



PROTOCOL NUMBER: 109MS310 / NCT02525874

PHASE OF DEVELOPMENT: 3b

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PROTOCOL TITLE: An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis

EUDRA CT NO: 2015-001973-42

DATE: 22 January 2016
Version 2
FINAL

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1. SPONSOR INFORMATION

The Sponsor is Biogen MA Inc. in North America and Biogen Idec Research Limited in the Rest of World. Biogen MA Inc. and Biogen Idec Research Limited are referred to as Biogen in this protocol.

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

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

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2. LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
AST	aspartate transaminase
BBB	blood-brain barrier
BID	twice daily
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DMT	disease modifying therapy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
██████	████████████████████
GA	glatiramer acetate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN	interferon
Ig	immunoglobulin
IV	intravenous
IVMP	intravenous methylprednisolone
IXRS	Interactive Voice and Web Response System
LLN	lower limit of normal
MMRM	mixed model for repeated measures
MS	multiple sclerosis
NK	natural killer (cells)
Nrf2	nuclear factor (erythroid-derived 2)-like 2
██████	████████████████████
PML	progressive multifocal leukoencephalopathy
██████	████████████████████
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event

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SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
T _{reg}	T regulatory (cells)
ULN	upper limit of normal
US	United States
WBC	white blood cell

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3. SYNOPSIS

Protocol Number:	109MS310
Protocol Title:	An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis
Version Number	2
Name of Study Treatment:	BG00012 (dimethyl fumarate [DMF]; Tecfidera [®])
Study Indication:	Multiple sclerosis (MS)
Study Rationale	Given the putative immunomodulatory properties of DMF and its observed effects on lymphocytes in humans, further evaluation of its effects on immune function is needed. The effect of BG00012 on lymphocyte subtypes is yet unknown, and its evaluation may provide insights into the mechanisms underlying BG00012-associated lymphopenia. This study is therefore being conducted to assess the effects of BG00012 on lymphocyte subset counts and immunoglobulins (Igs) within the first year of treatment and until the end of the study.
Phase of Development:	3b
Study Objectives and Endpoints:	<p>The primary objective of the study is to evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with relapse-remitting MS (RRMS).</p> <p>The primary endpoint that relates to this objective is the change in lymphocyte subset counts for up to 48 weeks.</p> <p>A secondary objective is to evaluate the pharmacodynamic effect of BG00012 on absolute lymphocyte counts (ALCs) and Igs during the first year of treatment.</p> <p>The endpoints that relate to this objective are the changes in IgG isotypes and ALCs for up to 48 weeks.</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Study Design:	This is an open-label, multicenter study to evaluate the

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effects of BG00012 on lymphocyte subtypes and Ig isotypes.

After the Screening Visit (up to 28 days), if required per local guidelines and if not already available within the previous 3 months, a magnetic resonance imaging scan should be performed locally before starting therapy with BG00012. Subjects will then receive BG00012 treatment for 96 weeks twice daily (BID). Blood samples for lymphocyte subset analysis, as well as blood samples for the determination of each subject's complete blood count with differential, will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 24, 36, 48, 60 (complete blood count [CBC] only), 72, 84 (CBC only), and 96. Clinical samples for the analysis of blood chemistries will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 24, 48, and 96. A post-treatment follow-up visit at which safety assessments will be performed will occur 4 weeks after the final dose of BG00012.

Subjects who develop a confirmed lymphocyte count of <500 cells/mm³ at any time during the study will be monitored every 4 weeks. If the lymphocyte count stays <500 cells/mm³ for 24 weeks, the subject will temporarily withhold study treatment. If the lymphocyte count does not recover to \geq the lower limit of normal (LLN) within an additional 24 weeks while study treatment is temporarily withheld, study treatment will be discontinued permanently and the subject will continue protocol-required visits and assessments.

Subjects who temporarily withhold or permanently discontinue study treatment for any other reason than lymphopenia and have a lymphocyte count $<$ LLN will continue protocol-required visits and assessments and will also be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is \geq LLN, or for up to 48 weeks following drug discontinuation, whichever occurs sooner.

Subjects whose lymphocyte counts are $<$ LLN at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this protocol at the Investigator's discretion.

Therapies directed toward the treatment of MS are

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permitted, at the discretion of the treating physician and only after consulting with the Medical Monitor, for subjects who have permanently discontinued BG00012 for any reason.

Subjects who withdraw from the study while on study treatment will complete the Discontinuation and/or Withdrawal Visit as soon as possible but no later than 2 weeks after their last dose of study treatment and will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment unless consent has been withdrawn.

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

Refer to [Table 1](#) and [Table 2](#) for the timing of all study assessments.

Study Location: Approximately 100 sites in North America and Europe

Number of Planned Subjects: Approximately 200 subjects will be treated.

Study Population: This study will be conducted in male and female subjects, aged 18 through 65 years, with a confirmed diagnosis of RRMS according to the revised McDonald criteria (2010) [[Polman 2011](#)].

Detailed criteria are described in [Section 8](#).

Treatment Groups: Approximately 200 subjects will receive oral BG00012 at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or gastrointestinal disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed.

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Duration of Treatment and Follow-up:

The study period will consist of a Screening Visit within 4 weeks of Baseline, a Treatment Period of 96 weeks and a final Follow-Up Visit. Subjects who temporarily withhold or permanently discontinue study treatment for any other reason than lymphopenia and have a lymphocyte count $<LLN$ will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq LLN$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner. Subjects whose lymphocyte counts are $<LLN$ at the end of the study (Week 96) will complete the final Follow-Up Visit and then be followed outside of this protocol at the Investigator's discretion.

Subjects will receive treatment for up to 96 weeks. The total duration of subject participation will be up to 104 weeks.

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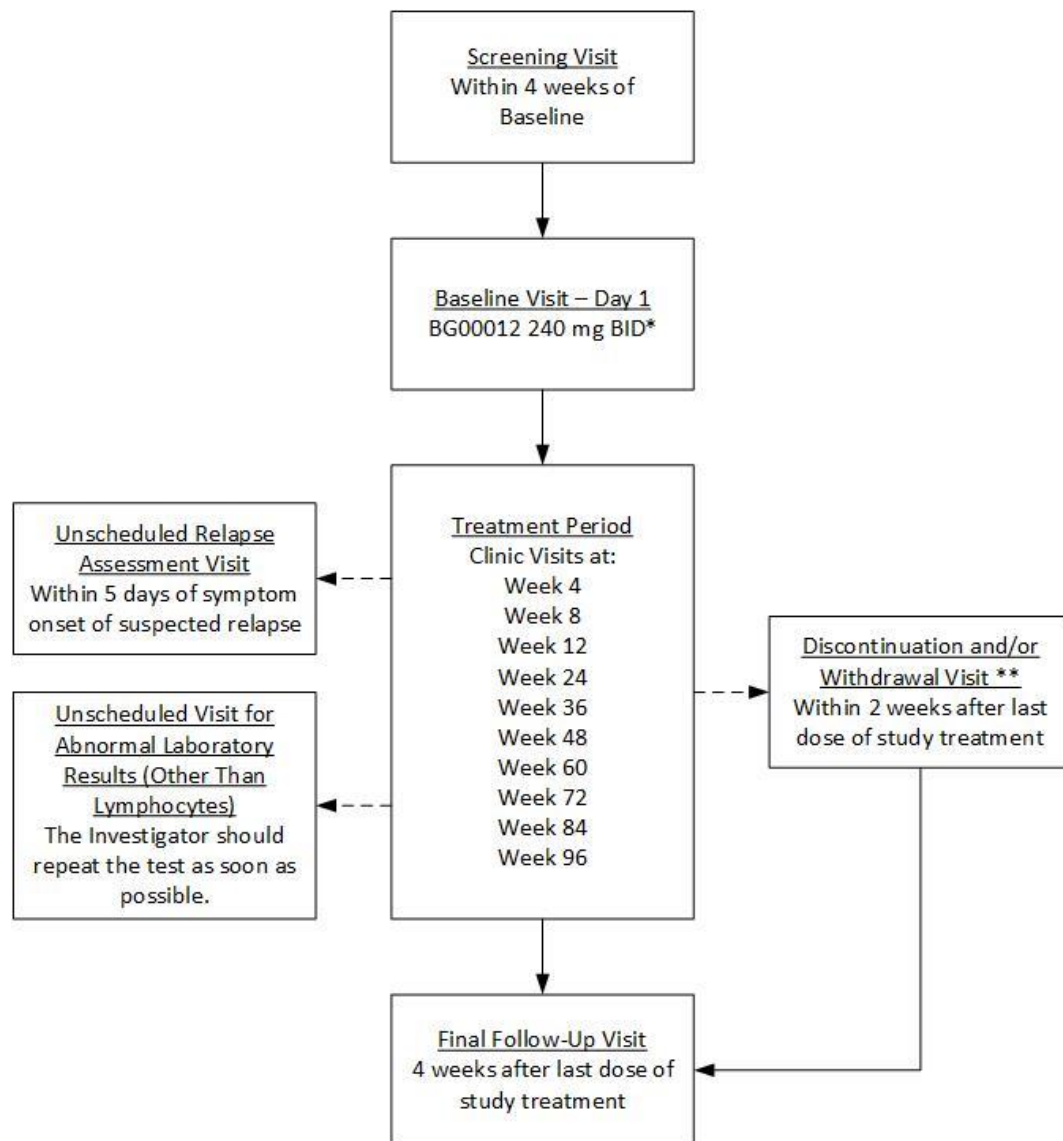
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4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 109MS310

4.1. Study Schematic

The study design for Study 109MS310 is shown in [Figure 1](#), and the study activities are shown in [Table 1](#) and [Table 2](#).

Figure 1: Study Design



BID = twice daily; LLN = lower limit of normal.

*Subjects will receive oral BG00012 at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered (see Section 11.2.4).

**Subjects with a lymphocyte count <LLN will continue protocol-required visits and assessments and will have additional lymphocyte and subset analysis (see Section 11.3).

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4.2. Schedule of Activities

Table 1: Study Activities for Study 109MS310 - Table 1 of 2

Tests and Assessments	Screening	Treatment Period											Final Follow-Up Visit ¹
	Within 28 days before Baseline	Baseline (Day 1)	Week 4 (Day 28 ±3 days)	Week 8 (Day 56 ±3 days)	Week 12 (Day 84 ±3 days)	Week 24 (Day 168 ±5 days)	Week 36 (Day 252 ±5 days)	Week 48 (Day 336 ±5 days)	Week 60 (Day 420 ±5 days)	Week 72 (Day 504 ±5 days)	Week 84 (Day 588 ±5 days)	Week 96 (Day 672 ±5 days)	4 weeks ±5 days after final dose
Informed Consent ²	X												
Medical History ³	X												
Hepatitis B and C Screen	X												
HIV Testing (As Per Local Guidelines) ⁴	X												
MRI Scan ⁵	X												
Physical Examination ⁶	X							X				X	
Vital Signs ⁷	X	X	X	X	X	X	X	X		X		X	X
12-Lead ECG		X						X				X	
Hematology (CBC With Differential) ⁸	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X		X		X				X	X

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Phase 3b Study on the Effect of BG00012 on Lymphocyte Subsets and Immunoglobulins in Subjects With RRMS

Tests and Assessments	Screenin g	Treatment Period											Final Follow-Up Visit ¹
	Within 28 days before Baseline	Baselin e (Day 1)	Week 4 (Day 28 ±3 days)	Week 8 (Day 56 ±3 days)	Week 12 (Day 84 ±3 days)	Week 24 (Day 168 ±5 days)	Week 36 (Day 252 ±5 days)	Week 48 (Day 336 ±5 days)	Week 60 (Day 420 ±5 days)	Week 72 (Day 504 ±5 days)	Week 84 (Day 588 ±5 days)	Week 96 (Day 672 ±5 days)	4 weeks ±5 days after final dose
Lymphocyte Subset Analysis ⁸	X	X	X	X	X	X	X	X		X		X	X
Serum Pregnancy Test ⁹	X												
Urine Pregnancy Test ^{9, 10}		X			X	X	X	X	X	X	X	X	
Dispense BG00012		X			X	X	X	X	X	X	X		
BG00012 Administration		X											
Concomitant Therapy and Procedures		X											
AE Recording		X											
SAE Recording	Monitor and record throughout the study.												

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AE = adverse event; CBC = complete blood count; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [REDACTED]; HIV = human immunodeficiency virus; Ig = immunoglobulin; LLN = lower limit of normal; MRI = magnetic resonance imaging; MS = multiple sclerosis; [REDACTED]; [REDACTED]; SAE = serious adverse event.

- ¹ Subjects will have a final Follow-Up Visit 4 weeks after taking their final dose, regardless of whether they complete the treatment period or discontinue prematurely, unless they have a lymphocyte count <LLN. Subjects who have a lymphocyte count <LLN will continue protocol-required visits and assessments per Section 11.3.
- ² Written informed consent must be obtained prior to performing any study-related procedures.
- ³ Medical history will include gastrointestinal abnormalities within the previous 6 months, as well as duration of MS (time since diagnosis), relapse history, and treatments for MS.
- ⁴ HIV testing will be done locally at Screening only if required, per local guidelines.
- ⁵ If required per local guidelines and if not already available within the previous 3 months, an MRI scan should be performed locally before starting therapy with BG00012.
- ⁶ Physical examination includes height and weight measurements, as well as a neurological examination.
- ⁷ Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.
- ⁸ Whole blood may also be collected for lymphocyte functional tests. Lymphocyte subset analysis will include total Ig and IgG subclasses, and may also include assays for [REDACTED] and VLA-4 expression. In subjects with a confirmed lymphocyte count <500/mm³ lymphocyte testing must be performed every 4 weeks; if the lymphocyte count remains <500/mm³ for 24 weeks, study treatment will be temporarily withheld for 24 weeks or until the lymphocyte count recovers to LLN, whichever is sooner, and testing continues to be every 4 weeks; if the lymphocyte count does not recover to LLN within 24 weeks while study treatment is temporarily withheld, study treatment will be withheld permanently, and testing will be performed every 12 weeks for an additional 24 weeks or until the lymphocyte count recovers to LLN, or until the end of the study, whichever is sooner.
- ⁹ Females of childbearing potential only. Results must be known to be negative prior to dispensing BG00012.
- ¹⁰ Pregnancy test may be repeated locally at additional timepoints if needed, per local guidelines.
- ¹¹ Sample can be collected at any point during the study in subjects who have signed a separate informed consent form.

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Table 2: Study Activities for Study 109MS310 - Table 2 of 2

Tests and Assessments		Discontinuation and/or Withdrawal Visit ²	Lymphocyte Follow-Up Visit ³	Unscheduled Visit for Abnormal Laboratory Results (Other Than Lymphocytes)
	These visits can be combined. If these visits are not combined, any assessment that was performed within the past 2 weeks (or the interval noted in the footnotes) does not need to be repeated unless clinically indicated.			
Physical Examination ⁴	X		X	
Vital Signs ⁵	X	X	X	
Hematology (CBC With Differential)	X	X	X	X ⁶
Blood Chemistry	X	X		X ⁷
Lymphocyte Subset Analysis		X	X	
Concomitant Therapy and Procedures	X			
AE Recording	X			
SAE Recording	Monitor and record throughout the study.			

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CBC = complete blood count; ; LLN = lower limit of normal; ; SAE = serious adverse event; ULN = upper limit of normal; WBC = white blood cell.

² Discontinuation refers to discontinuation of study treatment. Withdrawal refers to withdrawal of subjects from study. The Discontinuation and/or Withdrawal Visit should be conducted as soon as possible and no later than 2 weeks after their last dose of study treatment.

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- ³ Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count $<LLN$ will continue protocol-required visits and assessments and will also be followed up every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq LLN$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner.
- ⁴ Physical examination includes height and weight measurements, as well as a neurological examination.
- ⁵ Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.
- ⁶ The Investigator should repeat the test as soon as possible. If retest value confirms that WBC count is $<2000/mm^3$, study treatment must be withheld. If the value remains $<2000/mm^3$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.
- ⁷ The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT $>3 \times ULN$ or creatinine $>1.2 \times ULN$, the study treatment must be withheld. If the ALT/AST value remains $>3 \times ULN$ or creatinine is $>1.2 \times ULN$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.
- [REDACTED]

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4.3. Additional Information

4.3.1. Site Personnel

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

- a primary and backup Neurologist
- a primary and backup Study Nurse (or Study Coordinator)
- a Pharmacist (or authorized designee)

The primary and backup Neurologists must have a minimum of 2 years of neurology specialty training and anticipate a 2-year commitment to the study. [REDACTED]

[REDACTED] The backup Neurologist or a certified and trained nurse may conduct subject evaluations if the primary Neurologist is unavailable due to illness, vacation, or travel.

The roles and responsibilities of the Neurologist and Study Nurse are described below. Details for all roles are provided in the Study Reference Guide.

The primary Neurologist will be responsible for the following:

- Management of the routine neurological care of the subject.
- Assessment (including assignment of causality) and treatment of adverse events (AEs) [REDACTED].
- Review of hematology and blood chemistry results from the central laboratory to assess whether the subject's study treatment should be temporarily withheld or permanently discontinued, as per the criteria detailed in Section 10.
- Determination of whether new objective neurological findings have occurred (see Section 7.2.4).

- [REDACTED]
- [REDACTED]

The Neurologist may designate other medical personnel (i.e., the backup Neurologist or the Study Nurse) at the investigational site to perform some of the tests and evaluations listed under "Neurologist."

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

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4.3.2. Subject Management

Contraception requirements are described in Section 15.5. Study treatment dosing requirements and concomitant medication restrictions are described in Sections 11.1 and 11.6, respectively.

There are no restrictions regarding diet and alcohol use. Physical exertion atypical for the subject's normal activities of daily living should be avoided for 24 hours prior to assessments.

Subjects should not donate blood until 1 month after their last dose of study treatment in this study.

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5. INTRODUCTION

BG00012 is a fumarate ester drug product formulation containing the active ingredient dimethyl fumarate (DMF). In 2013, BG00012 was first approved in the United States (US) under the propriety name Tecfidera[®] as a treatment for patients with relapsing MS and has since been approved in other countries.

5.1. Overview of Multiple Sclerosis

MS is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide. Its prevalence is highest among Caucasians, with higher rates reported in North America, Europe, Australia, New Zealand, and northern Asia [Noseworthy 2000; Rosati 2001].

Relapsing MS is the most common clinical presentation of the disease. The term relapsing MS applies to patients with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) who experience relapses; both are considered part of the same disease spectrum. In the relapsing/remitting phase of the disease, patients experience episodes of neurological dysfunction (relapses) separated by periods of relative stability. Typical symptoms of relapse include weakness, sensory loss, visual loss, and imbalance. Relapses may completely subside in the early stage of the disease, but recovery tends to be incomplete over time, leading to the accumulation of physical disability and cognitive decline. RRMS is usually diagnosed between the ages of 20 and 40 years and affects twice as many women than men. The RRMS population ranges from patients with relatively benign, inactive, non-inflammatory disease to patients who experience frequent relapse and/or persistent, active, inflammatory disease. Most of these patients develop SPMS, which is characterized by progressive neurological decline with or without superimposed relapse; the median time to progression from RRMS to SPMS is approximately 10 years [Runmarker and Andersen 1993]. Approximately half of all MS patients are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989], and more than half of patients die from MS or its complications [Brønnum-Hansen 2004].

As patients progress along the continuum from RRMS to SPMS, disability progression is more likely to occur independently of relapses. The pathological changes underlying MS are thought to occur when activated T lymphocytes cross the blood-brain barrier (BBB) and initiate a series of events leading to activation of endothelial cells, recruitment of additional lymphocytes and monocytes, and release of pro-inflammatory cytokines. MS lesions consisting of immune cells can occur throughout the CNS, but certain sites appear to be particularly vulnerable, such as the optic nerve, brainstem, spinal cord, and periventricular regions of the cerebrum. The development of MS lesions is associated with inflammation, edema, and demyelination, and is often correlated with reversible disease symptoms, namely relapses, as well as oligodendrocyte death and axonal transection, which can be permanent and lead to disability. Alternatively, oligodendrocyte and axonal loss may be due to a neurodegenerative process. Ongoing

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inflammatory and neurodegenerative stimuli are mediated at least in part by toxic oxidative stress. Preclinical studies indicate that BG00012-dependent pharmacodynamic responses appear to be mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. While it is not yet fully understood how the inflammatory cascade is initiated, adhesion and trans-endothelial migration of inflammatory cells from the bloodstream across the BBB and into the CNS is thought to be an early and critical step in this process.

5.2. Current Therapies for Multiple Sclerosis

The most commonly used first-line MS therapies are interferons (IFNs) and glatiramer acetate (GA) [Waldman 2011]. Relative to placebo, IFNs have been shown to reduce relapse rate by approximately 27% to 36% [Calabresi 2014; Jacobs 1996; PRISMS Study Group 1998; The IFNB Multiple Sclerosis Study Group 1993], and GA by approximately 30% [Johnson 1995]. The interferon beta-1a (IFN β -1a) products have also been shown to delay disability progression [Jacobs 1996; PRISMS Study Group 1998].

Other currently approved therapies for MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α 4 integrins [Polman 2006].
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010].
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into deoxyribonucleic acid (DNA) and interferes with ribonucleic acid (RNA) [Chitnis 2012].
- Teriflunomide: an immunomodulatory drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011].
- Alemtuzumab: a humanized monoclonal antibody targeting cluster of differentiation (CD) 52 antigen expressed on the surface of most leukocytes [Coles 2012].

5.3. Profile of Previous Experience With BG00012

5.3.1. Nonclinical Experience

In nonclinical studies, DMF and its primary metabolite, monomethyl fumarate, were found to promote stabilization and transcriptional activity of Nrf2, as well as expression of Nrf2 target genes in cultured human cells and in vivo [Linker 2011]. Previous ex vivo and in vivo studies have demonstrated a central role of the Nrf2 pathway in the protection of cells and tissues against oxidative, xenobiotic, and inflammatory stress. Loss of Nrf2 function via genetic silencing has been shown to cause exaggerated inflammatory response and lead to development of systemic autoimmunity and CNS alterations, including widespread gliosis and white matter lesions. Conversely, pharmacological agents known to activate Nrf2 have been shown in nonclinical studies to exert anti-inflammatory effects, protect neurons from oxidative and excitotoxic stress-

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induced death, and improve the BBB integrity of the CNS. Activation of the Nrf2 pathway by DMF in MS may contribute to inhibition of inflammation and help support CNS integrity by promoting cellular resistance to oxidative stress.

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

5.3.2. Clinical Experience

In the Phase 2 and 3 placebo-controlled safety and efficacy studies (the completed 6-month Phase 2 Study C-1900 Part 1 and the 2 completed 2-year Phase 3 Studies 109MS301 and 109MS302) and/or their uncontrolled extensions (the completed 6-month Phase 2 Study C-1900 Part 2 and the ongoing Phase 3 long-term Study 109MS303) over 2500 subjects received treatment with BG00012. The overall exposure to BG00012 among these subjects was approximately 6100 subject-years as of September 2013.

DMF demonstrated robust efficacy and a favorable safety profile in subjects with RRMS in the 2 large Phase 3 studies (Study 109MS301 [DEFINE] [Gold 2012a] and Study 109MS302 [CONFIRM] [Fox 2012]). The benefit-risk profile of DMF was considered positive, and the drug has been approved.

Both Phase 3 studies demonstrated that treatment with DMF reduced the risk of MS relapse and slowed progression of disability. In an integrated analysis of DEFINE and CONFIRM, DMF 240 mg twice daily (BID) and 3 times daily significantly reduced the annualized relapse rate at 2 years by 49% relative to placebo ($p < 0.0001$). Significant reductions at 2 years were also observed in the proportion of subjects who relapsed (43% and 47%, respectively; $p < 0.0001$), the proportion of subjects with confirmed (12-week) progression of disability (32% and 30%, respectively; $p < 0.01$), and the proportion of subjects with confirmed (24-week) progression of disability (29% and 32%, respectively; $p < 0.03$) [Gold 2012b].

DMF was generally well tolerated and demonstrated an acceptable safety profile. The most common AEs associated with DMF were flushing and gastrointestinal (GI) events. In subjects who experienced these types of events, the events were generally mild or moderate in intensity, tended to decrease in incidence after the first month, and only infrequently led to treatment discontinuation. There are a number of potential management strategies for these side effects. In the Phase 2 and 3 controlled and uncontrolled clinical studies in subjects with RRMS, BG00012 treatment was associated with a gradual decrease from baseline in mean leukocyte counts driven primarily by decreases in mean lymphocyte counts; mean lymphocyte counts decreased by approximately 30% of their baseline value after 1 year and then plateaued and remained stable through more than 6 years of follow-up. While decreases in lymphocyte counts have been observed with BG00012 treatment, in the placebo controlled Phase 2 and 3 studies BG00012 was not associated with an increased risk of infection, serious infection, or opportunistic infection compared with placebo. However, in the long-term extension study (109MS303), progressive multifocal leukoencephalopathy (PML) has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. PML has also been reported in the postmarketing setting in the presence of prolonged moderate to severe lymphopenia. The majority of all cases occurred in patients with lymphocyte counts $< 0.5 \times 10^9/L$. With open-label

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and marketed use of BG00012, there has been no other evidence of an increased risk of infections, serious infections, or opportunistic infections.

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

5.4. Study Rationale

Given the putative immunomodulatory properties of DMF and its observed effects on lymphocytes in humans, further evaluation of its effects on lymphocytes is needed. The effect of BG00012 on lymphocyte subtypes is yet unknown, and its evaluation may provide insights into the mechanisms underlying BG00012-associated lymphopenia. This study is therefore being conducted to assess the effects of BG00012 on lymphocyte subset counts and immunoglobulins (Igs) within the first year of treatment and beyond.

5.5. Rationale for Dosing Regimen

The BG00012 dosage selected for this study (120 mg BID for the first 7 days and 240 mg BID thereafter) is the approved BG00012 dosing regimen in the US, Canada, European Union, and other countries around the world for the treatment of patients with MS.

Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or GI disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed.

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6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

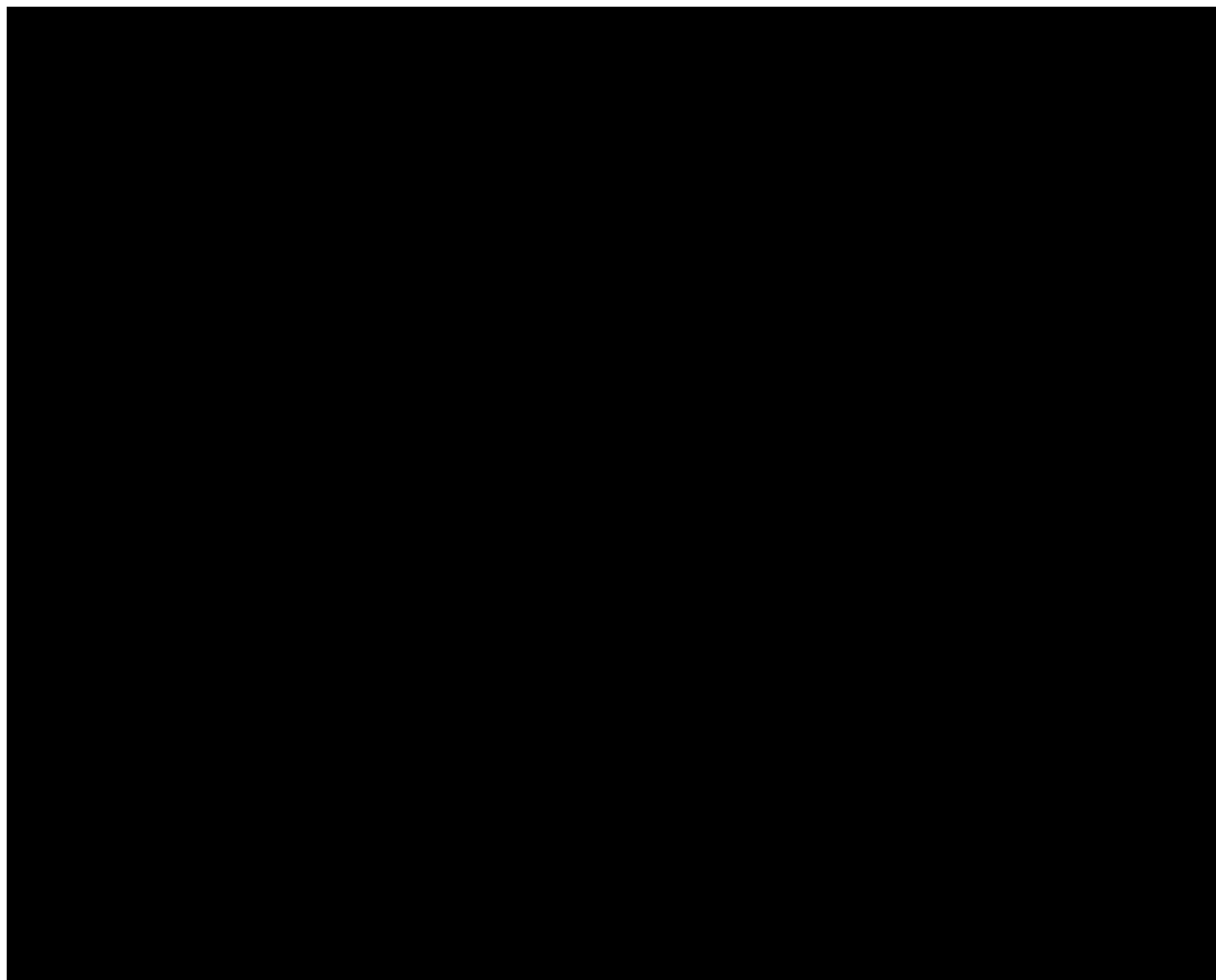
The primary objective of the study is to evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with RRMS.

The primary endpoint that relates to this objective is the change in lymphocyte subset counts for up to 48 weeks.

6.2. Secondary Objective and Endpoints

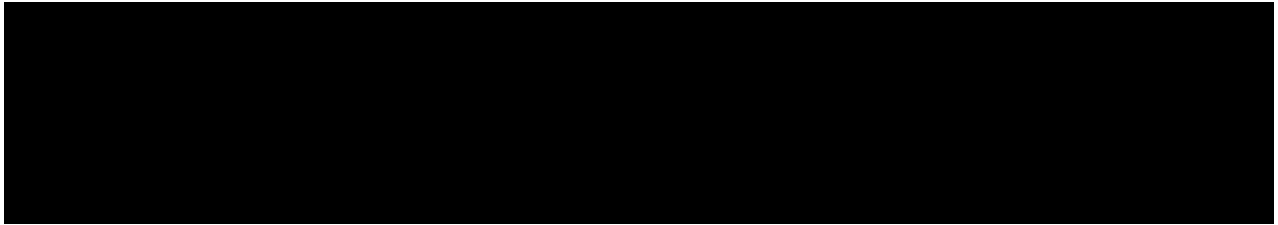
A secondary objective is to evaluate the pharmacodynamic effect of BG00012 on absolute lymphocyte counts (ALCs) and Igs during the first year of treatment.

The endpoints that relate to this objective are the changes in IgG isotypes and ALCs for up to 48 weeks.



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7. STUDY DESIGN

7.1. Study Overview

This is an open-label, multicenter study to evaluate the effects of BG00012 on lymphocyte subtypes and Ig isotypes. Approximately 200 subjects will be treated in approximately 100 sites in North America and Europe.

After the Screening Visit (up to 28 days) if required per local guidelines and if not already available within the previous 3 months, a magnetic resonance imaging scan should be performed locally before starting therapy with BG00012. Subjects will then receive BG00012 treatment for 96 weeks (Treatment Period). Blood samples for lymphocyte subset analysis, as well as blood samples for the determination of each subject's complete blood count with differential, will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 24, 36, 48, 60 (complete blood count [CBC only]), 72, 84 (CBC only), and 96. Clinical samples for the analysis of blood chemistries will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 24, 48, and 96. A post-treatment follow-up visit, at which safety assessments will be performed, will occur 4 weeks after the final dose of BG00012.

Subjects who temporarily withhold or permanently discontinue study treatment for any other reason than lymphopenia and have a lymphocyte count $<LLN$ will continue protocol-required visits and assessments and will also be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq LLN$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner.

Subjects who develop a confirmed lymphocyte count of <500 cells/mm³ at any time during the study will be monitored every 4 weeks. If the lymphocyte count stays <500 cells/mm³ for 24 weeks, the subject will temporarily withhold study treatment. If the lymphocyte count does not recover to LLN within 24 weeks while study treatment is temporarily withheld, study treatment will be discontinued permanently (see Section 11.3).

Subjects whose lymphocyte counts remain $<LLN$ at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this study at the Investigator's discretion.

Therapies directed toward the treatment of MS are permitted, at the discretion of the treating physician and only after consulting with the Medical Monitor, for subjects who have permanently discontinued BG00012 for any reason.

Subjects who withdraw from the study while on study treatment will complete the Discontinuation and/or Withdrawal Visit as soon as possible but no later than 2 weeks after their last dose of study treatment and will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment unless consent has been withdrawn.

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

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See [Figure 1](#) for a schematic of the study design. Refer to [Table 1](#) and [Table 2](#) for the timing of all study assessments.

7.2. Overall Study Duration and Follow-Up

The study period will consist of a Screening Visit within 4 weeks of Baseline, a Treatment Period of 96 weeks and a final Follow-Up Visit. Subjects will receive treatment for 96 weeks. The total duration of subject participation will be up to 104 weeks.

7.2.1. Screening

Subject eligibility for the study will be determined within 28 days prior to study entry. If required per local guidelines and if not already available within the previous 3 months, an MRI scan should be performed locally before starting therapy with BG00012.

7.2.2. Treatment Period

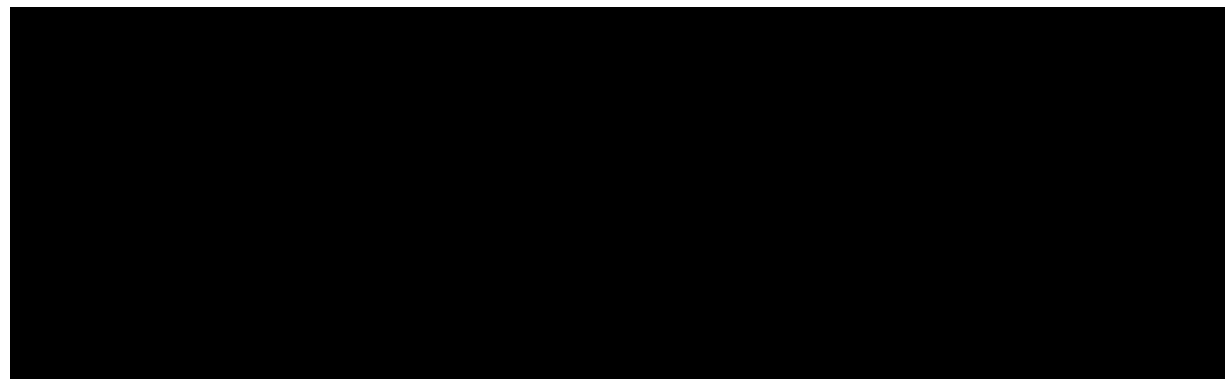
Eligible subjects will report to the study site every 4 weeks for the first 12 weeks and every 12 weeks thereafter for 96 weeks.

Discontinuation and/or Withdrawal Visits [REDACTED] Visits will be performed as necessary. Subjects who withdraw from the study early will be asked to return to complete a Discontinuation and/or Withdrawal Visit within 2 weeks of their last study treatment dose.

7.2.3. Follow-Up

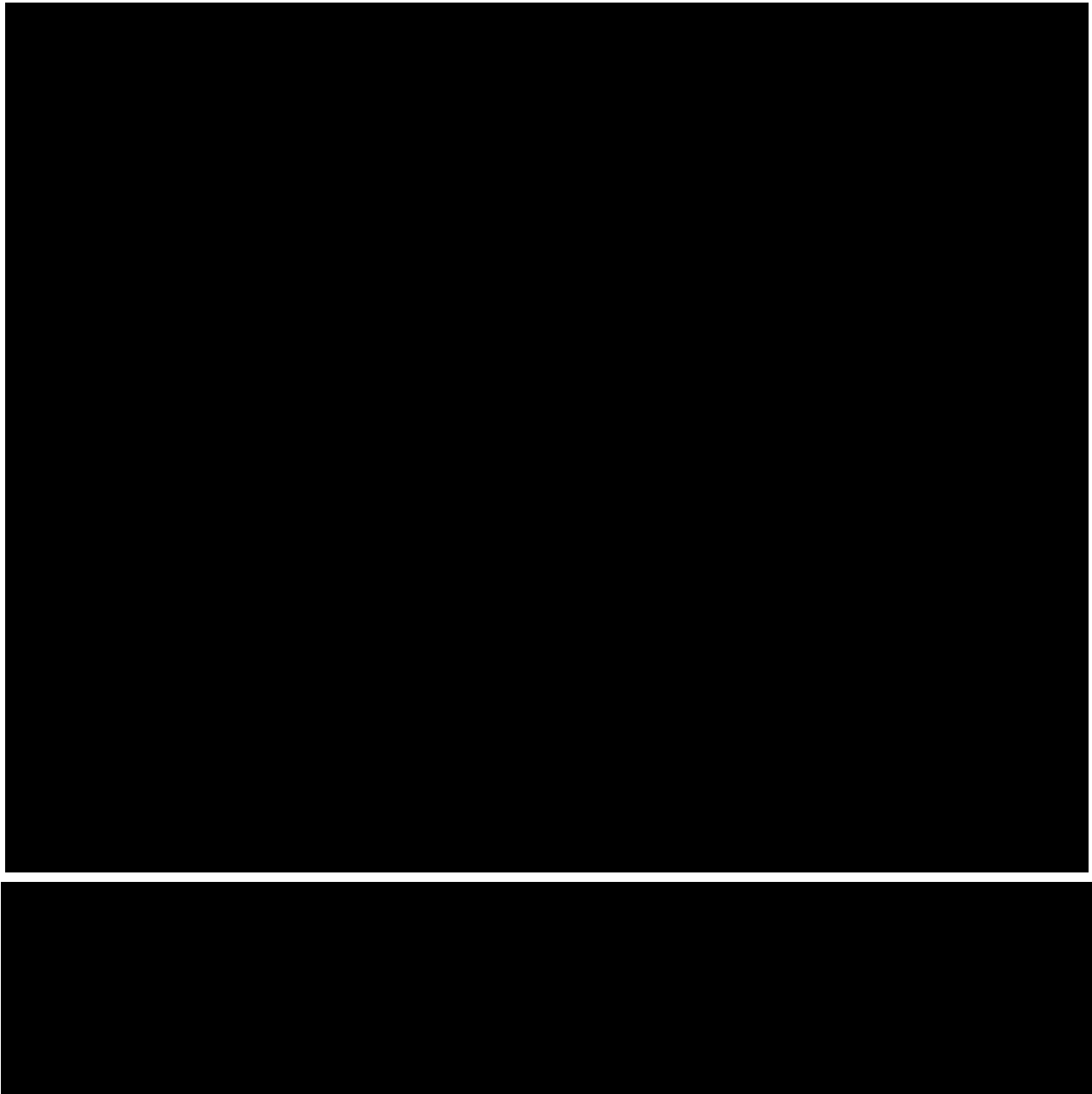
Subjects are to return to the study site for a Follow-Up Visit 4 weeks after their last dose of study treatment. The final study visit will be Week 100.

Subjects who temporarily withhold or permanently discontinue BG00012 for any reason and have a lymphocyte count $<LLN$ will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq LLN$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner; see Section 11.3). Subjects whose lymphocyte count remains $<LLN$ at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this protocol at the Investigator's discretion.



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7.2.6. Additional Assessments if Required by Local Tecfidera Prescribing Information

Any additional assessments that are needed to comply with the local prescribing information for Tecfidera should also be performed and will be reimbursed by Biogen while a subject is participating in this study.

7.3. Study Stopping Rules

There are no study-specific stopping rules. Biogen may terminate this study at any time after informing Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

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7.4. End of Study

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

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8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Age 18 to 65 years old, inclusive, at the time of informed consent.
3. Subjects of childbearing potential (including female subjects who are post-menopausal for less than 1 year) must practice effective contraception (as determined by the Investigator) during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have a confirmed diagnosis of RRMS according to the revised McDonald criteria (2010) [Polman 2011].

8.2. Exclusion Criteria

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

Medical History

1. History of or positive test result at Screening (if testing is required as per local guidelines) for human immunodeficiency virus.
2. History of or positive test result at Screening for hepatitis C virus antibody or current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
3. History of drug or alcohol abuse (as defined by the Investigator) within 1 year prior to Screening.
4. Any clinically significant (in the judgment of the Investigator) infectious illness (e.g., cellulitis, abscess, pneumonia, and septicemia) within 30 days prior to Screening.
5. History of clinically significant (in the judgment of the Investigator) cardiovascular, dermatologic, endocrinologic, GI, hematologic, hepatic, immunologic, metabolic, neurologic (other than MS), psychiatric, pulmonary, renal, urologic, and/or other major disease that would preclude participation in a clinical study.

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6. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.
7. Any of the following abnormal blood tests at Screening that are confirmed on repeat testing within 2 weeks:
 - leukocytes $<3500/\text{mm}^3$
 - ALC values $\leq \text{LLN}$
 - alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) or aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) ≥ 2 times the upper limit of normal (ULN)

Treatment History

8. Prior treatment with any of the following:
 - cladribine
 - mitoxantrone
 - total lymphoid irradiation
 - alemtuzumab
 - T-cell or T-cell receptor vaccination
 - any therapeutic monoclonal antibody, with the exception of natalizumab or daclizumab
9. Treatment with any of the following medications or procedures within 6 months prior to Baseline (Day 1):
 - DMF (given as Fumaderm[®]) or BG00012; enrollment will be limited to no more than 40 subjects (out of 200) with prior DMF exposure
 - cyclosporine
 - azathioprine
 - methotrexate
 - mycophenolate mofetil
 - intravenous (IV) Ig
 - plasmapheresis or cytapheresis
10. Treatment with another investigational drug or approved therapy for investigational use within 6 months prior to Baseline (Day 1).
11. Treatment with steroids (IV or oral corticosteroid treatment, including agents that may act through the corticosteroid pathway [e.g., low-dose naltrexone]) within 4 weeks (28 days) prior to Baseline (Day 1).

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Note: Subjects who are currently using other approved disease modifying therapies (DMTs) for RRMS that are not excluded above may be included in the trial if all other criteria are met. Subjects must discontinue these other DMT treatments upon entry into the trial. A washout period is not required by the protocol, but investigators should follow their local standards of care, taking into account the pharmacokinetic profile (ie, half-life) of the existing therapy, to manage the transition from the existing treatment to BG00012.

Miscellaneous

12. Female subjects who are currently pregnant or breastfeeding, or planning to become pregnant while in the study.
13. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 6 months prior to the Baseline Visit.
14. Previous enrollment in this study.
15. Inability to comply with study requirements.
16. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

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9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Subjects who have a nonclinically significant out-of-range laboratory result may be retested once to deem the eligibility per discretion of the Investigator.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Registration of Subjects

Subjects will be registered at Baseline (Day 1), after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

Not applicable. This is an open-label study.

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

10.1. Discontinuation of Study Treatment

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

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject is unable to tolerate study treatment at 240 mg BID (see Section 11.2.4).
- The subject receives any concomitant medications not allowed by the protocol.
- The subject experiences any of the laboratory abnormalities requiring permanent discontinuation of treatment defined in Table 3.
- The subject experiences more than 1 deviation of the same laboratory parameter that meets the threshold limits defined in Table 3 at any time during the study.
- The subject experiences more than 2 different deviations of laboratory parameters that meet the threshold limits defined in Table 3 at any time during the study. On a third occasion, the subject is required to discontinue dosing for the remainder of the study.
- If a subject has a lymphocyte count $<500/\text{mm}^3$ persisting for more than 24 weeks consecutively, study treatment must be temporarily withheld. Study treatment may be resumed after lymphocyte counts recover $>\text{LLN}$ on 2 consecutive occasions at least 4 weeks apart. If the subject develops a lymphocyte count $<500/\text{mm}^3$ on 1 occasion (confirmed by repeat testing) on resumption of study treatment, the subject must permanently discontinue study treatment and will continue protocol-required visits and assessments (see Section 11.3).
- If a subject's lymphocyte count remains $<\text{LLN}$ for 24 weeks consecutively after study treatment has been temporarily withheld due to lymphocyte count $<500/\text{mm}^3$ for more than 24 weeks, the subject must permanently discontinue study treatment.
- At the discretion of the Investigator for medical reasons or for noncompliance.

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

Subjects who discontinue treatment may remain in the study and continue protocol-required tests and assessments.

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10.2. Withdrawal of Subjects From Study

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

- The subject is unable to tolerate study treatment at 240 mg BID (see Section [11.2.4](#)).
- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

For details regarding follow-up for subjects who discontinue study treatment or withdraw from the study, see Section [7.2.3](#).

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

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

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11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

BG00012 will be taken orally at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or GI disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed. Subjects will receive treatment for 96 weeks.

Missed doses should be taken within 6 hours. If the subject does not remember to take the dose within 6 hours, this dose should be skipped, and the next dose should be taken as scheduled. Doses should not be doubled to make up for missed doses.

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dosing Interruption for Abnormal Laboratory Values

Study treatment must be temporarily withheld when any of the following laboratory values meet the threshold limits defined in [Table 3](#); laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified.

Table 3: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	$>3 \times \text{ULN}$	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT $>3 \times \text{ULN}$, the study treatment must be withheld. If the value remains $>3 \times \text{ULN}$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must <i>permanently</i> discontinue study treatment, and the event must be recorded as an AE.
Creatinine	$>1.2 \times \text{ULN}$	The Investigator should repeat the test as soon as possible. If the retest value confirms that creatinine is $>1.2 \times \text{ULN}$, the study treatment must be withheld. If the value remains $>1.2 \times \text{ULN}$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must <i>permanently</i> discontinue study treatment, and the event must be recorded as an AE.

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Laboratory Parameter	Laboratory Result	Required Action
WBC	<2000/mm ³	The Investigator should repeat the test as soon as possible. If retest value confirms that WBC count is <2000/mm ³ , the study treatment must be withheld. If the value remains <2000/mm ³ for ≥4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in Section 4.2 (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether dosing is temporarily withheld or permanently discontinued) must have the abnormal laboratory result retested at least every 2 weeks (retests will be run at the central laboratory) until resolution or stabilization of the laboratory value. Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

11.2.2. Resumption of Study Treatment Dosing

Resumption of study treatment is to be considered on a case-by-case basis and must be discussed with the Medical Monitor. However, subjects who have abnormal laboratory values, as described in Table 3, sustained on 3 consecutive occasions (i.e., for more than 4 consecutive weeks) must permanently discontinue study treatment (Section 10.1). Subjects who have temporarily withheld BG00012 due to lymphopenia may resume BG00012 according to Section 11.3.

Subjects with abnormal laboratory values after Week 12 (after which clinic visits occur once every 3 months), who are allowed to resume study treatment dosing following a 2- to 4-week interruption, will restart dosing at a reduced dose for 1 week. Subjects must also return to the initial every-4-week visit schedule for safety assessments (see Table 1) for 2 consecutive normal laboratory assessments before reverting to the every-3-month schedule. Subjects will take 120 mg BID for 1 week. After 1 week at the reduced dose, subjects will take 240 mg BID.

11.2.3. Subsequent Development of Additional Laboratory Abnormalities

Subjects who develop a subsequent abnormal value for the same laboratory parameter at any other time during the study must permanently discontinue dosing with study treatment, i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality. However, subjects who subsequently experience an abnormality of a different laboratory parameter can have study treatment withheld again. For example, if a subject had dosing temporarily withheld for an abnormal ALT/SGPT, then had dosing resumed after ALT/SGPT returned to acceptable limits, and subsequently developed abnormal white blood cells (WBCs), the subject may have

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study treatment withheld again. However, only 2 dosing interruptions are allowed for each subject.

Any subject who experiences abnormal laboratory results that meet the criteria defined in [Table 3](#) on a third occasion must permanently discontinue dosing.

11.2.4. Dosage Reductions

Dosage reduction will be allowed only for subjects who are unable to tolerate study treatment due to flushing and/or GI disturbances (dosage reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, refer to Sections [11.2.1](#), [11.2.2](#), and [11.2.3](#)). Subjects who do not tolerate study treatment will reduce their dosage by taking 120 mg BID for up to 4 weeks. Within 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg BID. If the subject is still unable to tolerate study treatment, the subject must discontinue study treatment as described in Section [10.1](#). Subjects who do not tolerate study treatment will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment and will then be withdrawn from the study (Section [10](#)).

11.3. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.3.1. Schedule for Subjects With Lymphocyte Count $<500/\text{mm}^3$

Study treatment must be temporarily withheld when the laboratory value for lymphocyte count meets the threshold limits defined in [Table 4](#).

Table 4: Lymphocyte Count Criteria Requiring Withholding of Study Treatment

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte Count	$<500/\text{mm}^3$	<p>The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is $<500/\text{mm}^3$, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is persistently $<500/\text{mm}^3$ for more than 24 weeks, study treatment must be temporarily withheld. If lymphocyte count is intermittently $<500/\text{mm}^3$ for more than 24 weeks, the Investigator should contact the Medical Monitor.</p> <p>All assessments should be performed at the central laboratory.</p>

While dosing is withheld, subjects will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq \text{LLN}$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner (see Lymphocyte Follow-Up in [Table 2](#)). If the lymphocyte count remains $< \text{LLN}$ for ≥ 24 weeks consecutively after the study treatment is withheld, the subject should be permanently discontinued from study treatment, and the Investigator should contact the Medical Monitor.

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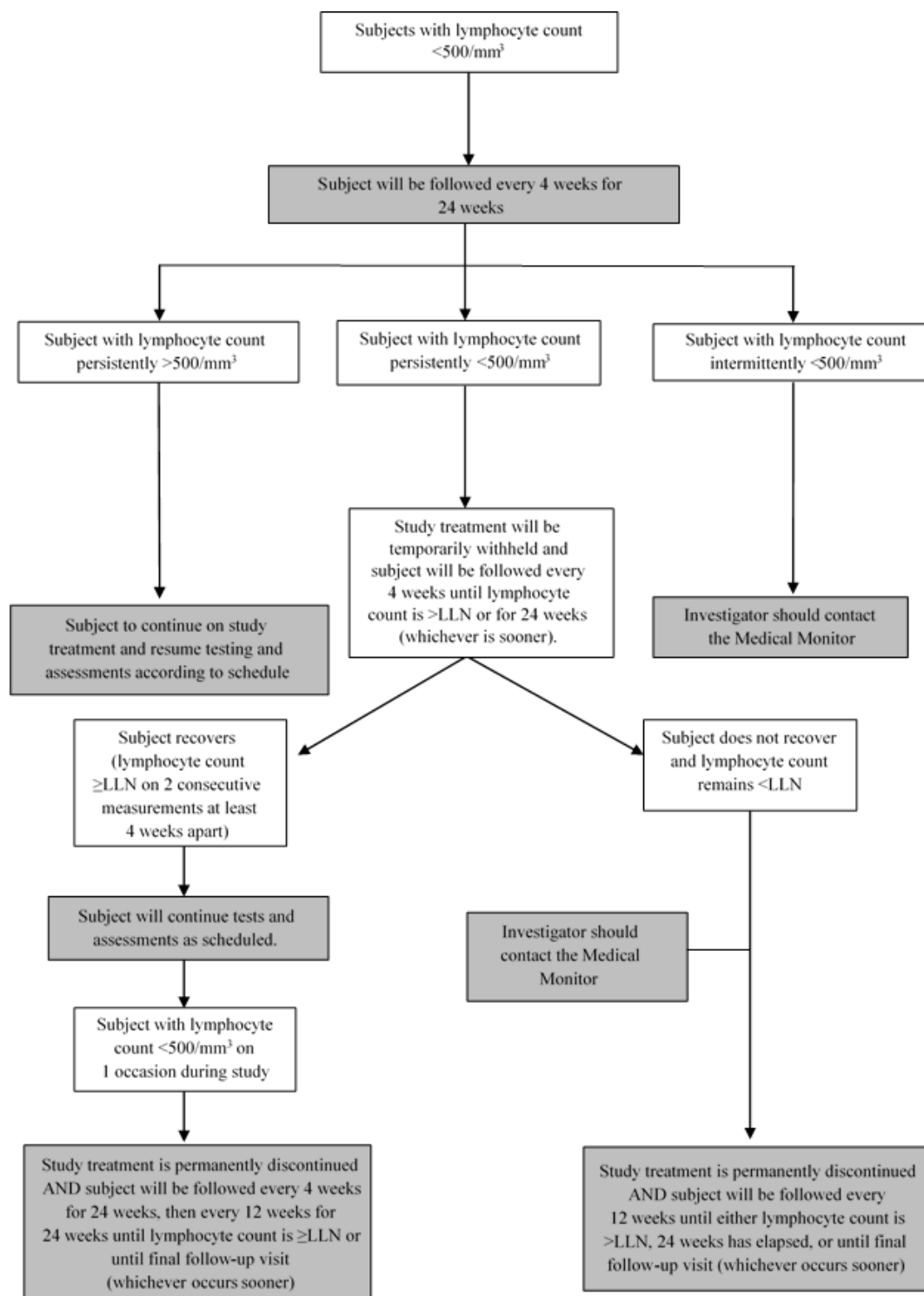
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Subjects who temporarily withhold study treatment due to decreases in lymphocyte count, as described in [Table 4](#), may resume study treatment when lymphocyte counts recover (defined as a lymphocyte count \geq LLN on 2 consecutive occasions at least 4 weeks apart). If the lymphocyte count is $<500/\text{mm}^3$ on 1 occasion (confirmed by repeat testing) on resumption of study treatment, then study treatment must be permanently discontinued. Subjects who discontinue study treatment due to lymphocyte count $<500/\text{mm}^3$ should continue tests and assessments according to the schedule defined in [Section 4](#) until the lymphocyte count recovers or until the final Follow-Up Visit (whichever is sooner). Subjects whose lymphocyte counts remain $<$ LLN at the end of the study (Week 96) will complete the final Follow-Up Visit and then be followed outside of this study at the Investigator's discretion.

See [Figure 2](#) for the treatment schedule of subjects with lymphocyte counts $<500/\text{mm}^3$.

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Figure 2: Schedule for Subjects With Lymphocyte Count $<500/\text{mm}^3$ 

LLN = lower limit of normal.

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11.3.2. Schedule for Subjects With Lymphocyte Counts $<LLN$ to $\geq 500/mm^3$

Subjects with lymphocyte count $<LLN$ to $\geq 500/mm^3$ will have tests and assessments according to the schedule defined in Section 4. If these subjects complete, temporarily withhold, or permanently discontinue study treatment for any reason, they will be followed as described in Section 11.3.3.

11.3.3. Schedule for Subjects Who Temporarily Withhold or Permanently Discontinue Study Treatment for Any Other Reason Than Lymphopenia and Have a Lymphocyte Count $<LLN$

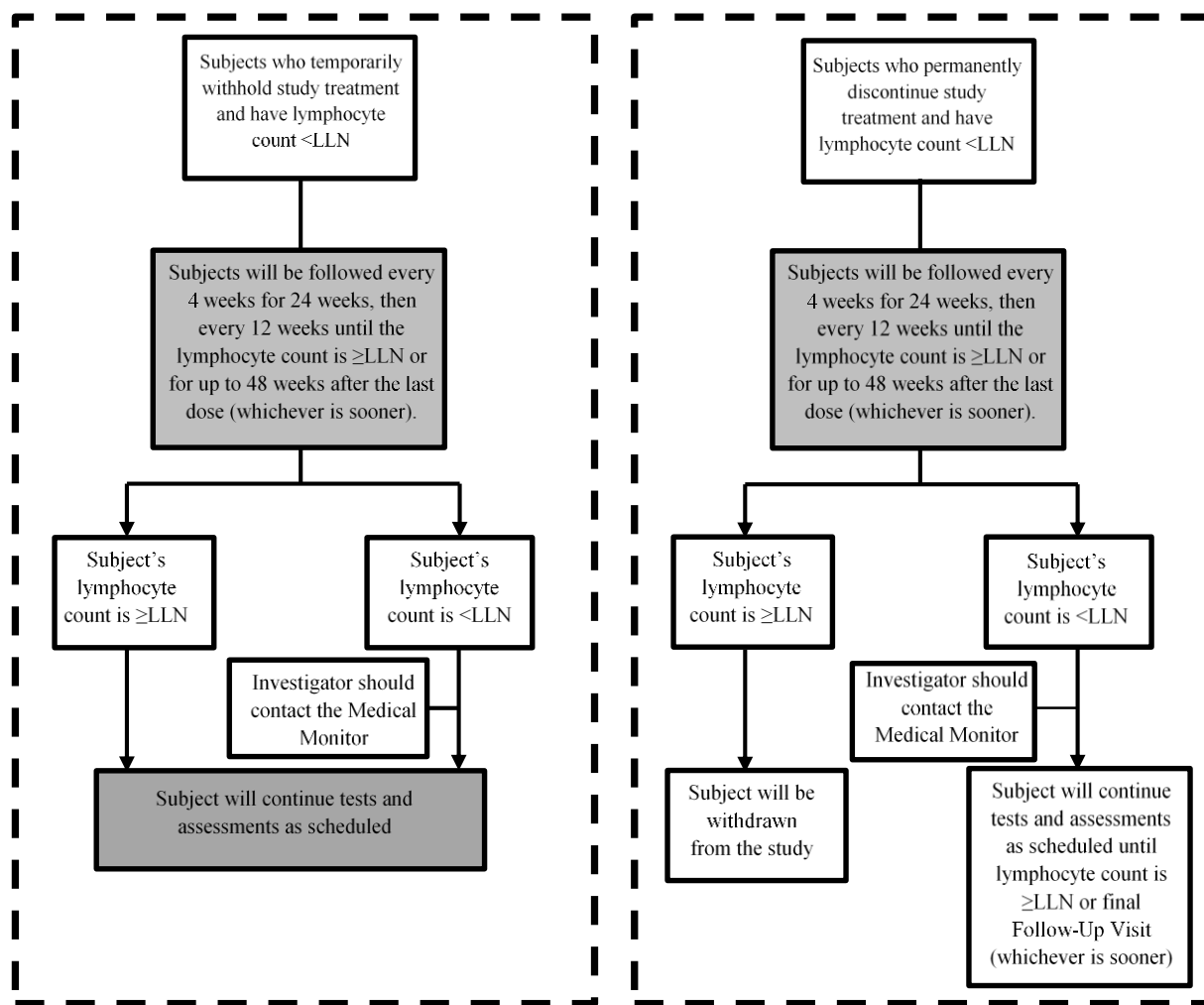
Subjects who temporarily withhold or permanently discontinue BG00012 for any other reason than lymphopenia (see Section 11.2) and who have a lymphocyte count $<LLN$ will be followed every 4 weeks for 24 weeks, then every 12 weeks (**unless clinically indicated more often or at the Investigator's discretion**) until the lymphocyte count is $\geq LLN$ or for up to 48 weeks following drug discontinuation, whichever occurs sooner. Subjects who temporarily withhold or permanently discontinue study treatment and have a lymphocyte count $<LLN$ for 48 weeks should continue tests and assessments according to the schedule defined in Section 4 until the lymphocyte count recovers or until the final Follow-Up Visit (whichever is sooner). Subjects whose lymphocyte counts remain $<LLN$ at the end of the study (Week 96) will complete the final Follow-Up Visit and will then be followed up outside of this study at the Investigator's discretion.

See Figure 3 for a schedule of subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any other reason and who have a lymphocyte count $<LLN$.

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Figure 3: Schedule for Subjects Who Temporarily Withhold or Permanently Discontinue Study Treatment for Any Other Reason Than Lymphopenia* and Have Lymphocyte Count <LLN



LLN = lower limit of normal.

*For subjects with low lymphocytes, refer to Section 11.3.1 and 11.3.2.

11.4. Precautions

Not applicable.

11.5. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance will be monitored by capsule count conducted by study personnel at protocol-scheduled visits.

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11.6. Concomitant Therapy and Procedures

11.6.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the subject's Screening Visit and the subject's last study visit.

11.6.1.1. Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be optimized as early as possible during Screening in an attempt to maintain consistent treatment for the duration of the study.

Subjects should be instructed not to start taking any new medications, including nonprescribed drugs, unless they have received permission from the Investigator.

11.6.1.2. Disallowed Concomitant Therapy

Concomitant treatment with any of the following is **not** allowed unless approved by the Medical Monitor:

- Any alternative drug treatments directed toward the treatment of MS, such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to, IFN- β , GA, natalizumab, cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products, etc.), with the exception of acute management of protocol-defined relapses (Section 11.6.3).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any systemic steroid therapy, including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP, except for protocol-defined treatment of relapses (Section 11.6.3). Steroids that are administered by nonsystemic routes (e.g., topical or inhaled) are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV Ig, plasmapheresis, or cytopheresis.

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

Subjects should be instructed not to start taking any new medications, including non-prescribed drugs, unless they have received permission from the Investigator.

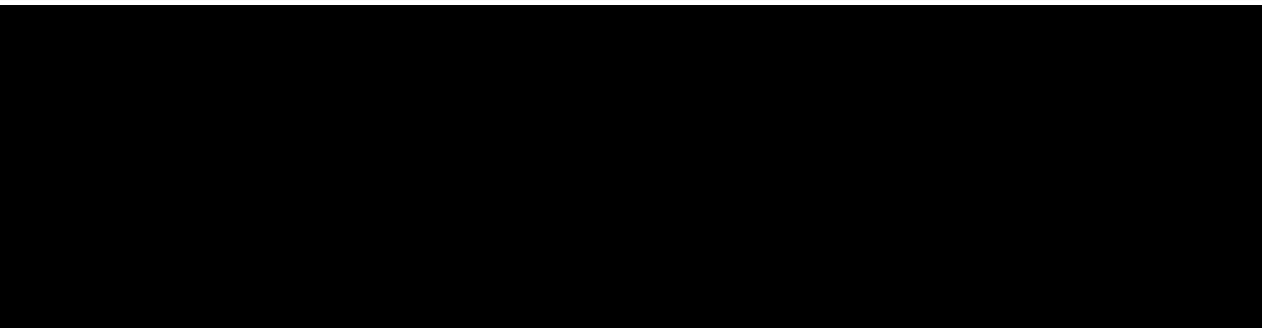
11.6.2. Concomitant Procedures

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

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



11.7. Continuation of Treatment

No further provisions are made for access to the study treatment.

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12. STUDY TREATMENT MANAGEMENT

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

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

12.1. BG00012

BG00012 is a drug product formulated as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. Each capsule contains 120 mg BG00012.

Excipients for the manufacturing of the enteric-coated microtablets include microcrystalline cellulose, croscarmellose sodium, talc, colloidal anhydrous silica (colloidal silicon dioxide), magnesium stearate, triethyl citrate, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, simethicone, sodium lauryl sulfate, and polysorbate 80. Excipients for the manufacturing of the capsule shell include gelatin, titanium dioxide, and indigotin.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. Do not use study treatment after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

12.1.1. BG00012 Preparation

The individual preparing BG00012 should carefully review the instructions provided in the DHA.

Drug wallets will be provided for the BG00012 treatment group to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from an Interactive Voice and Web Response System (IXRS) during the study so that the appropriate wallets are correctly dispensed to the subjects at the required timepoints throughout the study.

If the packaging is damaged or if there is anything unusual about the appearance or attributes of the drug wallet or drug, it should not be used. The drug wallet in question should be quarantined at the study site, and the problem should be immediately reported to Biogen.

12.1.2. BG00012 Storage

Study treatment must be stored in a secure location.

BG00012 is to be stored at room temperature (15°C to 25°C or 59°F to 77°F), in a secured, locked cabinet with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

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12.1.3. BG00012 Handling and Disposal

The Investigator must return all used and unused drug wallets of BG00012 as instructed by Biogen unless approved for onsite destruction.

If any BG00012 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen/contract research organization (CRO) by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen/CRO must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 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), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all drug wallets, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BG00012 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

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13. EFFICACY AND PHARMACODYNAMIC ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Efficacy Assessments

Not applicable; the study is not designed to assess efficacy.

13.2. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of BG00012:

- T cells, B cells, and natural killer (NK) cells
 - total T cells: CD4+ and CD8+
 - total B cells
 - total NK cells
- T regulatory (T_{reg}) cells, resting/naïve T_{reg}, and activated T_{reg}
- naïve T cells, effector T cells, central/effector memory T cells, and activated (expressing human leukocyte antigen [HLA] DR/CD38) T cells
- dendritic cells, monocytes, and NK cells (CD56^{dim}/CD56^{bright})
- transitional B cells, naïve B cells, memory B cells (IgD+/IgD-), and plasmablast cells

13.3. Clinical Assessments

The following clinical assessments will be performed:

- [REDACTED]
- [REDACTED]

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14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BG00012:

- AEs, SAEs, and concomitant therapy and procedures recording
- physical examinations, including body weight and height
- vital sign measurements, including diastolic and systolic blood pressure, heart rate, body temperature, and respiratory rate. Subjects must remain in a supine or seated position for 5 minutes prior to having heart rate and blood pressure taken.
- 12-lead electrocardiogram (ECG) readings

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BG00012:

- hematology parameters: hemoglobin, hematocrit, red blood cell count, WBC count (with differential), and platelet count
- blood chemistry parameters: albumin, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SPGT, AST/SGOT, blood urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose

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15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value 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 an 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

15.1.2. Serious Adverse Event

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

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

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

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

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.
- The severity of the event as defined in Section 15.2.3.

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15.2.2. Relationship of Events to Study Treatment

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

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

15.2.3. Severity of Events

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

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

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the final Follow-Up Visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

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15.3.2. Serious Adverse Events

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

Subjects will be followed for all SAEs until the final Follow-Up Visit. Thereafter, the event should be reported to Biogen or designee only if the Investigator considers the SAE to be related to study treatment.

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

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen 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 SAE that occurs between the time that the subject has signed the ICF and the final Follow-Up Visit must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

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

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

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

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send

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death certificates and autopsy reports to Biogen or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

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

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

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy by faxing the appropriate form to Biogen or designee within 24 hours of the study site staff becoming aware of the pregnancy at the fax number provided in the Study Reference Guide. The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee.

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

15.4.2. Overdose

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

15.4.3. Medical Emergency

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

15.4.3.1. Unblinding for Medical Emergency

Not applicable.

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15.5. Contraception Requirements

Subjects of childbearing potential must practice effective contraception (as determined by the Investigator) during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment. In addition, male subjects should not donate sperm for the duration of the study and for at least 30 days after their last dose of study treatment.

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

- Postmenopausal
 - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL
 - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 or more of the following:

For females:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.
- Male surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). (For female subjects participating in the study, male sexual partners must have undergone surgical sterilization.)

For males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms with spermicide.

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

Pregnancy reporting is described in Section [15.4.1](#).

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15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

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

15.6.2. Biogen

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

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16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

16.1. Pharmacokinetics

Not applicable.

16.2. Pharmacodynamics

16.2.1. Analysis Population

The pharmacodynamic population is defined as all subjects who receive at least 1 dose of study treatment and have at least 1 pharmacodynamic measurement after Baseline.

16.2.2. Methods of Analysis

Statistical analyses will be [REDACTED] and descriptive in nature, with appropriate measures of precision provided where applicable. There is no planned statistical hypothesis testing in this study.

16.2.2.1. Analysis of the Primary Endpoint

Counts and change from Baseline in counts for each of the lymphocyte subsets will be descriptively summarized at each applicable visit. Furthermore, the primary endpoints will be summarized in various ALC subgroups to evaluate the nature of change in each subset in relation to the change in ALC. Additionally, a mixed model for repeated measures (MMRM) will be used, which will be fit with the change from Baseline for each of the lymphocyte subsets as the dependent variable and will include ALC subgroups, visit, corresponding Baseline counts, age, gender, and ALC groups-by-visit interaction as fixed effects to estimate the difference between ALC subgroups. Point estimates and 2-sided 90% confidence intervals (CIs) will be derived from the model. Appropriate transformation may be performed based on the distribution of data.

ALC subgroups of interest include (1) subjects who have all ALC values \geq LLN up to Week 48, (2) subjects who have at least 1 ALC value $<$ LLN over 48 weeks, and (3) subjects who have at least 2 ALC values $<$ LLN over 48 weeks. Additional subgroups will be further defined in the Statistical Analysis Plan.

16.2.2.2. Analysis of the Secondary Endpoints

For the secondary endpoints (IgG isotypes and ALCs), actual values and change from Baseline will be descriptively summarized at each applicable visit. In addition, the same type of MMRM used for analysis of primary endpoints will be employed, which will be fit with the change from Baseline in each of the IgG isotypes and ALCs as the dependent variable and will include visit, corresponding baseline value, age, and gender as fixed effects.

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16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment.

16.4.2. Methods of Analysis

All AEs, concomitant therapy and procedures, clinical laboratory results, physical examinations, vital signs, and 12-lead ECG readings data will be evaluated for safety.

16.4.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. Only treatment-emergent AEs will be presented in the summary tables. Treatment emergent is defined as having an onset date on or after start of study treatment or having worsened after the start of study treatment.

Subject incidences of all AEs, SAEs, AEs leading to treatment discontinuation and study withdrawal, and other AEs of special interest will be tabulated by system organ class and preferred term in descending order of frequency.

16.4.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology and blood chemistry. Laboratory data will be summarized using shift tables. Each laboratory value for each subject will be flagged as “low,” “normal,” or “high,” relative to the parameter’s normal range. For each parameter, the number (percentage) of subjects experiencing post-Baseline shifts to “low” or “high” based on their minimum or maximum values at any time postdose will be summarized. In addition, a

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summary of laboratory values categorized based on Common Toxicity Criteria grade will also be generated. Summary statistics for actual values and change from Baseline will also be presented for quantitative laboratory data.

16.4.2.3. Physical Examinations

The analyses of physical examinations will include summary statistics (actual value and change from Baseline for body weight and height) over time by visit.

16.4.2.4. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-Baseline abnormalities will be presented by group.

The definitions of these clinically relevant abnormalities are shown in [Table 5](#).

Table 5: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from Baseline of $\geq 1^\circ\text{C}$
Pulse	>120 bpm or an increase from Baseline of >20 bpm <50 bpm or a decrease from Baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from Baseline of >40 mmHg <90 mmHg or a decrease from Baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from Baseline of >30 mmHg <50 mmHg or a decrease from Baseline of >20 mmHg

The analyses of vital signs will also include summary statistics (actual value and change from Baseline for temperature, pulse, and systolic and diastolic blood pressure) over time by visit.

16.4.2.5. ECG Data

A listing of subjects with abnormal ECG status will be presented. Changes from Baseline in ECG will be summarized using shift tables. The number and percentage of subjects with shifts to categorical values (abnormal, not AE/abnormal, AE) will be summarized.

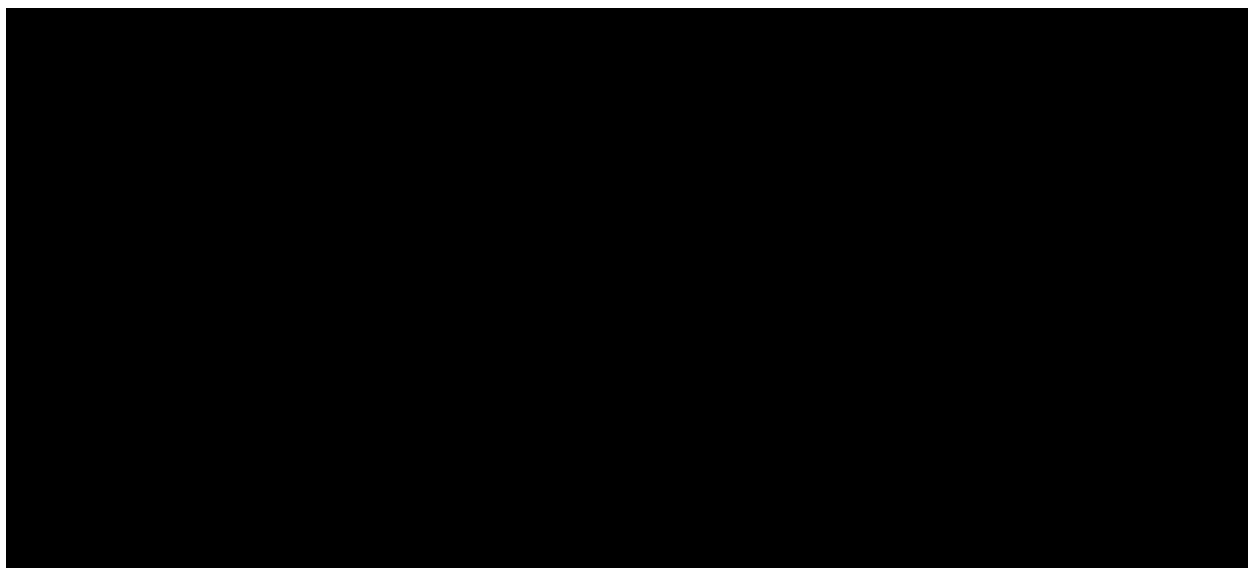
16.5. Clinical Assessments

16.5.1. Analysis Population

The evaluable population for clinical assessments is defined as all subjects who receive at least 1 dose of study treatment and at least 1 measurement for each of the clinical assessments after Baseline.

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16.6. Interim Analyses

Interim analyses may be performed to support regulatory filings and/or publications and will be documented in the Statistical Analysis Plan.

16.7. Sample Size Considerations

The sample size for this study is not based on formal hypothesis testing but on the precision of the estimation of the primary endpoints and the ratios between various ALC subgroups.

For example, the Phase 2 and 3 controlled and uncontrolled efficacy and safety studies in MS, based on data available as of May 2014 from 2470 subjects with at least 1 post-Baseline value from the interim analysis of the Integrated Summary of Safety of Tecfidera, showed that 76% of subjects had all ALC values \geq LLN and 24% had at least 1 ALC value $<$ LLN up to Week 48. Assuming the same proportion of subjects in this study will have 1 or more ALC values $<$ LLN, it is expected that approximately 137 subjects will have all ALC values \geq LLN and approximately 43 subjects will have at least 1 ALC value $<$ LLN at Week 48, based on a total of 180 evaluable subjects at Week 48. With this sample size, the 90% CIs for the ratio of the 2 subgroups for the change from Baseline at Week 48 in lymphocyte subsets are illustrated below using the scenario of a true ratio of 0.8 (20% decrease) and 0.7 (30% decrease), respectively. When assessing lymphocyte subsets between subjects with at least 2 ALC values $<$ LLN up to the first 48 weeks of treatment versus subjects who have all ALC values \geq LLN throughout the study, the 90% CIs of the ratio would be wider, as historical data suggest that 16% of the patients treated with Tecfidera may have 2 or more ALC values $<$ LLN during the first 48 weeks of treatment.

To allow for a 10% discontinuation rate, a total of 200 subjects are planned for enrollment.

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Table 6: Sample Size Calculations

Primary Endpoints	SD ¹	Ratio	90% CI for the Ratio Based on N = 180	
			Subjects With At Least 1 ALC <LLN ² vs. Subjects With All ALC ≥LLN ²	Subjects With At Least 2 ALC <LLN ² vs. Subjects With All ALC ≥LLN ²
CD4 T cell count	0.32	0.8	0.73, 0.88	0.71, 0.90
		0.7	0.63, 0.77	0.63, 0.78
CD8 T cell count	0.35	0.8	0.72, 0.89	0.71, 0.91
		0.7	0.63, 0.78	0.62, 0.79
CD56 ^{bright} NK cell count	0.57	0.8	0.68, 0.95	0.65, 0.98
		0.7	0.59, 0.83	0.57, 0.86
T _{reg} count	0.95	0.8	0.60, 1.07	0.57, 1.12
		0.7	0.52, 0.93	0.50, 0.98

ALC = absolute lymphocyte count; CD = cluster of differentiation; CI = confidence interval; LLN = lower limit of normal; NK = natural killer; SD = standard deviation; T_{reg} = T regulatory; vs. = versus.

¹ Common standard deviation for the log-transformed change from Baseline.

² Up to Week 48.

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17. ETHICAL REQUIREMENTS

Biogen, [REDACTED], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

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

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

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

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

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

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

17.3. Subject Information and Consent

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

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

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

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

17.4. Subject Data Protection

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

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 partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

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18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

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

18.5. Publications

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

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19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

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

19.1.2. Interactive Response Technology

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

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool supported by iMedidata RAVE and configured by [REDACTED].

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Biogen to analyze the laboratory samples collected for this study.

19.2. Study Committees

Not applicable. Given the established safety and efficacy of DMF via the Phase 2 and Phase 3 studies, advisory committees were deemed not necessary for this study.

19.3. Changes to Final Study Protocol

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

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

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

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19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. 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 offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

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

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, “An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis,” and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Investigator’s Signature

Date

Investigator’s Name (Print)

Study Site (Print)


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Signature Page

Document Name: 109MS310 Protocol V2 Final 22Jan16

Document Title: An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis

Signed by	Role	Date / Time (UTC)
	Signing as Approver	01/29/2016 18:34:34



PROTOCOL NUMBER: 109MS310

PHASE OF DEVELOPMENT: 3b

PROTOCOL TITLE: An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis

EUDRA CT NO: 2015-001973-42

DATE: 30 April 2015
Version 1
FINAL

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SPONSOR SIGNATURE

Protocol 109MS310 was approved by:

[REDACTED]

[REDACTED] MD, MAS

Biogen MA Inc.

6/14/15

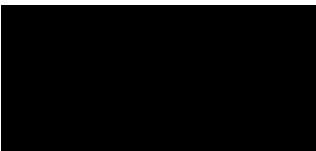
Date

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SIGNATURE PAGE

Protocol 109MS310 was approved by:



 MD, PhD








Biogen Idec Research Limited

03 May 2015
Date

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1. SPONSOR INFORMATION

The Sponsor is Biogen MA Inc. in North America and Biogen Idec Research Limited in the Rest of World. Biogen MA Inc. and Biogen Idec Research Limited are referred to as Biogen in this protocol.

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	SL6 4AY
	United Kingdom

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

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

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2. LIST OF ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
AST	aspartate transaminase
BBB	blood-brain barrier
BID	twice daily
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CRF	case report form
CRO	contract research organization
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
DMT	disease modifying therapy
DNA	deoxyribonucleic acid
ECG	electrocardiogram
██████	████████████████████
GA	glatiramer acetate
GCP	Good Clinical Practice
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
ICF	informed consent form
ICH	International Conference on Harmonization
IFN	interferon
Ig	immunoglobulin
IV	intravenous
IVMP	intravenous methylprednisolone
IXRS	Interactive Voice and Web Response System
LLN	lower limit of normal
MMRM	mixed model for repeated measures
MS	multiple sclerosis
NK	natural killer (cells)
Nrf2	nuclear factor (erythroid-derived 2)-like 2
██████	████████████████████
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase

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SGPT	serum glutamic pyruvic transaminase
SPMS	secondary progressive multiple sclerosis
SUSAR	suspected unexpected serious adverse reaction
T _{reg}	T regulatory (cells)
ULN	upper limit of normal
US	United States
WBC	white blood cell

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3. SYNOPSIS

Protocol Number:	109MS310
Protocol Title:	An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis
Version Number	1
Name of Study Treatment:	BG00012 (dimethyl fumarate [DMF]; Tecfidera [®])
Study Indication:	Multiple sclerosis (MS)
Study Rationale	<p>Given the putative immunomodulatory properties of DMF and its observed effects on lymphocytes in humans, further evaluation of its effects on immune function is needed. The effect of BG00012 on lymphocyte subtypes is yet unknown, and its evaluation may provide insights into the mechanisms underlying BG00012-associated lymphopenia. This study is therefore being conducted to assess the effects of BG00012 on lymphocyte subset counts and immunoglobulins (Igs) within the first year of treatment and until the end of the study.</p>
Phase of Development:	3b
Study Objectives and Endpoints:	<p>The primary objective of the study is to evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with RRMS.</p> <p>The primary endpoint that relates to this objective is the change in lymphocyte subset counts for up to 48 weeks.</p> <p>A secondary objective is to evaluate the pharmacodynamic effect of BG00012 on absolute lymphocyte counts (ALCs) and Igs during the first year of treatment.</p> <p>The endpoints that relate to this objective are the changes in IgG isotypes and ALCs for up to 48 weeks.</p>

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Study Design:	<p>This is an open-label, multicenter study to evaluate the effects of BG00012 on lymphocyte subtypes and Ig isotypes.</p> <p>After the Screening Visit (up to 28 days), subjects will receive BG00012 treatment for 48 weeks (Treatment Period) and will then continue on 240 mg BG00012 twice daily (BID) for an additional 48 weeks (Extension Period). Blood samples for lymphocyte subset analysis, as well as blood samples for the determination of each subject's complete blood count with differential, will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 24, 36, 48, 72, and 96. Clinical samples for the analysis of blood chemistries will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 24, 48, and 96. A post-treatment follow-up visit at which safety assessments will be performed will occur 4 weeks after the final dose of BG00012.</p> <p>Subjects who withdraw from the study while on study treatment will complete the Discontinuation and/or Withdrawal Visit as soon as possible but no later than 2 weeks after their last dose of study treatment and will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment unless consent has been withdrawn. Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count $<LLN$ will continue protocol-required visits and assessments and will also be followed every 4 weeks until the lymphocyte count is $\geq LLN$ or for 24 weeks after the last dose (whichever is sooner). Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.</p> <p>Refer to Table 1 and Table 2 for the timing of all study assessments.</p>
Study Location:	Approximately 100 sites in North America and Europe
Number of Planned Subjects:	Approximately 200 subjects will be treated.
Study Population:	This study will be conducted in male and female subjects, aged 18 through 65 years, with a confirmed diagnosis of RRMS according to the revised McDonald criteria (2010) [Polman 2011].

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Detailed criteria are described in Section 8.

Treatment Groups:

Approximately 200 subjects will receive oral BG00012 at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or gastrointestinal disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed.

Duration of Treatment and Follow-up:

The study period will consist of a Screening Visit within 4 weeks of Baseline, a Treatment Period of 48 weeks, an Extension Period of 48 weeks, and a final Follow-Up Visit. Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count $<LLN$ will be followed every 4 weeks until the lymphocyte count is $\geq LLN$ or for 24 weeks after the last dose (whichever is sooner). If the lymphocyte count remains $<LLN$ for 24 weeks after the last dose, subjects who had temporarily withheld or permanently discontinued study treatment will continue assessments specified in the protocol. Subjects will receive treatment for 96 weeks. The study duration may vary from approximately 104 to 124 weeks.

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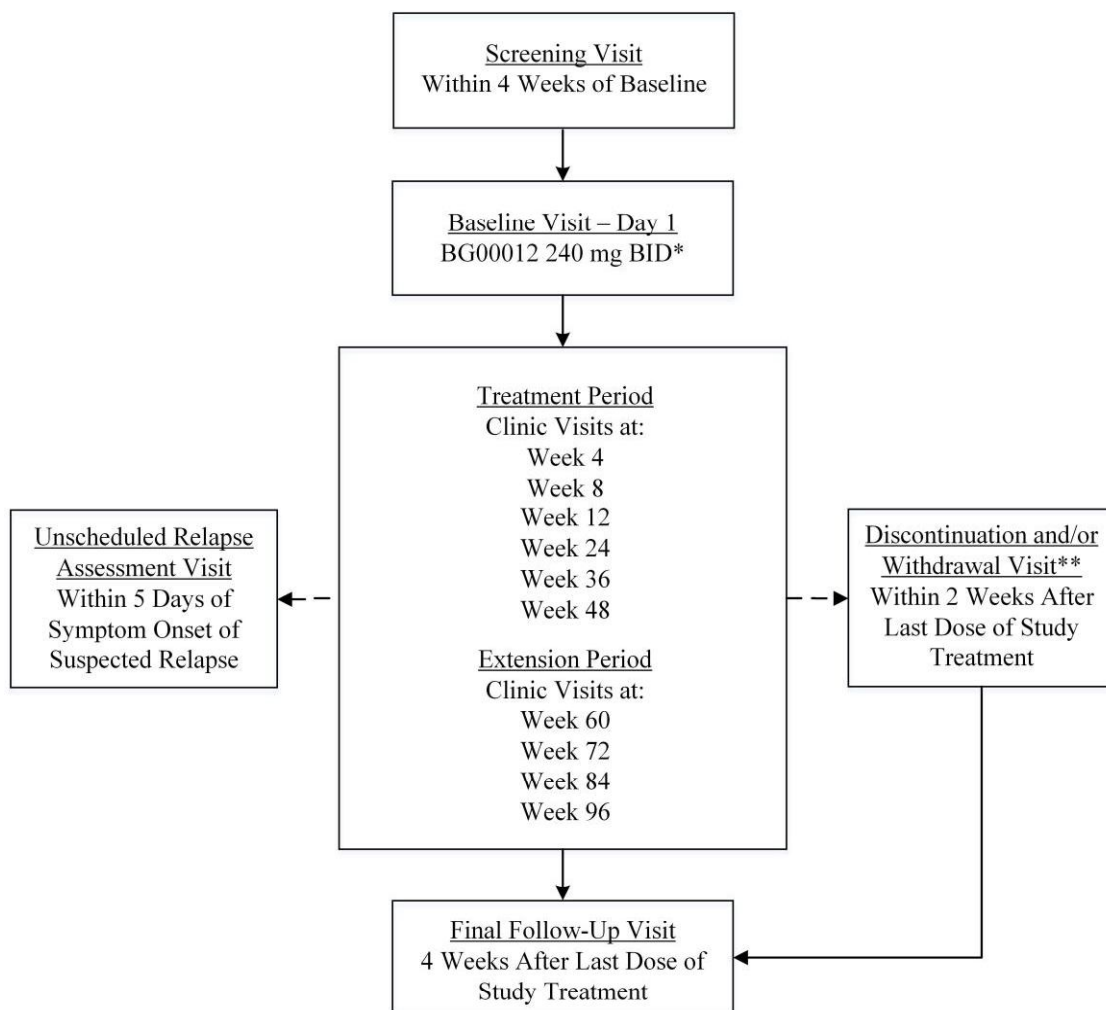
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4. STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES FOR STUDY 109MS310

4.1. Study Schematic

The study design for Study 109MS310 is shown in [Figure 1](#), and the study activities are shown in [Table 1](#) and [Table 2](#).

Figure 1: Study Design



BID = twice daily; LLN = lower limit of normal.

*Subjects will receive oral BG00012 at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered (see Section 11.2.4).

**Subjects with a lymphocyte count <LLN will have additional lymphocyte and subset analysis (see Section 11.3).

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4.2. Schedule of Activities

Table 1: Study Activities for Study 109MS310 - Table 1 of 2

Tests and Assessments	Screening	Treatment Period							Extension Period				Final Follow-Up Visit ¹
	Within 28 days before Baseline	Baseline (Day 1)	Week 4 (Day 28 ±3 days)	Week 8 (Day 56 ±3 days)	Week 12 (Day 84 ±3 days)	Week 24 (Day 168 ±5 days)	Week 36 (Day 252 ±5 days)	Week 48 (Day 336 ±5 days)	Week 60 (Day 420 ±5 days)	Week 72 (Day 504 ±5 days)	Week 84 (Day 588 ±5 days)	Week 96 (Day 672 ±5 days)	4 weeks ±5 days after final dose
Informed Consent ²	X												
Medical History ³	X												
Hepatitis B and C Screen	X												
Physical Examination ⁴	X							X				X	
Vital Signs ⁵	X	X	X	X	X	X	X	X		X		X	X
12-Lead ECG		X						X				X	
Hematology (CBC With Differential) ⁶	X	X	X	X	X	X	X	X		X		X	X
Blood Chemistry	X	X	X	X		X		X				X	X
Lymphocyte Subset Analysis ⁶	X	X	X	X	X	X	X	X		X		X	X

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Phase 3b Study on the Effect of BG00012 on Lymphocyte Subsets and Immunoglobulins in Subjects With RRMS

Tests and Assessments	Screening	Treatment Period							Extension Period				Final Follow-Up Visit ¹
	Within 28 days before Baseline	Baseline (Day 1)	Week 4 (Day 28 ±3 days)	Week 8 (Day 56 ±3 days)	Week 12 (Day 84 ±3 days)	Week 24 (Day 168 ±5 days)	Week 36 (Day 252 ±5 days)	Week 48 (Day 336 ±5 days)	Week 60 (Day 420 ±5 days)	Week 72 (Day 504 ±5 days)	Week 84 (Day 588 ±5 days)	Week 96 (Day 672 ±5 days)	4 weeks ±5 days after final dose
Serum Pregnancy Test ⁷	X												
Urine Pregnancy Test ⁷						X		X		X		X	
Dispense BG00012		X			X	X	X	X	X	X	X		
BG00012 Administration		X											
Concomitant Therapy and Procedures		X											
AE Recording		X											
SAE Recording	Monitor and record throughout the study.												

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Phase 3b Study on the Effect of BG00012 on Lymphocyte Subsets and Immunoglobulins in Subjects With RRMS

AE = adverse event; CBC = complete blood count; DNA = deoxyribonucleic acid; ECG = electrocardiogram; [REDACTED]; LLN = lower limit of normal; MS = multiple sclerosis; [REDACTED]; SAE = serious adverse event.

- ¹ Subjects will have a final Follow-Up Visit 4 weeks after taking their final dose, regardless of whether they complete the treatment period or discontinue prematurely, unless they have a lymphocyte count <LLN.
 - ² Written informed consent must be obtained prior to performing any study-related procedures.
 - ³ Medical history will include gastrointestinal abnormalities within the previous 6 months, as well as duration of MS (time since diagnosis), relapse history, and treatments for MS.
 - ⁴ Physical examination includes height and weight measurements, as well as a neurological examination.
 - ⁵ Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.
 - ⁶ Whole blood may also be collected for lymphocyte functional tests. Lymphocyte subset testing must be performed every 4 weeks in subjects with lymphocyte count <500/mm³ and followed until recovery or for 24 weeks after the last dose (whichever is sooner).
 - ⁷ Females of childbearing potential only. Results must be known to be negative prior to dispensing BG00012.
- [REDACTED]

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Table 2: Study Activities for Study 109MS310 - Table 2 of 2

Tests and Assessments	[REDACTED]	Discontinuation and/or Withdrawal Visit ²	Lymphocyte Follow-Up Visit ³
		These visits can be combined. If these visits are not combined, any assessment that was performed within the past 2 weeks (or the interval noted in the footnotes) does not need to be repeated unless clinically indicated.	
Physical Examination ⁴	X		X
Vital Signs ⁵	X	X	X
Hematology (CBC With Differential)	X	X	X
Blood Chemistry	X	X	
Blood for Exploratory Serum and Plasma Biomarkers		X	X
[REDACTED]			
Lymphocyte Subset Analysis		X	X
[REDACTED]			
Concomitant Therapy and Procedures	X		
AE Recording	X		
SAE Recording	Monitor and record throughout the study.		

AE = adverse event; CBC = complete blood count; [REDACTED]; LLN = lower limit of normal; [REDACTED]
[REDACTED]; SAE = serious adverse event.

² Discontinuation refers to discontinuation of study treatment. Withdrawal refers to withdrawal of subjects from study. The Discontinuation and/or Withdrawal Visit should be conducted as soon as possible and no later than 2 weeks after their last dose of study treatment.

³ Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count <LLN will continue protocol-required visits and assessments and will also be followed up every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner).

⁴ Physical examination includes height and weight measurements, as well as a neurological examination.

⁵ Vital signs will include diastolic and systolic blood pressure, heart rate, and temperature. Subjects must be seated for 5 minutes prior to having their pulse and blood pressure measured.

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4.3. Additional Information

4.3.1. Site Personnel

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

- a primary and backup Neurologist
- a primary and backup Study Nurse (or Study Coordinator)
- a Pharmacist (or authorized designee)

The primary and backup Neurologists must have a minimum of 2 years of neurology specialty training and anticipate a 2-year commitment to the study. [REDACTED]

[REDACTED] The backup Neurologist may conduct subject evaluations if the primary Neurologist is unavailable due to illness, vacation, or travel.

The roles and responsibilities of the Neurologist and Study Nurse are described below. Details for all roles are provided in the Study Reference Guide.

The primary Neurologist will be responsible for the following:

- Management of the routine neurological care of the subject.
- Assessment (including assignment of causality) and treatment of adverse events (AEs) [REDACTED].
- Review of hematology and blood chemistry results from the central laboratory to assess whether the subject's study treatment should be temporarily withheld or permanently discontinued, as per the criteria detailed in Section 10.
- Determination of whether new objective neurological findings have occurred (see Section 7.2.4).

- [REDACTED]
- [REDACTED]

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The Neurologist may designate other medical personnel (i.e., the backup Neurologist or the Study Nurse) at the investigational site to perform some of the tests and evaluations listed under “Neurologist.”

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

4.3.2. Subject Management

Contraception requirements are described in Section 15.5. Study treatment dosing requirements and concomitant medication restrictions are described in Sections 11.1 and 11.6, respectively.

There are no restrictions regarding diet and alcohol use. Physical exertion atypical for the subject’s normal activities of daily living should be avoided for 24 hours prior to assessments.

Subjects should not donate blood until 1 month after their last dose of study treatment in this study.

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5. INTRODUCTION

BG00012 is a fumarate ester drug product formulation containing the active ingredient dimethyl fumarate (DMF). In 2013, BG00012 was first approved in the United States (US) under the propriety name Tecfidera[®] as a treatment for patients with relapsing MS and has since been approved in other countries.

5.1. Overview of Multiple Sclerosis

MS is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and oligodendrocyte and neuronal loss. It is the most common demyelinating disorder of the CNS, affecting approximately 2.5 million people worldwide. Its prevalence is highest among Caucasians, with higher rates reported in North America, Europe, Australia, New Zealand, and northern Asia [Noseworthy 2000; Rosati 2001].

Relapsing MS is the most common clinical presentation of the disease. The term relapsing MS applies to patients with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) who experience relapses; both are considered part of the same disease spectrum. In the relapsing/remitting phase of the disease, patients experience episodes of neurological dysfunction (relapses) separated by periods of relative stability. Typical symptoms of relapse include weakness, sensory loss, visual loss, and imbalance. Relapses may completely subside in the early stage of the disease, but recovery tends to be incomplete over time, leading to the accumulation of physical disability and cognitive decline. RRMS is usually diagnosed between the ages of 20 and 40 years and affects twice as many women than men. The RRMS population ranges from patients with relatively benign, inactive, non-inflammatory disease to patients who experience frequent relapse and/or persistent, active, inflammatory disease. Most of these patients develop SPMS, which is characterized by progressive neurological decline with or without superimposed relapse; the median time to progression from RRMS to SPMS is approximately 10 years [Runmarker and Andersen 1993]. Approximately half of all MS patients are unable to walk without assistance within 15 years of their initial diagnosis [Runmarker and Andersen 1993; Weinshenker 1989], and more than half of patients die from MS or its complications [Brønnum-Hansen 2004].

As patients progress along the continuum from RRMS to SPMS, disability progression is more likely to occur independently of relapses. The pathological changes underlying MS are thought to occur when activated T lymphocytes cross the blood-brain barrier (BBB) and initiate a series of events leading to activation of endothelial cells, recruitment of additional lymphocytes and monocytes, and release of pro-inflammatory cytokines. MS lesions consisting of immune cells can occur throughout the CNS, but certain sites appear to be particularly vulnerable, such as the optic nerve, brainstem, spinal cord, and periventricular regions of the cerebrum. The development of MS lesions is associated with inflammation, edema, and demyelination, and is often correlated with reversible disease symptoms, namely relapses, as well as oligodendrocyte

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death and axonal transection, which can be permanent and lead to disability. Alternatively, oligodendrocyte and axonal loss may be due to a neurodegenerative process. Ongoing inflammatory and neurodegenerative stimuli are mediated at least in part by toxic oxidative stress. Preclinical studies indicate that BG00012-dependent pharmacodynamic responses appear to be mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli through up-regulation of antioxidant response genes. While it is not yet fully understood how the inflammatory cascade is initiated, adhesion and trans-endothelial migration of inflammatory cells from the bloodstream across the BBB and into the CNS is thought to be an early and critical step in this process.

5.2. Current Therapies for Multiple Sclerosis

The most commonly used first-line MS therapies are interferons (IFNs) and glatiramer acetate (GA) [Waldman 2011]. Relative to placebo, IFNs have been shown to reduce relapse rate by approximately 27% to 36% [Calabresi 2014; Jacobs 1996; PRISMS Study Group 1998; The IFNB Multiple Sclerosis Study Group 1993], and GA by approximately 30% [Johnson 1995]. The interferon beta-1a (IFN β -1a) products have also been shown to delay disability progression [Jacobs 1996; PRISMS Study Group 1998].

Other currently approved therapies for MS include the following:

- Natalizumab: a humanized monoclonal antibody directed against α 4 integrins [Polman 2006].
- Fingolimod: a selective oral immunosuppressant that is metabolized to a functional antagonist of sphingosine 1-phosphate receptors on lymphocytes [Kappos 2010].
- Mitoxantrone: a synthetic antineoplastic anthracenedione that intercalates into deoxyribonucleic acid (DNA) and interferes with ribonucleic acid (RNA) [Chitnis 2012].
- Teriflunomide: an immunomodulatory drug inhibiting pyrimidine synthesis by blocking dihydroorotate dehydrogenase [O'Connor 2011].
- Alemtuzumab: a humanized monoclonal antibody targeting CD-52 antigen expressed on the surface of most leukocytes [Coles 2012].

5.3. Profile of Previous Experience With BG00012

5.3.1. Nonclinical Experience

In nonclinical studies, DMF and its primary metabolite, monomethyl fumarate, were found to promote stabilization and transcriptional activity of Nrf2, as well as expression of Nrf2 target genes in cultured human cells and in vivo [Linker 2011]. Previous ex vivo and in vivo studies

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have demonstrated a central role of the Nrf2 pathway in the protection of cells and tissues against oxidative, xenobiotic, and inflammatory stress. Loss of Nrf2 function via genetic silencing has been shown to cause exaggerated inflammatory response and lead to development of systemic autoimmunity and CNS alterations, including widespread gliosis and white matter lesions. Conversely, pharmacological agents known to activate Nrf2 have been shown in nonclinical studies to exert anti-inflammatory effects, protect neurons from oxidative and excitotoxic stress-induced death, and improve the BBB integrity of the CNS. Activation of the Nrf2 pathway by DMF in MS may contribute to inhibition of inflammation and help support CNS integrity by promoting cellular resistance to oxidative stress.

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

5.3.2. Clinical Experience

In the Phase 2 and 3 placebo-controlled safety and efficacy studies (the completed 6-month Phase 2 Study C-1900 Part 1 and the 2 completed 2-year Phase 3 Studies 109MS301 and 109MS302) and/or their uncontrolled extensions (the completed 6-month Phase 2 Study C-1900 Part 2 and the ongoing Phase 3 long-term Study 109MS303) over 2500 subjects received treatment with BG00012. The overall exposure to BG00012 among these subjects was approximately 6100 subject-years as of September 2013.

DMF demonstrated robust efficacy and a favorable safety profile in subjects with RRMS in the 2 large Phase 3 studies (Study 109MS301 [DEFINE] [Gold 2012a] and Study 109MS302 [CONFIRM] [Fox 2012]). The benefit-risk profile of DMF was considered positive, and the drug has been approved.

Both Phase 3 studies demonstrated that treatment with DMF reduced the risk of MS relapse and slowed progression of disability. In an integrated analysis of DEFINE and CONFIRM, DMF 240 mg twice daily (BID) and 3 times daily significantly reduced the annualized relapse rate at 2 years by 49% relative to placebo ($p < 0.0001$). Significant reductions at 2 years were also observed in the proportion of subjects who relapsed (43% and 47%, respectively; $p < 0.0001$), the proportion of subjects with confirmed (12-week) progression of disability (32% and 30%, respectively; $p < 0.01$), and the proportion of subjects with confirmed (24-week) progression of disability (29% and 32%, respectively; $p < 0.03$) [Gold 2012b].

DMF was generally well tolerated and demonstrated an acceptable safety profile. The most common AEs associated with DMF were flushing and gastrointestinal (GI) events. In subjects who experienced these types of events, the events were generally mild or moderate in intensity, tended to decrease in incidence after the first month, and only infrequently led to treatment discontinuation. There are a number of potential management strategies for these side effects. In the Phase 2 and 3 controlled and uncontrolled clinical studies in subjects with RRMS, BG00012 treatment was associated with a gradual decrease from baseline in mean leukocyte counts driven primarily by decreases in mean lymphocyte counts; mean lymphocyte counts decreased by approximately 30% of their baseline value after 1 year and then plateaued and remained stable through more than 6 years of follow-up. While decreases in lymphocyte counts

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have been observed with BG00012 treatment, in the placebo controlled Phase 2 and 3 studies BG00012 was not associated with an increased risk of infection, serious infection, or opportunistic infection compared with placebo. However, in the long-term extension study (109MS303), progressive multifocal leukoencephalopathy has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. With open-label and marketed use of BG00012, there has been no other evidence of an increased risk of infections, serious infections, or opportunistic infections.

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

5.4. Study Rationale

Given the putative immunomodulatory properties of DMF and its observed effects on lymphocytes in humans, further evaluation of its effects on lymphocytes is needed. The effect of BG00012 on lymphocyte subtypes is yet unknown, and its evaluation may provide insights into the mechanisms underlying BG00012-associated lymphopenia. This study is therefore being conducted to assess the effects of BG00012 on lymphocyte subset counts and immunoglobulins (Igs) within the first year of treatment and beyond.

5.5. Rationale for Dosing Regimen

The BG00012 dosage selected for this study (120 mg BID for the first 7 days and 240 mg BID thereafter) is the approved BG00012 dosing regimen in the US, Canada, European Union, and other countries around the world for the treatment of patients with MS.

Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or GI disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed.

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6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Primary Objective and Endpoint

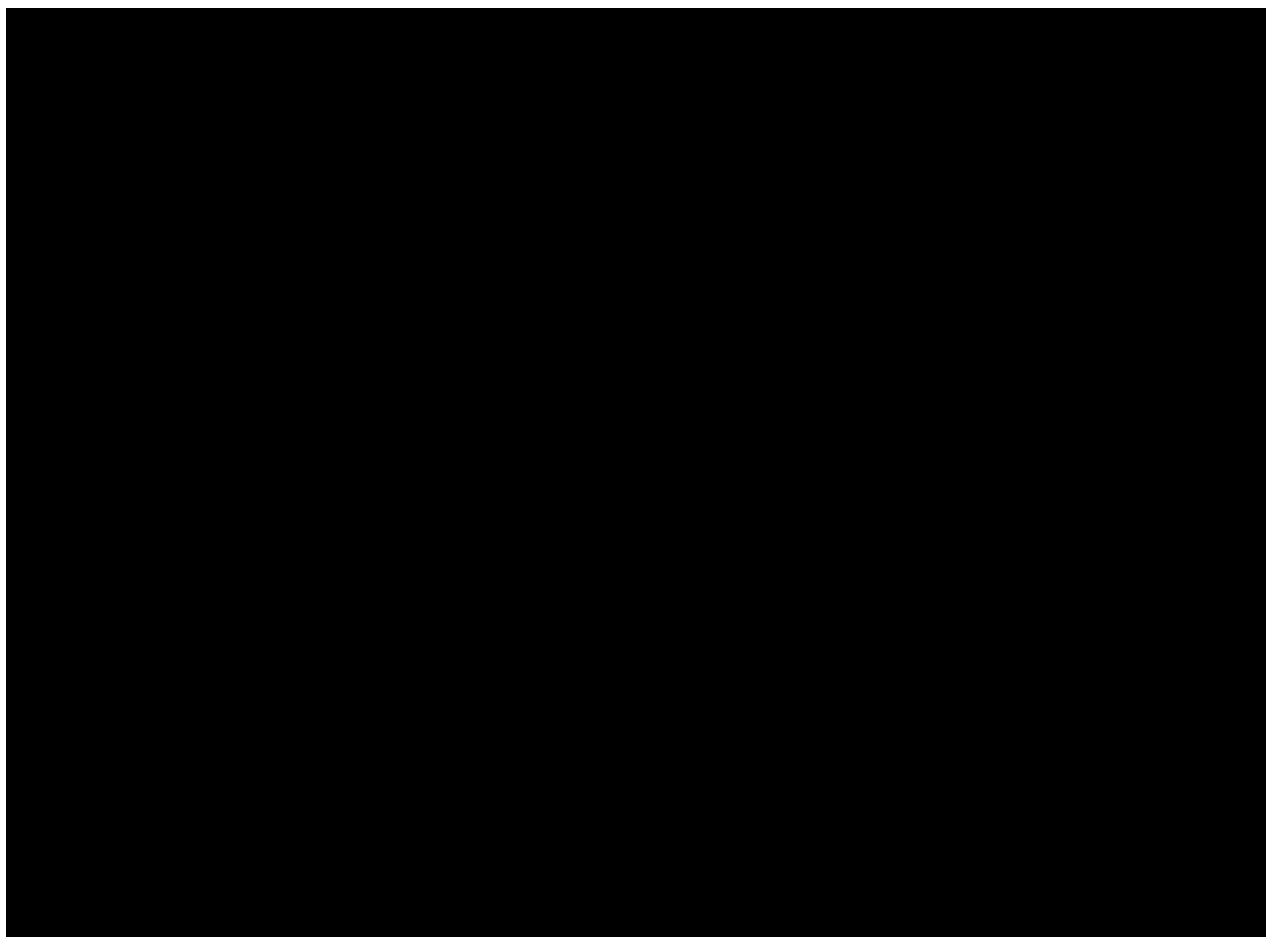
The primary objective of the study is to evaluate the effect of BG00012 on lymphocyte subset counts during the first year of treatment in subjects with RRMS.

The primary endpoint that relates to this objective is the change in lymphocyte subset counts for up to 48 weeks.

6.2. Secondary Objective and Endpoints

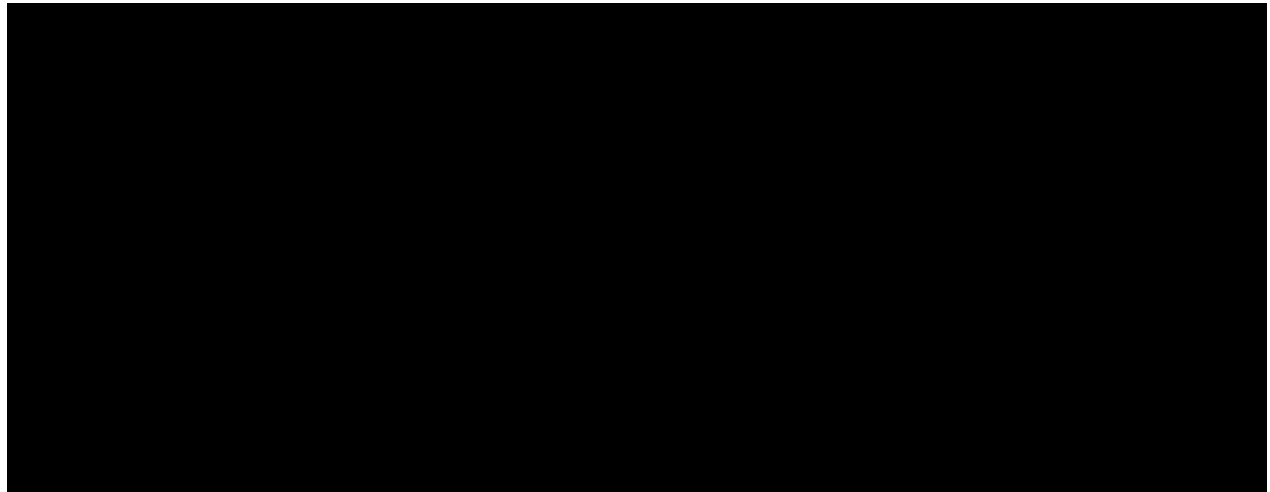
A secondary objective is to evaluate the pharmacodynamic effect of BG00012 on absolute lymphocyte counts (ALCs) and Igs during the first year of treatment.

The endpoints that relate to this objective are the changes in IgG isotypes and ALCs for up to 48 weeks.



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7. STUDY DESIGN

7.1. Study Overview

This is an open-label, multicenter study to evaluate the effects of BG00012 on lymphocyte subtypes and Ig isotypes. Approximately 200 subjects will be treated in approximately 100 sites in North America and Europe.

After the Screening Visit (up to 28 days), subjects will receive BG00012 treatment for 48 weeks (Treatment Period) and will then continue on 240 mg BG00012 BID for an additional 48 weeks (Extension Period). Blood samples for lymphocyte subset analysis, as well as blood samples for the determination of each subject's complete blood count with differential, will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 24, 36, 48, 72, and 96. Clinical samples for the analysis of blood chemistries will be collected at Screening, Baseline (Day 1), and Weeks 4, 8, 24, 48, and 96. A post-treatment follow-up visit, at which safety assessments will be performed, will occur 4 weeks after the final dose of BG00012.

Subjects who withdraw from the study while on study treatment will complete the Discontinuation and/or Withdrawal Visit as soon as possible but no later than 2 weeks after their last dose of study treatment and will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment unless consent has been withdrawn. Subjects who complete, temporarily withhold, or permanently discontinue study treatment for any reason and have a lymphocyte count $<LLN$ will continue protocol-required visits and assessments and will also be followed every 4 weeks until the lymphocyte count is $\geq LLN$ or for 24 weeks after the last dose (whichever is sooner). If the lymphocyte count remains $<LLN$ for 24 weeks after the last dose, subjects who had temporarily withheld or permanently discontinued study treatment will continue assessments specified in the protocol. Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

See [Figure 1](#) for a schematic of the study design. Refer to [Table 1](#) and [Table 2](#) for the timing of all study assessments.

7.2. Overall Study Duration and Follow-Up

The study period will consist of a Screening Visit within 4 weeks of Baseline, a Treatment Period of 48 weeks, an Extension Period of 48 weeks, and a final Follow-Up Visit. Subjects will receive treatment for 96 weeks. The study duration may vary from approximately 104 to 124 weeks.

7.2.1. Screening

Subject eligibility for the study will be determined within 28 days prior to study entry.

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7.2.2. Treatment Period and Extension Period

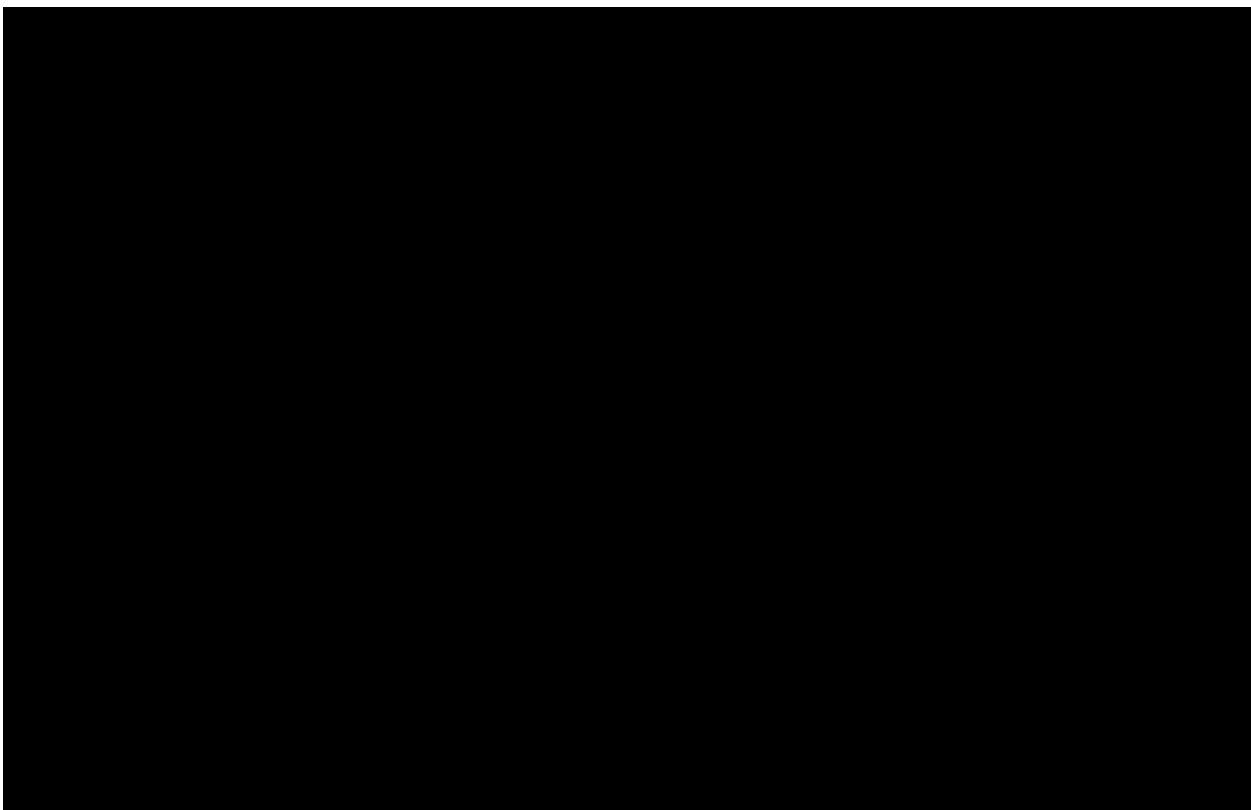
Eligible subjects will report to the study site every 4 weeks for the first 12 weeks and every 12 weeks thereafter for 96 weeks.

Discontinuation and/or Withdrawal Visits [REDACTED] Visits will be performed as necessary. Subjects who withdraw from the study early will be asked to return to complete a Discontinuation and/or Withdrawal Visit within 2 weeks of their last study treatment dose.

7.2.3. Follow-Up

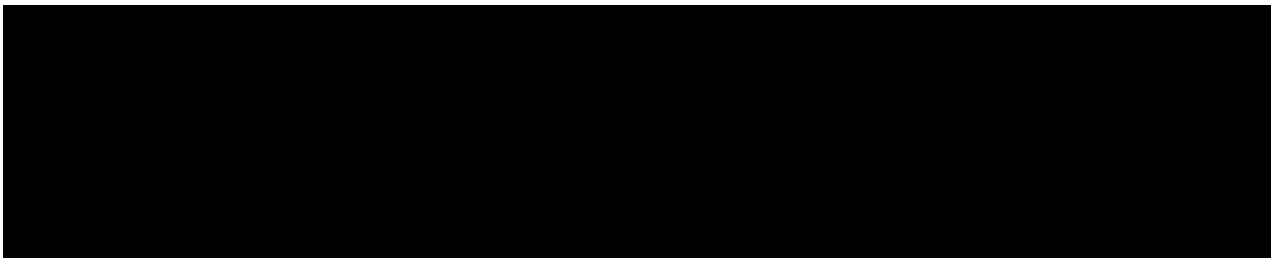
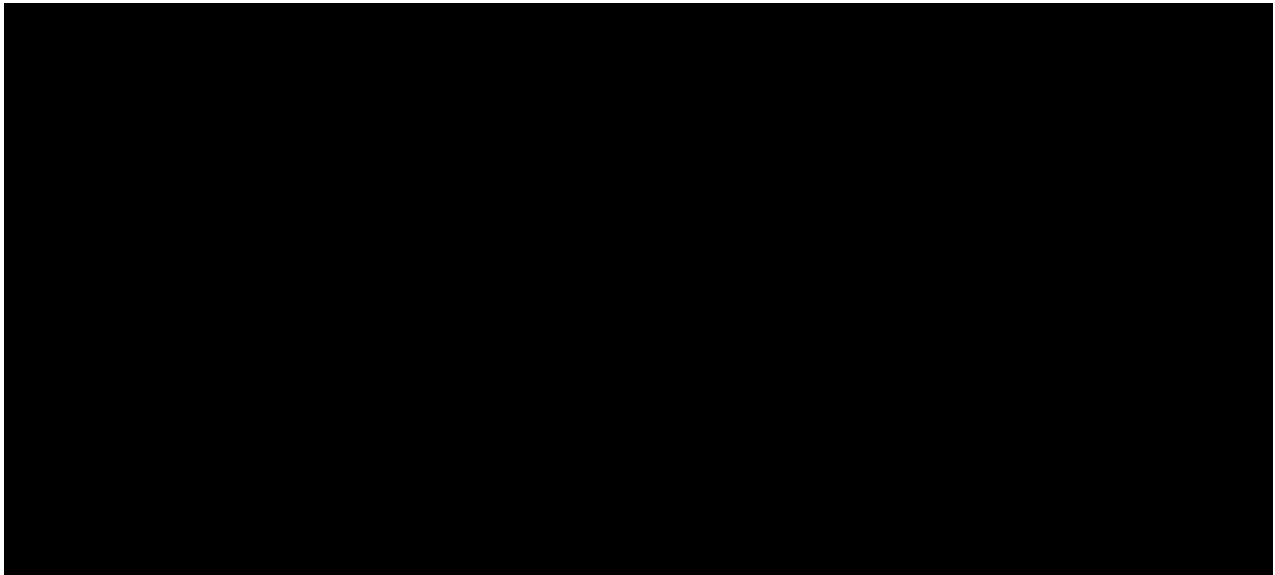
Subjects are to return to the study site for a Follow-Up Visit 4 weeks after their last dose of study treatment. The final study visit will be Week 100.

Subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any reason and have a lymphocyte count $<LLN$ will be followed every 4 weeks until the lymphocyte count is $\geq LLN$ or for 24 weeks after the last dose (whichever is sooner; see Section 11.3). If the lymphocyte count remains $<LLN$ for 24 weeks after the last dose, subjects who had temporarily withheld or permanently discontinued study treatment will continue assessments specified in the protocol.



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**7.2.6. Additional Assessments if Required by Local Tecfidera Prescribing Information**

Any additional assessments that are needed to comply with the local prescribing information for Tecfidera should also be performed and will be reimbursed by Biogen while a subject is participating in this study.

7.3. Study Stopping Rules

There are no study-specific stopping rules. Biogen may terminate this study at any time after informing Investigators. Biogen will notify Investigators when the study is to be placed on hold, completed, or terminated.

7.4. End of Study

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

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8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

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

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.
2. Age 18 to 65 years old, inclusive, at the time of informed consent.
3. Subjects of childbearing potential (including female subjects who are post-menopausal for less than 1 year) must practice effective contraception (as determined by the Investigator) during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.
4. Must have a confirmed diagnosis of RRMS according to the revised McDonald criteria (2010) [Polman 2011].

8.2. Exclusion Criteria

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

Medical History

1. History of or positive test result at Screening for human immunodeficiency virus.
2. History of or positive test result at Screening for hepatitis C virus antibody or current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or hepatitis B core antibody [HBcAb]). Subjects with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive hepatitis B surface antibody IgG, and positive HBcAb) are eligible to participate in the study (US Centers for Disease Control and Prevention's interpretation of the hepatitis B serology panel).
3. History of drug or alcohol abuse (as defined by the Investigator) within 1 year prior to Screening.
4. Any clinically significant (in the judgment of the Investigator) infectious illness (e.g., cellulitis, abscess, pneumonia, and septicemia) within 30 days prior to Screening.

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5. History of clinically significant (in the judgment of the Investigator) cardiovascular, dermatologic, endocrinologic, GI, hematologic, hepatic, immunologic, metabolic, neurologic (other than MS), psychiatric, pulmonary, renal, urologic, and/or other major disease that would preclude participation in a clinical study.
6. History of severe allergic or anaphylactic reactions or known drug hypersensitivity to DMF or fumaric acid esters.
7. Any of the following abnormal blood tests at Screening that are confirmed on repeat testing within 2 weeks:
 - leukocytes $<3500/\text{mm}^3$
 - ALC values $\leq \text{LLN}$
 - alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) or aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) ≥ 2 times the upper limit of normal (ULN)

Treatment History

8. Prior treatment with any of the following:
 - cladribine
 - mitoxantrone
 - total lymphoid irradiation
 - alemtuzumab
 - T-cell or T-cell receptor vaccination
 - any therapeutic monoclonal antibody, with the exception of natalizumab or daclizumab
9. Treatment with any of the following medications or procedures within 6 months prior to Baseline (Day 1):
 - DMF (given as Fumaderm[®]) or BG00012; enrollment will be limited to no more than 40 subjects (out of 200) with prior DMF exposure
 - cyclosporine
 - azathioprine

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- methotrexate
 - mycophenolate mofetil
 - intravenous (IV) Ig
 - plasmapheresis or cytapheresis
10. Treatment with another investigational drug or approved therapy for investigational use within 6 months prior to Baseline (Day 1).
11. Treatment with steroids (IV or oral corticosteroid treatment, including agents that may act through the corticosteroid pathway [e.g., low-dose naltrexone]) within 4 weeks (28 days) prior to Baseline (Day 1).

Note: Subjects who are currently using other approved disease modifying therapies (DMTs) for RRMS that are not excluded above may be included in the trial if all other criteria are met. Subjects must discontinue these other DMT treatments upon entry into the trial. A washout period is not required by the protocol, but investigators should follow their local standards of care to manage the transition from the existing treatment to BG00012.

Miscellaneous

12. Female subjects who are currently pregnant or breastfeeding, or planning to become pregnant while in the study.
13. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 6 months prior to the Baseline Visit.
14. Previous registration in this study.
15. Inability to comply with study requirements.
16. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

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9. ENROLLMENT, REGISTRATION, AND RANDOMIZATION

9.1. Screening and Enrollment

Subjects must provide informed consent before any screening tests are performed (see Section 17.3). When a subject signs the informed consent form (ICF), that subject is considered to be enrolled in the study. Subjects who have a nonclinically significant out-of-range laboratory result may be retested once to deem the eligibility per discretion of the Investigator.

Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and on the screening log.

9.2. Registration of Subjects

Subjects will be registered at Baseline (Day 1), after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. No subject may begin treatment prior to assignment of a unique identification number (registration). Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

Refer to the Study Reference Guide for details on registration.

9.3. Blinding Procedures

Not applicable. This is an open-label study.

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

10.1. Discontinuation of Study Treatment

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

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject experiences a medical emergency that necessitates permanent discontinuation of study treatment.
- The subject is unable to tolerate study treatment at 240 mg BID (see Section 11.2.4).
- The subject receives any concomitant medications not allowed by the protocol.
- The subject experiences any of the laboratory abnormalities requiring permanent discontinuation of treatment defined in Table 3.
- The subject experiences more than 1 deviation of the same laboratory parameter that meets the threshold limits defined in Table 3 at any time during the study.
- The subject experiences more than 2 different deviations of laboratory parameters that meet the threshold limits defined in Table 3 at any time during the study. On a third occasion, the subject is required to discontinue dosing for the remainder of the study.
- If a subject has a lymphocyte count $<500/\text{mm}^3$ persisting for more than 24 weeks consecutively, study treatment must be temporarily withheld. Study treatment may be resumed after lymphocyte counts recover. If the subject develops a lymphocyte count $<500/\text{mm}^3$ on 1 occasion (confirmed by repeat testing) on resumption of study treatment, the subject must permanently discontinue study treatment.
- If a subject's lymphocyte count remains $<\text{LLN}$ for 24 weeks consecutively after study treatment has been temporarily withheld due to lymphocyte count $<500/\text{mm}^3$ for more than 24 weeks, the subject must permanently discontinue study treatment.
- At the discretion of the Investigator for medical reasons or for noncompliance.

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

Subjects who discontinue treatment may remain in the study and continue protocol-required tests and assessments.

10.2. Withdrawal of Subjects From Study

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

- The subject is unable to tolerate study treatment at 240 mg BID (see Section [11.2.4](#)).
- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

For details regarding follow-up for subjects who discontinue study treatment or withdraw from the study, see Section [7.2.3](#).

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

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of Biogen.

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11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

BG00012 will be taken orally at a dose of 120 mg BID for the first 7 days and at a maintenance dose of 240 mg BID thereafter. Temporary dose reductions to 120 mg BID may be considered for individuals who do not tolerate the maintenance dose due to flushing and/or GI disturbances. Within 4 weeks, the recommended dose of 240 mg BID should be resumed. Subjects will receive treatment for 96 weeks.

Missed doses should be taken within 6 hours. If the subject does not remember to take the dose within 6 hours, this dose should be skipped, and the next dose should be taken as scheduled. Doses should not be doubled to make up for missed doses.

11.2. Modification of Dose and/or Treatment Schedule

11.2.1. Dosing Interruption for Abnormal Laboratory Values

Study treatment must be temporarily withheld when any of the following laboratory values meet the threshold limits defined in [Table 3](#); laboratory abnormalities that require immediate and permanent discontinuation of study treatment are also specified.

Table 3: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	$>3 \times \text{ULN}$	The Investigator should repeat the test as soon as possible. If the retest value confirms AST or ALT $>3 \times \text{ULN}$, the study treatment must be withheld. If the value remains $>3 \times \text{ULN}$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must <i>permanently</i> discontinue study treatment, and the event must be recorded as an AE.
Creatinine	$>1.2 \times \text{ULN}$	The Investigator should repeat the test as soon as possible. If the retest value confirms that creatinine is $>1.2 \times \text{ULN}$, the study treatment must be withheld. If the value remains $>1.2 \times \text{ULN}$ for ≥ 4 weeks after discontinuation of study treatment, then the subject must <i>permanently</i> discontinue study treatment, and the event must be recorded as an AE.

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Laboratory Parameter	Laboratory Result	Required Action
WBC	<2000/mm ³	The Investigator should repeat the test as soon as possible. If retest value confirms that WBC count is <2000/mm ³ , the study treatment must be withheld. If the value remains <2000/mm ³ for ≥4 weeks after discontinuation of study treatment, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.
Urine Cytology	Positive	Urine cytology must be performed on any subject who has hematuria of unknown etiology on 2 consecutive tests. If urine cytology is positive, then the subject must permanently discontinue study treatment, and the event must be recorded as an AE.

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal; WBC = white blood cell.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in Section 4.2 (and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice). In addition, subjects (whether dosing is temporarily withheld or permanently discontinued) must have the abnormal laboratory result retested at least every 2 weeks (retests will be run at the central laboratory) until resolution or stabilization of the laboratory value. Depending on the severity and clinical significance of the abnormality, the Investigator may need to perform the retests more frequently.

11.2.2. Resumption of Study Treatment Dosing

Resumption of study treatment is to be considered on a case-by-case basis and must be discussed with the Medical Monitor. However, subjects who have abnormal laboratory values, as described in Table 3, sustained on 3 consecutive occasions (i.e., for more than 4 consecutive weeks) must permanently discontinue study treatment (Section 10.1).

Subjects with abnormal laboratory values after Week 12 (after which clinic visits occur once every 3 months), who are allowed to resume study treatment dosing following a 2- to 4-week interruption, will restart dosing at a reduced dose for 1 week. Subjects must also return to the initial every-4-week visit schedule for safety assessments (see Section 14 for clinical and laboratory safety assessments) for 2 consecutive normal laboratory assessments before reverting to the every-3-month schedule. Subjects will take 120 mg BID for 1 week. After 1 week at the reduced dose, subjects will take 240 mg BID.

11.2.3. Subsequent Development of Additional Laboratory Abnormalities

Subjects who develop a subsequent abnormal value for the same laboratory parameter at any other time during the study must permanently discontinue dosing with study treatment, i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality. However,

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subjects who subsequently experience an abnormality of a different laboratory parameter can have study treatment withheld again. For example, if a subject had dosing temporarily withheld for an abnormal ALT/SGPT, then had dosing resumed after ALT/SGPT returned to acceptable limits, and subsequently developed abnormal white blood cells (WBCs), the subject may have study treatment withheld again. However, only 2 dosing interruptions are allowed for each subject.

Any subject who experiences abnormal laboratory results that meet the criteria defined in [Table 3](#) on a third occasion must permanently discontinue dosing.

11.2.4. Dosage Reductions

Dosage reduction will be allowed only for subjects who are unable to tolerate study treatment due to flushing and/or GI disturbances (dosage reductions will not be allowed for abnormal laboratory values; for management of abnormal laboratory values, refer to Sections [11.2.1](#), [11.2.2](#), and [11.2.3](#)). Subjects who do not tolerate study treatment will reduce their dosage by taking 120 mg BID for 4 weeks. After 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg BID. If the subject is still unable to tolerate study treatment, the subject must discontinue study treatment as described in Section [10.1](#). Subjects who do not tolerate study treatment will complete the final Follow-Up Visit 4 weeks after their last dose of study treatment and will then be withdrawn from the study (Section [10](#)).

11.3. Treatment Schedule for Subjects With Abnormal Lymphocyte Count

11.3.1. Schedule for Subjects With Lymphocyte Count $<500/\text{mm}^3$

Study treatment must be temporarily withheld when the laboratory value for lymphocyte count meets the threshold limits defined in [Table 4](#).

Table 4: Lymphocyte Count Criteria Requiring Withholding of Study Treatment

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte Count	$<500/\text{mm}^3$	<p>The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is $<500/\text{mm}^3$, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is $<500/\text{mm}^3$ for more than 24 weeks, study treatment must be temporarily withheld.</p> <p>All assessments should be performed at the central laboratory.</p>

While dosing is withheld, subjects will be followed every 4 weeks until the lymphocyte count is $\geq \text{LLN}$ or for 24 weeks after the last dose (whichever is sooner) [see Lymphocyte Follow-Up in [Table 2](#)]. If the lymphocyte count remains $< \text{LLN}$ for 24 weeks consecutively after the study

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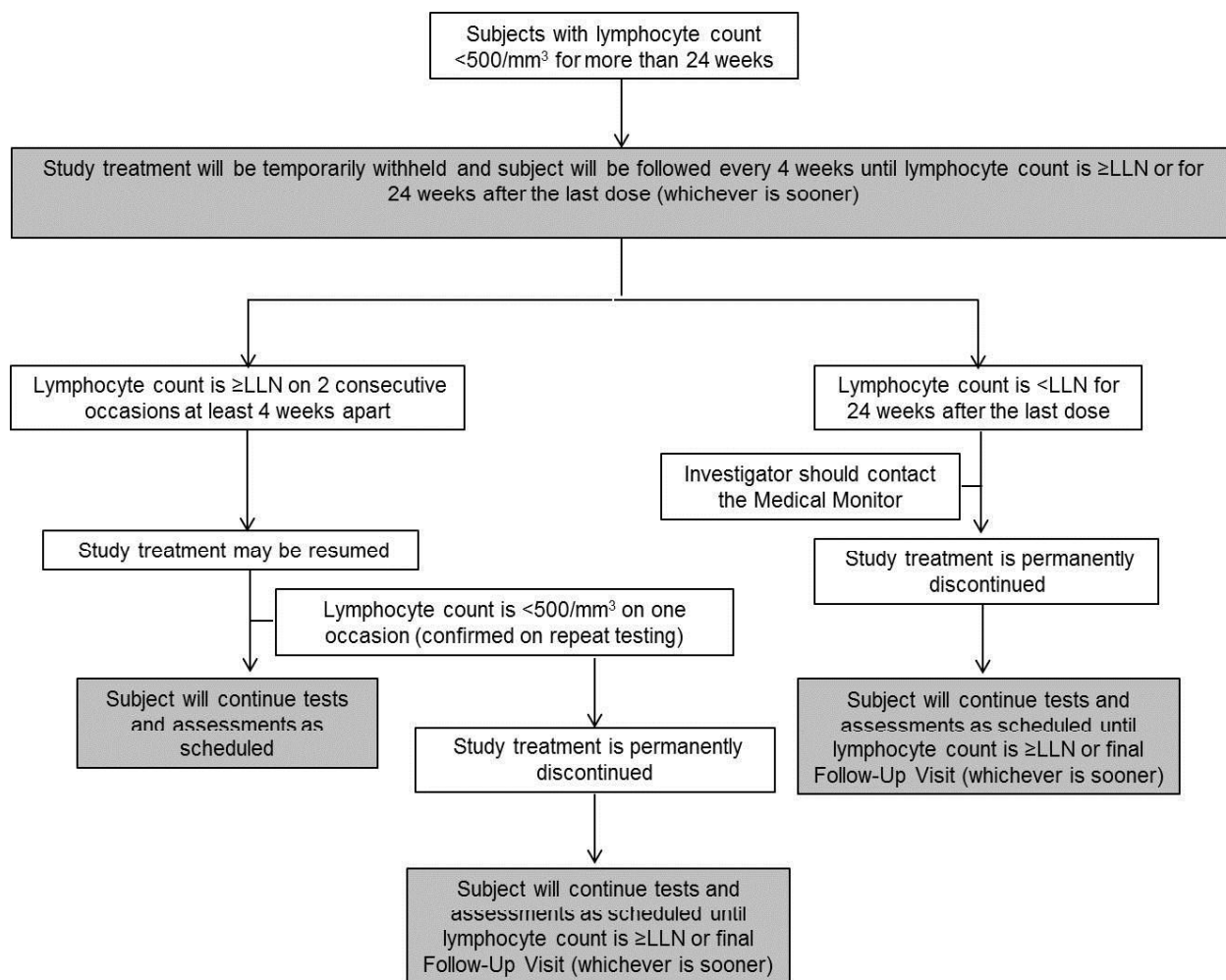
treatment is withheld, the subject should be permanently discontinued from study treatment, and the Investigator should contact the Medical Monitor.

Subjects who temporarily withhold study treatment due to decreases in lymphocyte count, as described in [Table 4](#), may resume study treatment when lymphocyte counts recover (defined as a lymphocyte count \geq LLN on 2 consecutive occasions at least 4 weeks apart). If the lymphocyte count is $<500/\text{mm}^3$ on 1 occasion (confirmed by repeat testing) on resumption of study treatment, then study treatment must be permanently discontinued. Subjects who discontinue study treatment due to lymphocyte count $<500/\text{mm}^3$ should continue tests and assessments according to the schedule defined in [Section 4](#) until the lymphocyte count recovers or until the final Follow-Up Visit (whichever is sooner).

See [Figure 2](#) for the treatment schedule of subjects with lymphocyte counts $<500/\text{mm}^3$.

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Figure 2: Schedule for Subjects With Lymphocyte Count $<500/\text{mm}^3$ 

LLN = lower limit of normal.

11.3.2. Schedule for Subjects With Lymphocyte Counts $<\text{LLN}$ to $\geq 500/\text{mm}^3$

Subjects with lymphocyte count $<\text{LLN}$ to $\geq 500/\text{mm}^3$ will have tests and assessments according to the schedule defined in Section 4. If these subjects complete, temporarily withhold, or permanently discontinue study treatment for any reason, they will be followed as described in Section 11.3.3.

11.3.3. Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have a Lymphocyte Count $<\text{LLN}$

Subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any other reason (see Section 11.2) and who have a lymphocyte count $<\text{LLN}$ will be followed every 4 weeks until the lymphocyte count is $\geq \text{LLN}$ or for 24 weeks after the last dose (whichever is

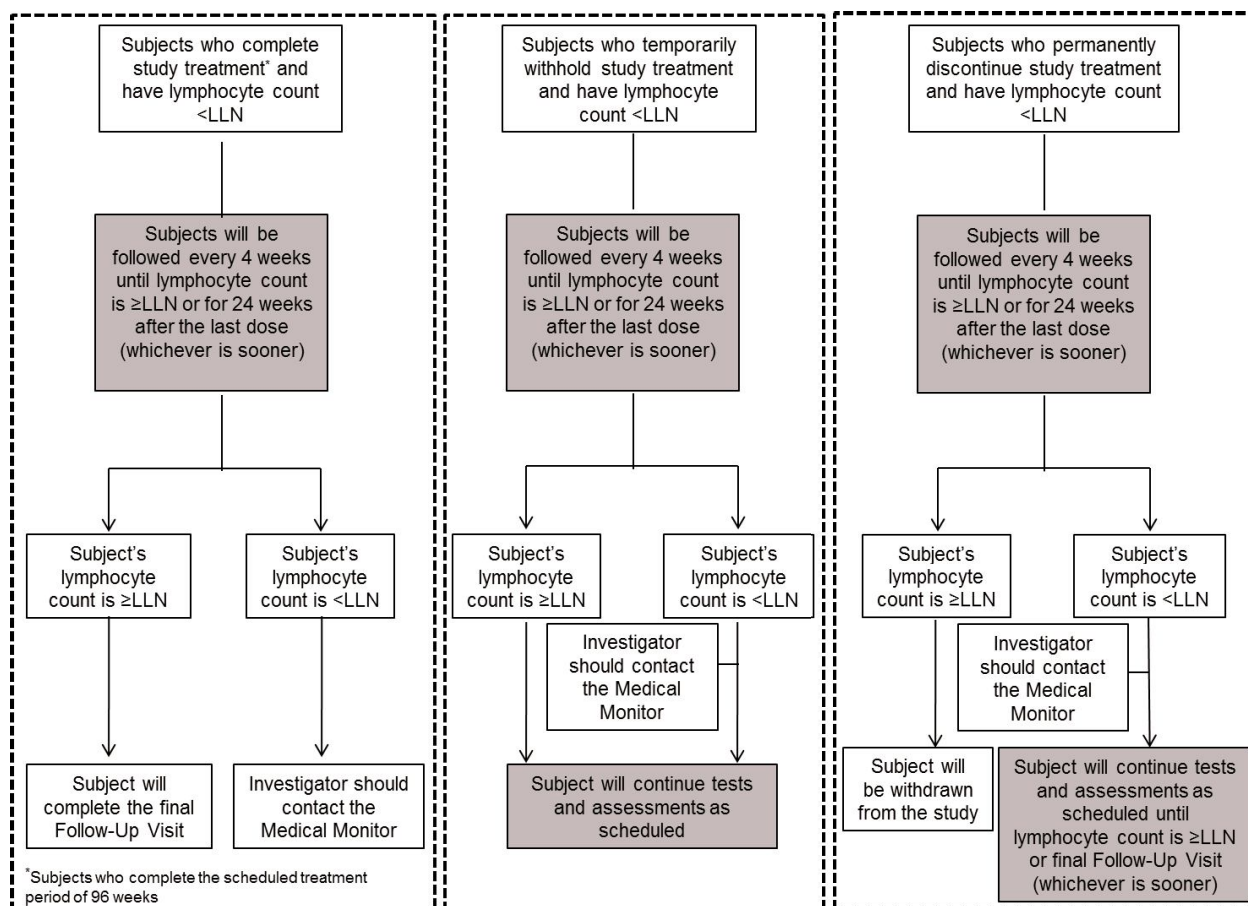
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sooner). Subjects who temporarily withhold or permanently discontinue study treatment and have a lymphocyte count $<LLN$ for 24 weeks should continue tests and assessments according to the schedule defined in Section 4 until the lymphocyte count recovers or until the final Follow-Up Visit (whichever is sooner).

See Figure 3 for a schedule of subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any other reason and who have a lymphocyte count $<LLN$.

Figure 3: Schedule for Subjects Who Complete, Temporarily Withhold, or Permanently Discontinue Study Treatment for Any Reason and Have Lymphocyte Count $<LLN$



LLN = lower limit of normal.

11.4. Precautions

Not applicable.

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11.5. Compliance

Compliance with treatment dosing is to be monitored and recorded by site staff. Compliance will be monitored by capsule count conducted by study personnel at protocol-scheduled visits.

11.6. Concomitant Therapy and Procedures

11.6.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the subject's Screening Visit and the subject's last study visit.

11.6.1.1. Allowed Concomitant Therapy

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, is not restricted but should be optimized as early as possible during Screening in an attempt to maintain consistent treatment for the duration of the study.

Subjects should be instructed not to start taking any new medications, including nonprescribed drugs, unless they have received permission from the Investigator.

11.6.1.2. Disallowed Concomitant Therapy

Concomitant treatment with any of the following is **not** allowed unless approved by the Medical Monitor:

- Any alternative drug treatments directed toward the treatment of MS, such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to, IFN- β , GA, natalizumab, cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products, etc.), with the exception of acute management of protocol-defined relapses (Section 11.6.3).
- Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.
- Any systemic steroid therapy, including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IVMP, except for protocol-defined treatment of relapses (Section 11.6.3). Steroids that are administered by nonsystemic routes (e.g., topical or inhaled) are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV Ig, plasmapheresis, or cytapheresis.

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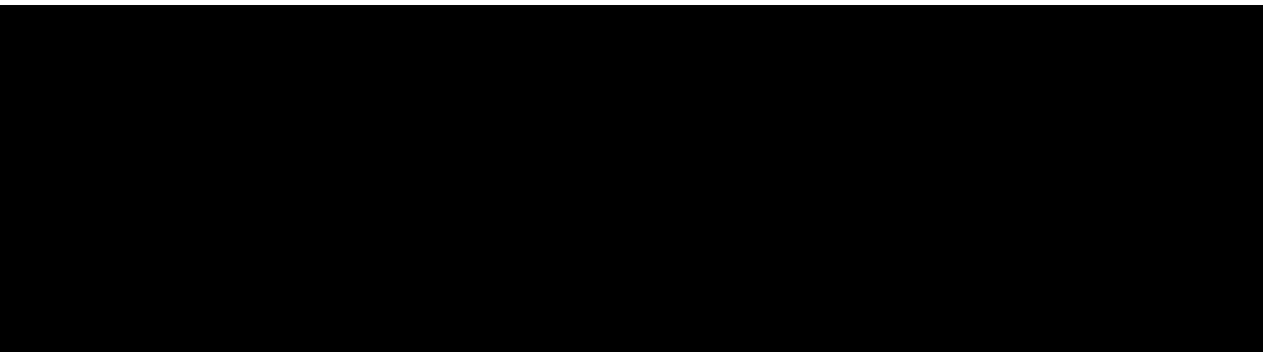
The use of concomitant therapies defined above must be recorded on the subject's CRF, according to instructions for CRF completion. AEs related to administration of these therapies must be documented on the appropriate CRF.

Subjects should be instructed not to start taking any new medications, including non-prescribed drugs, unless they have received permission from the Investigator.

11.6.2. Concomitant Procedures

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

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



11.7. Continuation of Treatment

No further provisions are made for access to the study treatment.

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12. STUDY TREATMENT MANAGEMENT

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

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

12.1. BG00012

BG00012 is a drug product formulated as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. Each capsule contains 120 mg BG00012.

Excipients for the manufacturing of the enteric-coated microtablets include microcrystalline cellulose, croscarmellose sodium, talc, colloidal anhydrous silica (colloidal silicon dioxide), magnesium stearate, triethyl citrate, methacrylic acid-methyl methacrylate copolymer, methacrylic acid-ethyl acrylate copolymer, simethicone, sodium lauryl sulfate, and polysorbate 80. Excipients for the manufacturing of the capsule shell include gelatin, titanium dioxide, and indigotin.

The contents of the study treatment label will be in accordance with all applicable regulatory requirements. Do not use study treatment after the expiration date unless a written notification of an expiration date extension is provided by Biogen.

12.1.1. BG00012 Preparation

The individual preparing BG00012 should carefully review the instructions provided in the DHA.

Drug wallets will be provided for the BG00012 treatment group to ensure that the appropriate treatment is provided to each subject. Drug wallets will be supplied from an Interactive Voice and Web Response System (IXRS) during the study so that the appropriate wallets are correctly dispensed to the subjects at the required timepoints throughout the study.

If the packaging is damaged or if there is anything unusual about the appearance or attributes of the drug wallet or drug, it should not be used. The drug wallet in question should be quarantined at the study site, and the problem should be immediately reported to Biogen.

12.1.2. BG00012 Storage

Study treatment must be stored in a secure location.

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BG00012 is to be stored at room temperature (15°C to 25°C or 59°F to 77°F), in a secured, locked cabinet with limited access. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. BG00012 Handling and Disposal

The Investigator must return all used and unused drug wallets of BG00012 as instructed by Biogen unless approved for onsite destruction.

If any BG00012 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen/contract research organization (CRO) by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen/CRO must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00012 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), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all drug wallets, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made between the amount of BG00012 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

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13. EFFICACY AND PHARMACODYNAMIC ASSESSMENTS

See Section 4 for the timing of all assessments.

13.1. Efficacy Assessments

Not applicable; the study is not designed to assess efficacy.

13.2. Pharmacodynamic Assessments

The following tests will be performed to assess the pharmacodynamic properties of BG00012:

- T cells, B cells, and natural killer (NK) cells
 - total T cells: CD4+ and CD8+
 - total B cells
 - total NK cells
- T regulatory (T_{reg}) cells, resting/naïve T_{reg}, and activated T_{reg}
- naïve T cells, effector T cells, central/effector memory T cells, and activated (expressing HLA DR/CD38) T cells
- dendritic cells, monocytes, and NK cells (CD56^{dim}/CD56^{bright})
- transitional B cells, naïve B cells, memory B cells (IgD+/IgD-), and plasmablast cells

13.3. Clinical Assessments

The following clinical assessments will be performed:

- [REDACTED]
- [REDACTED]

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14. SAFETY ASSESSMENTS

Refer to Section 4 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BG00012:

- AEs, SAEs, and concomitant therapy and procedures recording
- physical examinations, including body weight and height
- vital sign measurements, including diastolic and systolic blood pressure, heart rate, body temperature, and respiratory rate. Subjects must remain in a supine or seated position for 5 minutes prior to having heart rate and blood pressure taken.
- 12-lead electrocardiogram (ECG) readings

14.2. Laboratory Safety Assessments

The following laboratory assessments will be performed to evaluate the safety profile of BG00012:

- hematology parameters: hemoglobin, hematocrit, red blood cell count, WBC count (with differential), and platelet count
- blood chemistry parameters: albumin, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT/SPGT, AST/SGOT, blood urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose

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15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

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

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

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value 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 an 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

15.1.2. Serious Adverse Event

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

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

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- Results in persistent or significant disability/incapacity
- 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.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.
- The severity of the event as defined in Section 15.2.3.

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15.2.2. Relationship of Events to Study Treatment

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

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

15.2.3. Severity of Events

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

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

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the final Follow-Up Visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

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15.3.2. Serious Adverse Events

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

Subjects will be followed for all SAEs until the final Follow-Up Visit. Thereafter, the event should be reported to Biogen or designee only if the Investigator considers the SAE to be related to study treatment.

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

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen 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 SAE that occurs between the time that the subject has signed the ICF and the final Follow-Up Visit must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of the event. Thereafter, the event should be reported only if the Investigator considers it related to study treatment.

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

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

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

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15.3.3.1. Deaths

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

15.3.4. Suspected Unexpected Serious Adverse Reactions

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

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

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 30 days after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy by faxing the appropriate form to Biogen or designee within 24 hours of the study site staff becoming aware of the pregnancy at the fax number provided in the Study Reference Guide. The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee.

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

15.4.2. Overdose

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

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15.4.3. Medical Emergency

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

15.4.3.1. Unblinding for Medical Emergency

Not applicable.

15.5. Contraception Requirements

Subjects of childbearing potential must practice effective contraception (as determined by the Investigator) during the study and be willing and able to continue contraception for 30 days after their last dose of study treatment. In addition, male subjects should not donate sperm for the duration of the study and for at least 30 days after their last dose of study treatment.

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

- Postmenopausal
 - 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL
 - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 or more of the following:

For females:

- Established use of oral, injected, or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception with use of a spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

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- Male surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate). (For female subjects participating in the study, male sexual partners must have undergone surgical sterilization.)

For males:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms with spermicide.

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

Pregnancy reporting is described in Section [15.4.1](#).

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

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

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15.6.2. Biogen

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

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16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

16.1. Pharmacokinetics

Not applicable.

16.2. Pharmacodynamics

16.2.1. Analysis Population

The pharmacodynamic population is defined as all subjects who receive at least 1 dose of study treatment and have at least 1 pharmacodynamic measurement after Baseline.

16.2.2. Methods of Analysis

Statistical analyses will be [REDACTED] and descriptive in nature, with appropriate measures of precision provided where applicable. There is no planned statistical hypothesis testing in this study.

16.2.2.1. Analysis of the Primary Endpoint

Counts and change from Baseline in counts for each of the lymphocyte subsets will be descriptively summarized at each applicable visit. Furthermore, the primary endpoints will be summarized in various ALC subgroups to evaluate the nature of change in each subset in relation to the change in ALC. Additionally, a mixed model for repeated measures (MMRM) will be used, which will be fit with the change from Baseline for each of the lymphocyte subsets as the dependent variable and will include ALC subgroups, visit, corresponding Baseline counts, age, gender, and ALC groups-by-visit interaction as fixed effects to estimate the difference between ALC subgroups. Point estimates and 2-sided 90% confidence intervals (CIs) will be derived from the model. Appropriate transformation may be performed based on the distribution of data.

ALC subgroups of interest include (1) subjects who have all ALC values \geq LLN up to Week 48, (2) subjects who have at least 1 ALC value $<$ LLN over 48 weeks, and (3) subjects who have at least 2 ALC values $<$ LLN over 48 weeks. Additional subgroups will be further defined in the Statistical Analysis Plan.

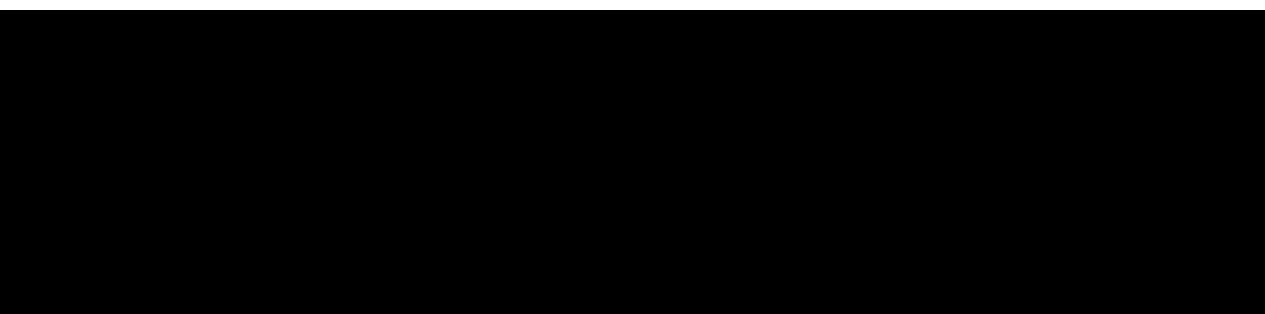
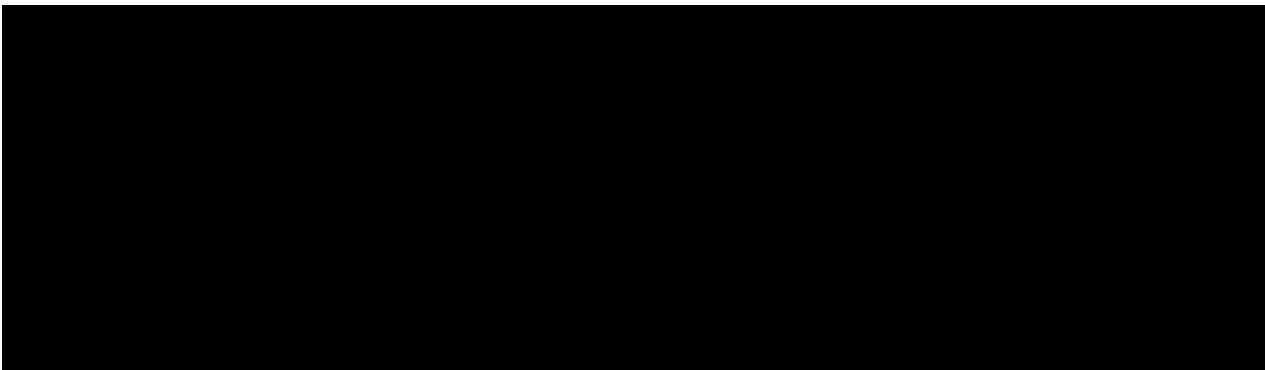
16.2.2.2. Analysis of the Secondary Endpoints

For the secondary endpoints (IgG isotypes and ALCs), actual values and change from Baseline will be descriptively summarized at each applicable visit. In addition, the same type of MMRM used for analysis of primary endpoints will be employed, which will be fit with the change from

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Baseline in each of the IgG isotypes and ALCs as the dependent variable and will include visit, corresponding baseline value, age, and gender as fixed effects.



16.4. Safety

16.4.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment.

16.4.2. Methods of Analysis

All AEs, concomitant therapy and procedures, clinical laboratory results, physical examinations, vital signs, and 12-lead ECG readings data will be evaluated for safety.

16.4.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only treatment-emergent AEs will be presented in the summary tables. Treatment emergent is defined as having an onset date on or after start of study treatment or having worsened after the start of study treatment.

Subject incidences of all AEs, SAEs, AEs leading to treatment discontinuation and study withdrawal, and other AEs of special interest will be tabulated by system organ class and preferred term in descending order of frequency.

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16.4.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology and blood chemistry. Laboratory data will be summarized using shift tables. Each laboratory value for each subject will be flagged as “low,” “normal,” or “high,” relative to the parameter’s normal range. For each parameter, the number (percentage) of subjects experiencing post-Baseline shifts to “low” or “high” based on their minimum or maximum values at any time postdose will be summarized. In addition, a summary of laboratory values categorized based on Common Toxicity Criteria grade will also be generated. Summary statistics for actual values and change from Baseline will also be presented for quantitative laboratory data.

16.4.2.3. Physical Examinations

The analyses of physical examinations will include summary statistics (actual value and change from Baseline for body weight and height) over time by visit.

16.4.2.4. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-Baseline abnormalities will be presented by group.

The definitions of these clinically relevant abnormalities are shown in [Table 5](#).

Table 5: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Criteria for Abnormalities
Temperature	>38°C or an increase from Baseline of $\geq 1^{\circ}\text{C}$
Pulse	>120 bpm or an increase from Baseline of >20 bpm <50 bpm or a decrease from Baseline of >20 bpm
Systolic Blood Pressure	>180 mmHg or an increase from Baseline of >40 mmHg <90 mmHg or a decrease from Baseline of >30 mmHg
Diastolic Blood Pressure	>105 mmHg or an increase from Baseline of >30 mmHg <50 mmHg or a decrease from Baseline of >20 mmHg

The analyses of vital signs will also include summary statistics (actual value and change from Baseline for temperature, pulse, and systolic and diastolic blood pressure) over time by visit.

16.4.2.5. ECG Data

A listing of subjects with abnormal ECG status will be presented. Changes from Baseline in ECG will be summarized using shift tables. The number and percentage of subjects with shifts to categorical values (abnormal, not AE/abnormal, AE) will be summarized.

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16.5. Clinical Assessments

16.5.1. Analysis Population

The evaluable population for clinical assessments is defined as all subjects who receive at least 1 dose of study treatment and at least 1 measurement for each of the clinical assessments after Baseline.

16.6. Interim Analyses

Interim analyses may be performed to support regulatory filings and/or publications and will be documented in the Statistical Analysis Plan.

16.7. Sample Size Considerations

The sample size for this study is not based on formal hypothesis testing but on the precision of the estimation of the primary endpoints and the ratios between various ALC subgroups.

For example, the Phase 2 and 3 controlled and uncontrolled efficacy and safety studies in MS, based on data available as of May 2014 from 2470 subjects with at least 1 post-Baseline value from the interim analysis of the Integrated Summary of Safety of Tecfidera, showed that 76% of subjects had all ALC values \geq LLN and 24% had at least 1 ALC value $<$ LLN up to Week 48. Assuming the same proportion of subjects in this study will have 1 or more ALC values $<$ LLN, it is expected that approximately 137 subjects will have all ALC values \geq LLN and approximately 43 subjects will have at least 1 ALC value $<$ LLN at Week 48, based on a total of 180 evaluable subjects at Week 48. With this sample size, the 90% CIs for the ratio of the 2 subgroups for the change from Baseline at Week 48 in lymphocyte subsets are illustrated below using the scenario of a true ratio of 0.8 (20% decrease) and 0.7 (30% decrease), respectively. When assessing lymphocyte subsets between subjects with at least 2 ALC values $<$ LLN up to the first 48 weeks

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of treatment versus subjects who have all ALC values \geq LLN throughout the study, the 90% CIs of the ratio would be wider, as historical data suggest that 16% of the patients treated with Tecfidera may have 2 or more ALC values $<$ LLN during the first 48 weeks of treatment.

To allow for a 10% discontinuation rate, a total of 200 subjects are planned for enrollment.

Table 6: Sample Size Calculations

Primary Endpoints	SD ¹	Ratio	90% CI for the Ratio Based on N = 180	
			Subjects With At Least 1 ALC $<$ LLN ² vs. Subjects With All ALC \geq LLN ²	Subjects With At Least 2 ALC $<$ LLN ² vs. Subjects With All ALC \geq LLN ²
CD4 T cell count	0.32	0.8	0.73, 0.88	0.71, 0.90
		0.7	0.63, 0.77	0.63, 0.78
CD8 T cell count	0.35	0.8	0.72, 0.89	0.71, 0.91
		0.7	0.63, 0.78	0.62, 0.79
CD56 ^{bright} NK cell count	0.57	0.8	0.68, 0.95	0.65, 0.98
		0.7	0.59, 0.83	0.57, 0.86
T _{reg} count	0.95	0.8	0.60, 1.07	0.57, 1.12
		0.7	0.52, 0.93	0.50, 0.98

ALC = absolute lymphocyte count; CD = cluster of differentiation; CI = confidence interval; LLN = lower limit of normal; NK = natural killer; SD = standard deviation; T_{reg} = T regulatory; vs. = versus.

¹ Common standard deviation for the log-transformed change from Baseline.

² Up to Week 48.

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17. ETHICAL REQUIREMENTS

Biogen, [REDACTED], and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

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

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

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

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

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

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

17.3. Subject Information and Consent

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

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or subject's legally authorized representative (e.g., parent or legal guardian), 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. The signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

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

17.4. Subject Data Protection

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

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 partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

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

17.6. Conflict of Interest

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

17.7. Registration of Study and Disclosure of Study Results

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

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18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

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

18.2. Quality Assurance

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

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor will visit the Investigator at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

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

18.5. Publications

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

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19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

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

19.1.2. Interactive Response Technology

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

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool supported by iMedidata RAVE and configured by [REDACTED].

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Biogen to analyze the laboratory samples collected for this study.

19.2. Study Committees

Not applicable. Given the established safety and efficacy of DMF via the Phase 2 and Phase 3 studies, advisory committees were deemed not necessary for this study.

19.3. Changes to Final Study Protocol

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

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

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

19.4. Ethics Committee Notification of Study Completion or Termination

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

19.5. 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 offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

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

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, “An Open-Label Study to Assess the Effects of BG00012 on Lymphocyte Subsets in Subjects With Relapsing-Remitting Multiple Sclerosis,” and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Investigator’s Signature

Date

Investigator’s Name (Print)

Study Site (Print)

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