local law.

12.6. Biogen Responsibilities

Biogen's responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor or designee is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting SAEs.
- Determine the expectedness of all SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ECs, and Investigators of SAEs, as required by local law, within required time frames.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size Justification

This study will enroll approximately 100 subjects. The sample size is estimated based on the proportion of subjects who are relapse-free at Month 6.

Assuming a drop-out rate of 10%, the evaluable sample size will be 90. A two-sided 95% confidence interval (CI) for a single proportion of subjects on daclizumab 150 mg remaining free of relapses at the end of Month 6 will extend between 8.3% and 6.7% from the observed proportion for an expected proportion of 80% to 88%, respectively.

13.2. Analysis Population

The analysis population is based on intent-to-treat (ITT), where the subjects should receive at least 1 dose of the medication during follow-up. Subjects discontinuing treatment will also be included in the analysis.

13.3. Methods of Analysis

Baseline disease and demographic characteristics will be summarized overall. The demographic profile (age, sex, and race/ethnicity), relevant medical history, MS disease history, MS treatment prior to start of natalizumab treatment, and concomitant medications and therapies used will be listed and summarized using the appropriate descriptive statistics for continuous and categorical variables.

Descriptive analyses corresponding to the specific research objectives will be performed to characterize the subjects studied. Continuous variables will be reported as mean, standard deviation, median, 25th and 75th percentile (Q1, Q3), minimum and maximum where appropriate. Categorical variables will be summarized as frequencies and percentage. Proportions will be presented with exact 95% CIs as further specified in the statistical analysis plan (SAP).

Details on handling of all missing data, which are common in observational studies, will be described fully in the SAP. The proportion of missing data will be reported for each measured variable in the study. In general, missing data will not be imputed and the data will be analyzed as they are recorded in the study electronic case report forms (eCRFs).

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC, USA).

Analyses corresponding to the specific research objectives of the study are described in the sections below.

13.4. Primary Endpoint Analysis

13.4.1. Efficacy Analysis

The proportion of subjects relapse-free at Month 6 will be estimated using the Kaplan-Meier approach. This will be calculated as 1 minus the proportion of subjects with relapses at Month 6.

For the Kaplan-Meier approach, the time to relapse is the number of days from the date of the first dose of daclizumab to the date of first relapse, or end of study, whichever comes first. The Cox proportional hazard model will be used to estimate the hazard ratio of relapses within subject subgroups of interest. The subgroups of interest will be defined in the SAP.

The proportion of subjects relapse-free 6 months before and 6 months after switching to daclizumab will be compared using McNemar's Test for subjects who had relapse information available at the above time points.

For primary endpoints, sensitivity analyses will be performed on the ITT population excluding those patients who missed 2 or more consecutive doses within 6 months. Additional details regarding the sensitivity analysis will be described in the SAP.

13.5. Secondary Endpoints Analysis

13.5.1. Efficacy Analysis

The proportion of subjects relapse-free at Month 12 will be estimated using Kaplan-Meier approach. This will be calculated as 1 minus the proportion of subjects with relapses at Month 12. For the Kaplan Meier approach, the time to relapse is the number of days from the date of the first dose of daclizumab to the date of first relapse, or end of study, whichever comes first. The Cox proportional hazard model will be used to estimate the hazard ratio of relapses between subject subgroups of interest.

The proportion of subjects relapse-free 12 months before and 12 months after switching to daclizumab will be compared using McNemar's Test for subjects who had relapse information available at the above time points (study completers).

The proportion of subjects experiencing relapse requiring hospitalization and/or steroid treatment at Month 12 will be estimated using the Kaplan-Meier approach. For the Kaplan-Meier approach, the time to relapse requiring hospitalization and/or steroid treatment will be the number of days from the date of the first dose of daclizumab to the date of first relapse requiring hospitalization and/or steroids treatment, or end of study, whichever comes first. A Cox proportional hazard model will be used to estimate the hazard ratio of relapses requiring hospitalization and/or steroids treatment between subject subgroups of interest.

The ARR with 95% CI at Month 12 (calculated as the total number of relapses divided by the total number of person-years in the study at the end of Month 12 for each subject) will be estimated using a negative binomial model. If the data are under-dispersed or if the negative binomial regression does not converge, a Poisson regression model with the same covariates will be used instead. Given that subjects may have more than 1 relapse in 12 months, the number of relapses will be summarized both as a continuous variable and as a categorical variable.

The number of new Gd+ enhanced and T1 hypointense lesions at Month 6 and Month 12 and the number of new or newly enlarged T2 hyperintense lesions at Month 6 and Month 12 when compared with baseline will be summarized both as continuous variables and as categorical variables. A negative binomial model adjusting for the corresponding baseline MRI lesion counts will be used to estimate the adjusted mean and lesion mean ratio between subject subgroups of interest.

The daclizumab permanent discontinuation rate at Month 12 will be summarized as the ratio of number of subjects who had permanently discontinued daclizumab prior to Month 12 over the total number of subjects who received at least 1 dose of daclizumab in the study, along with a 95% CI for the proportion.

The number of patients who missed 2 or more consecutive doses within 6 months and within 12 months will be reported. For secondary endpoints, sensitivity analyses may be considered on the ITT population, excluding those patients who missed 2 or more consecutive doses within 6 months for endpoints evaluated at/up to 6 months, and within 12 months for endpoints evaluated at/up to 12 months. Additional details regarding sensitivity analyses will be described in the SAP.

13.5.2. Safety

13.5.2.1. Analysis Population

The safety population will be defined as all subjects who received at least 1 dose of study treatment.

13.5.2.2. Methods of Analysis

All AEs, SAEs, laboratory abnormalities, physical examination results, and vital signs will be evaluated for safety.

13.5.2.3. Adverse Events

The incidence of treatment-emergent AEs will be summarized by severity and by relationship to study treatment. The summary tables will include AEs by system organ class as well as by preferred term within each system organ class. AEs will be coded using the Medical Dictionary for Regulatory Activities.

13.5.2.4. Laboratory Data

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

13.5.2.5. Physical Examination Results

A listing of subjects with normal status at baseline but abnormal status at any time after the date of the first dose will be presented.

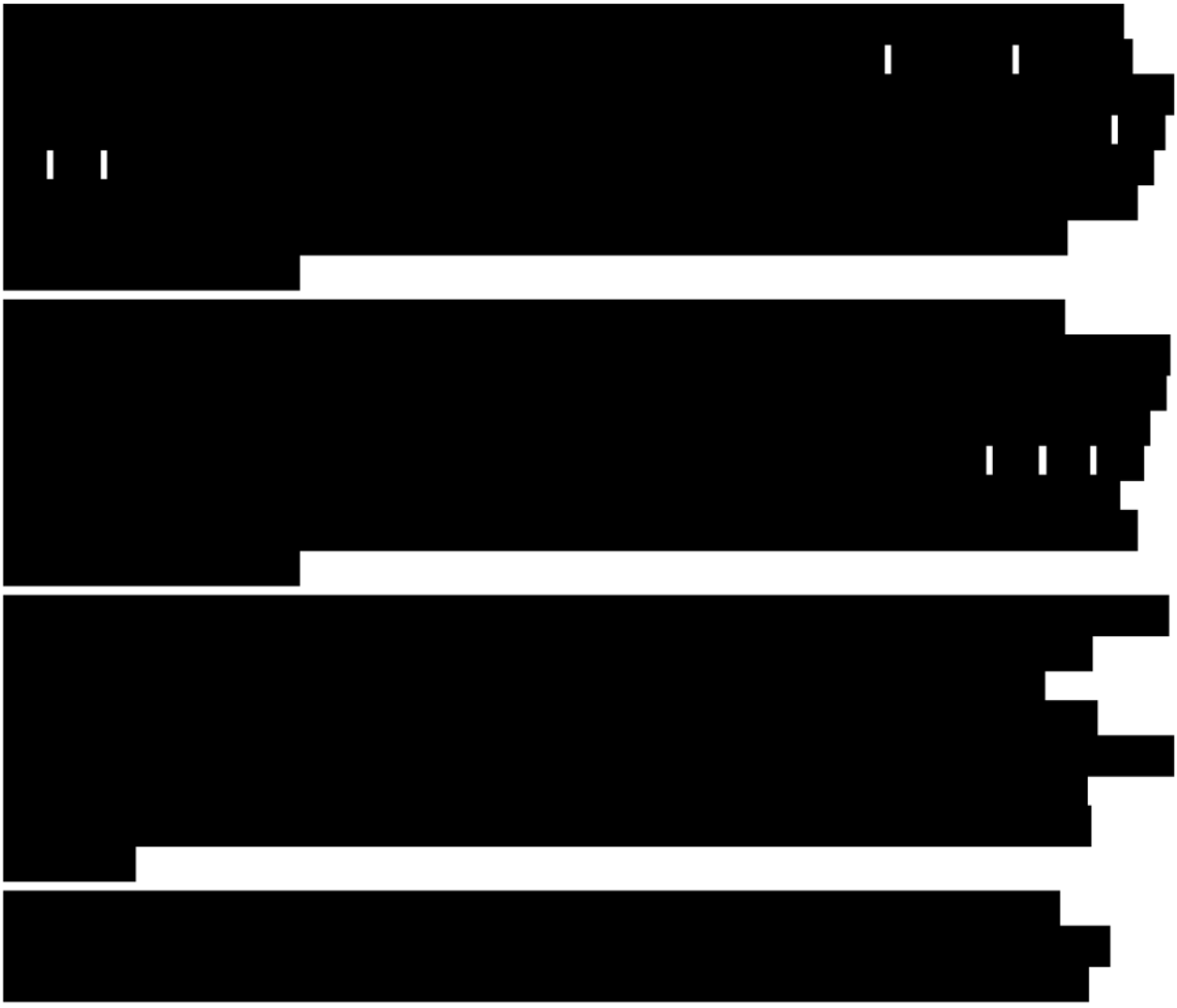
13.5.2.6. Vital Signs

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities (Table 2:) will be presented. Summary statistics for actual values and change from baseline will also be presented.

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

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from baseline of at least 1°C
Pulse	>120 beats per minute (bpm) or an increase from baseline of >20 bpm, or <50 bpm or a decrease from baseline of >20 bpm
Systolic Blood Pressure	>150 mmHg or an increase from baseline of >40 mmHg, or <90 mmHg or a decrease from baseline of >30 mmHg
Diastolic Blood Pressure	>100 mmHg or an increase from baseline of >30 mmHg, or <50 mmHg or a decrease from baseline of >20 mmHg

13.6. Exploratory Analysis



13.7. Interim Analysis

There are no planned interim analyses for this study.

14. ETHICAL REQUIREMENTS

Biogen, [redacted] and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) guidelines and conduct the study according to local regulations. The subject's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

14.1. Institutional Review Board/Ethics Committee

The Investigator must obtain IRB/EC approval of the protocol, ICF, and other required study documents prior to starting the study.

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

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen must receive a letter documenting IRB/EC approval, which specifically identifies the protocol, tracking number, and ICF version, 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 IRB/EC at required intervals and not less than annually. Documentation of the submission must be provided to Biogen.

At the completion or termination of the study, the investigational site must submit a close-out letter to the IRB/EC and Biogen

14.2. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations.

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

A copy of the signed and dated ICF must be given to the subject or the subject's legally authorized representative. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

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

14.3. Subject Data Protection

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

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), ECs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

14.4. Compensation for Injury

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

14.5. Conflict of Interest

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

14.6. Registration of Study and Disclosure of Study Results

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

15. ADMINISTRATIVE PROCEDURES

15.1. Study Site Initiation

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

15.2. Quality Assurance

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

15.3. Monitoring of the Study

Biogen or its designee representatives may conduct onsite visits at the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Biogen-authorized personnel having direct access to subject (or associated) files for the purpose of verifying entries made in the CRF, and assist with their activities, if requested. Adequate space and time for monitoring visits should be made available by the Investigator or study staff. The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

15.4. Study Funding

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

15.5. Publications

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

16. FURTHER REQUIREMENTS AND GENERAL INFORMATION

16.1. External Contract Organizations

16.1.1. Contract Research Organization

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

16.1.2. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a web-based EDC tool developed and supported by EDC vendor and configured by Biogen.

16.1.3. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to analyze hematology, blood chemistry, immunology and urine samples collected for this study.

16.1.4. Central Facility for MRI Assessments

[redacted] has been selected by Biogen to read and interpret all MRIs.

All of the MRI scans with and without Gd will be evaluated at a central MRI reading center, [redacted]. All investigational sites will be required to send a test scan of a healthy volunteer subject to the MRI central reading center for evaluation in order to ensure that the site's scanning techniques are appropriate. This review will take place before the investigational site is permitted to enroll any subjects into the study.

MRI digital data should be sent over the internet, if possible. If not possible, MRI digital data can be sent on a compact disk.

Refer to the MRI Acquisition and Procedures Manual for more information and detailed instructions.

16.2. Advisory Committee

An Advisory Committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The Advisory Committee will meet at regular intervals to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended.

Members of the Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees), and participating Investigators. Biogen will designate one of the participating Investigators to be the Chairperson of the Advisory Committee.

16.3. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be formed to monitor benefit/risk during the course of the trial. The DSMB will review all AEs, clinical observations, vital signs, and laboratory tests for all subjects. The DSMB may also request and review data and monitor efficacy endpoints. The DSMB will be comprised of members with appropriate expertise who are all independent of the Sponsor. Members will not be blinded to subject treatment assignment as this is an open-label trial. Investigational sites will be notified of any relevant safety findings that may jeopardize subject safety. The DSMB will meet routinely throughout the study duration. A charter will be established between Biogen and the DSMB to outline the DSMB's responsibilities and procedures.

16.4. Changes to Final Study Protocol

All protocol amendments must be submitted to the EC and Regulatory Authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the EC 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, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the subject consent form may require similar modifications (see Sections 14.1 and 14.2).

16.5. Institutional Review Board/Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and IRBs/ECs must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

16.6. 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 laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

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18. INVESTIGATORS SIGNED AGREEMENT OF STUDY PROTOCOL

I have read the foregoing protocol, "A Phase 3b, 12-month, Open-label, Multicenter Study to Evaluate the Efficacy and Safety of BIIB019, Daclizumab, in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) Switching from Natalizumab," and agree to conduct the study according to the protocol and the applicable ICH guidelines and local 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)