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

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

PROTOCOL NUMBER: 109MS303 / NCT00835770

STUDY PHASE: 3b

PROTOCOL TITLE: A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

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1. CONTACT LIST

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
USA

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

1.1. Biogen Personnel

For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide 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.

SIGNATURE PAGE

Protocol 109MS303, Version 8.0 was approved by:

[redacted] 12 Feb 2018

[redacted] MD Date

[redacted]

Biogen

SIGNATURE PAGE

Protocol 109MS303, Version 8.0 was approved by:

[redacted] 09 Feb 2018

[redacted] PharmD Date

[redacted]

Biogen

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ARR	annualized relapse rate
AST	aspartate transaminase
BID	twice a day
CD	cluster of differentiation
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
DCC	Data Coordinating Center
DHA	Directions for Handling and Administration
DMF	dimethyl fumarate
[redacted]	[redacted]
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol EQ-5D Health Survey
FAE	fumaric acid ester
GA	glatiramer acetate
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyl-transferase
GI	gastrointestinal
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
IVMP	intravenous methylprednisolone
IXRS	Interactive Voice and Web Response System
LLN	lower limit of normal
MMF	monomethyl fumarate
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTR	magnetization transfer ratio
PBMC	peripheral blood mononuclear cell
PHI	Protected Health Information
QD	once daily
[redacted]	[redacted]
RRMS	relapsing-remitting MS
SAE	serious adverse event
SF-36®	Short-form 36 Health Survey
SUSAR	suspected unexpected serious adverse reaction
TID	3 times a day

TNF	tumor necrosis factor
ULN	upper limit of normal
WBC	white blood cell

3. SYNOPSIS

Protocol Number:	109MS303
Version Number:	8
Protocol Title:	A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis
Study Phase:	3b
Rationale for the Study:	This study will extend BG00012 therapy from Biogen Studies 109MS301 and 109MS302. This extension will further evaluate the long-term safety and efficacy profile of BG00012 monotherapy.
Rationale for the Dose and Schedule Selection:	The initial BG00012 dosage for the extension study (240 mg twice a day [BID] or 240 mg 3 times a day [TID]) was the same as that used in the Phase 3 Studies 109MS301 and 109MS302. BG00012 has since been approved in several countries for the treatment of multiple sclerosis (MS) at a dose of 240 mg BID. For this reason, all subjects continuing in this extension study are currently receiving the currently marketed dose of 240 mg BID. Subjects randomized to BG00012 240 mg TID were switched to BID dosing following BG00012 approval.
Study Design:	Multicenter parallel-group, randomized, dose-blind, dose-comparison phase, followed by an open-label phase.
Duration of Study Participation:	It is intended that eligible subjects from Studies 109MS301 and 109MS302 will be followed for at least 8 years in this extension study, assuming BG00012 continues to have a positive benefit-risk ratio.
Study Location:	Global; approximately 300 sites

Study Objectives:	Primary: To evaluate the long-term safety profile of BG00012. Additional: To evaluate the long-term efficacy of BG00012 using clinical endpoints (including relapse and annualized relapse rate [ARR]) and disability progression (Expanded Disability Status Scale [EDSS]). To evaluate further the long-term effects of BG00012 on MS brain lesions on magnetic resonance imaging (MRI) scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of gadolinium-enhancing lesions, number of new or newly-enlarging T2 lesions and volume of total T2 lesions, number of new T1 hypointense lesions and volume of T1 hypointense lesions, brain atrophy, and magnetization transfer ratio (MTR). To evaluate the long-term effects of BG00012 on health economics assessments and the visual function test. The endpoints are the Short-form 36 Health Survey (SF-36®) and EuroQol EQ-5D Health Survey (EQ-5D) quality of life questionnaire, and the visual function test scores.
Number of Planned Subjects:	Approximately 1700 subjects will be enrolled.
Sample Size Determination:	There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Studies 109MS301 and 109MS302.
Study Population:	Subjects who participated in and completed as per protocol previous BG00012 clinical studies 109MS301 or 109MS302, including those subjects who received an open-label, approved MS therapy and completed the modified visit schedule, are eligible to participate in this study. Reasons for study exclusion include: • Any significant change in medical history in subjects from 109MS301 or 109MS302, including laboratory tests, or current clinically significant condition that in the opinion of the Investigator would have excluded the subjects' participation from their previous study. The Investigator must re-review the subject's medical fitness for participation and consider any diseases that would preclude treatment. • Subjects from 109MS301 or 109MS302 who discontinued BG00012 due to an adverse event (AE) or due to reasons other than protocol-defined relapse/disability progression. • Subjects from 109MS301 or 109MS302 who discontinued BG00012 due to disability progression or relapses and did not follow the modified visit schedule up to Week 96.

- Alanine transaminase (ALT), aspartate transaminase (AST), or gamma-glutamyl-transferase >3 times the upper limit of normal (ULN).

Treatment Groups:

At enrollment into the study, all subjects received either:

- BG00012 240 mg BID (2 capsules [120 mg each] twice a day and 2 placebo capsules once a day).

OR

- BG00012 240 mg TID (2 capsules [120 mg each] 3 times a day).

Subjects randomized to BG00012 in Study 109MS301 or 109MS302 continued on the same BG000012 dose in this extension study.

Subjects randomized to placebo in Study 109MS301 or 109MS302 or glatiramer acetate in Study 109MS302 were randomized to BG00012 in a 1:1 ratio to 240 mg BID or 240 mg TID in this extension study.

Subjects who switched to an alternate approved MS therapy in Study 109MS301 or 109MS302 were randomized in this extension study as outlined above according to their original treatment group in 109MS301 or 109MS302.

All subjects continuing in this extension study are currently receiving the currently marketed dose of BG00012 240 mg BID. Subjects randomized to 240 mg TID were switched to BID dosing following BG00012 approval.

Visit Schedule:

Eligible subjects will be enrolled at Week 96 (Visit 24) of their previous BG00012 study (109MS301 or 109MS302), which will serve as the Baseline Visit for this extension study. If the Baseline Visit cannot be combined with Visit 24 of their previous BG00012 study, subjects may be randomized within 6 months of Visit 24, provided that they are still eligible for enrollment.

Subjects will report to the study site every 4 weeks for the first 24 weeks (Visit 1 through Visit 6) and every 12 weeks thereafter.

- Subjects who reach Week 384 (Visit 36) should complete an End of Study Visit 4 weeks later (Week 388).
- Subjects who already completed Visit 36 should complete an End of Study Visit 4 weeks after their next visit (scheduled or unscheduled).
- Subjects who permanently discontinue BG00012 prior to Week 384 (Visit 36) should complete a Premature Study Treatment Withdrawal Visit within 4 weeks of their last dose. The Premature Study Treatment Withdrawal Visit will serve as the End of Study Visit.

Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count less than the lower limit of normal (<LLN) should not be withdrawn from the study. These subjects will be followed

	according to Section 11.3.
Discontinuation of Study Treatment/Withdrawal from Study:	A subject must permanently discontinue BG00012 and be withdrawn from the study for any of the following reasons: • The subject becomes pregnant. Treatment must be discontinued immediately. • The subject desires to discontinue treatment and/or to discontinue participation under this protocol. • The subject experiences a medical emergency that necessitates permanent discontinuation of treatment. • The subject develops >3×ULN elevations in ALT or AST that are sustained for 4 consecutive weeks after BG00012 has been withheld. • The subject experiences more than 1 deviation of the same laboratory parameter that requires temporary withholding as defined in Table 1 at any time during the study. • The subject experiences more than 2 different deviations of laboratory parameters that require temporary withholding as defined in Table 1 at any time during the study. On a third occasion, the subject must permanently discontinue dosing. • The subject cannot tolerate BG00012. • The subject receives any of the disallowed concomitant medications. • The subject is unwilling or unable to comply with the protocol. • At the discretion of the Investigator for medical reasons or for noncompliance. NOTE: Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any of the aforementioned reasons and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.
Efficacy Assessments:	Relapse assessment, EDSS, MRI analysis (on subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6), visual function as measured by low-contrast Sloan letter charts.
Health Economic Assessments:	SF-36, EQ-5D Quality of Life questionnaire.
Safety Assessments:	Physical examination, including vital signs, blood chemistry, hematology, urinalysis, urine cytology, and AE monitoring.
Statistical Analysis:	Efficacy: ARR will be summarized for the extension study, as well as from the original baseline of the Phase 3 studies (i.e., extension study + 2 years in the previous Phase 3 studies). A negative binomial regression model will be used for the

	analysis of ARR. In addition to ARR, disability progression, proportion of subjects relapsed, visual function test scores, and MRI endpoints will also be analyzed. The Cox proportional hazards model will be used for the analysis of time to relapse/proportion relapsed and disability progression. Visual function test will be analyzed by an analysis of covariance (ANCOVA) model. For MRI endpoints, analyses will be conducted on all MRI data collected up through and including Amendment 6 of this protocol: the number of lesions will be analyzed by logit regression, and the volume of lesions, brain atrophy, and MTR will be analyzed by ANCOVA models. Safety: Safety data will be summarized for the extension study for all treatment groups. Long-term safety data (extension study + 2 years in the previous Phase 3 studies) will be summarized by treatment groups. In addition, analysis by 3- or 6-month intervals may also be performed. Lymphocyte count and lymphocyte subset data will be summarized by timepoints on BG00012 as well as post-treatment timepoints for subjects who permanently discontinue BG00012. Health Economics: Actual scores and change from baseline in EQ-5D and SF-36 will be analyzed by ANCOVA model.
Interim Analysis:	Interim analyses may be performed as needed.
End of Study:	The end of study is Last Patient, Last Visit for final collection of data for the primary outcome.

4. STUDY ACTIVITIES 109MS303

4.1. Study Activities (Year 1 Visits)

Tests and Assessments[1]	Baseline Visit (Day 1)[2]	Visit 1 (Week 4 ±5 days)	Visit 2 (Week 8 ±5 days)	Visit 3 (Week 12 ±5 days)	Visit 4 (Week 16 ±5 days)	Visit 5 (Week 20 ±5 days)	Visit 6 (Week 24 ±5 days)	Visit 7 (Week 36 ±7 days)	Visit 8 (Week 48 ±7 days)
Informed Consent	X								
Randomization	X								
Medical History Update	X								
Physical Examination	X						X		X
Vital Signs	X	X	X	X	X	X	X	X	X
Hematology	X			X			X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[3]	X	X	X	X	X	X	X	X	X
Urinalysis	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Brain MRI[5] Scan ± Gd[6]	Scheduled MRI scans were performed in protocol versions 1 through 6.								
EDSS	X			X[7]			X		X
Visual Function Test	X						X		X
SF-36 and EQ-5D	X								X
Dispense Study Treatment (BG00012)	X	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6								
AE/SAE Reporting	Monitor and record throughout the study as per Section 15								

AE = adverse event; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol EQ-5D Health Survey; Gd = gadolinium; MRI = magnetic resonance imaging; SAE = serious adverse event; SF-36 = Short-form 36 Health Survey.

1. Tests and assessments must be completed prior to BG00012 distribution.
2. The Week 96 visit (Visit 24) for 109MS301 and 109MS302 will serve as the Baseline Visit for this extension study; activities should be completed (where appropriate) by staff of the parent study.
3. For women of childbearing potential. Results must be known prior to BG00012 distribution.
4. If urinalysis is abnormal, see Section 11.2.
5. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.
6. MRI must not be performed within 30 days of receiving a course of steroids.
7. To be performed only for subjects who at the Week 96 visit (Visit 24) in 109MS301 or 109MS302 had a 1.0 point increase in their EDSS score from a baseline EDSS ≥1.0 or a 1.5 point increase in their EDSS from a baseline EDSS = 0.

4.2. Study Activities (Years 2 and 3 Treatment Visits)

Year	Year 2				Year 3			
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Study Week (±7 days)	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**
Tests and Assessments[1]								
Physical Examination	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X
Urinalysis	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Brain MRI[4] Scan ± Gd[5]	Scheduled MRI scans were performed in protocol versions 1 through 6.							
EDSS	X	X	X	X	X	X	X	X
Visual Function Test	X	X	X	X	X	X	X	X
SF-36 and EQ-5D				X				X
Dispense Study Treatment (BG0012)	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6							
AE/SAE Reporting	Monitor and record throughout the study as per Section 15							

AE = adverse event; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol EQ-5D Health Survey; Gd = gadolinium; MRI = magnetic resonance imaging; SAE = serious adverse event; SF-36 = Short-form 36 Health Survey.

1. Tests and assessments must be completed prior to BG00012 distribution.
2. For women of childbearing potential. Results must be known prior to BG00012 distribution.
3. If urinalysis is abnormal, see Section 11.2.
4. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.
5. MRI must not be performed within 30 days of receiving a course of steroids.

4.3. Study Activities (Years 4 Through 8 Treatment Visits)

Year	Year 4				Year 5				Year 6				Year 7				Year 8			
Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36[1]**
Study Week (±7 days)	**156**	**168**	**180**	**192**	**204**	**216**	**228**	**240**	**252**	**264**	**276**	**288**	**300**	**312**	**324**	**336**	**348**	**360**	**372**	**384**
Tests and Assessments[2]																				
Physical Examination		X		X		X		X		X		X		X		X		X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	See Section 4.5																			
Blood Chemistry		X		X		X		X		X		X		X		X		X		X
[redacted]																				
Urine Pregnancy Test[3]		X		X		X		X		X		X		X		X		X		X
Urinalysis		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]		X[4]
Brain MRI[5] Scan ± Gd[6]	Scheduled MRI scans were performed in protocol versions 1 through 6.																			
EDSS		X		X		X		X		X		X		X		X		X		X
Visual Function Test		X		X		X		X		X		X		X		X		X		X
SF-36 and EQ-5D				X				X				X				X				X
Dispense Study Treatment (BG00012)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6																			
AE/SAE Reporting	Monitor and record throughout the study as per Section 15																			

AE = adverse event; CRF = case report form[redacted]; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol EQ-5D Health Survey; Gd = gadolinium; MRI = magnetic resonance imaging; [redacted]; SAE = serious adverse event; SF-36 = Short-form 36 Health Survey.

1. For subjects who have already completed Visit 36 (or beyond), an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study.
2. Tests and assessments must be completed prior to BG00012 distribution.
3. For women of childbearing potential. Results must be known prior to BG00012 distribution.
4. If urinalysis is abnormal, see Section 11.2.
5. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.

6. MRI must not be performed within 30 days of receiving a course of steroids.
7. The date and Study Visit/Week at which subjects are switched to open-label treatment should be recorded on the dosing CRF.

4.4. Study Activities for Subjects Who Already Completed Visit 36

For subjects who have already completed Visit 36 (or beyond) prior to Protocol Version 8, an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study. For subjects who have not completed Visit 36 prior to Protocol Version 8, Visit 36 will serve as the last scheduled Visit and an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study.

Year	Year 9				Year 10				Year 11				Year 12			
Visit	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
Study Week (±7 days)	396	408	420	432	444	456	468	480	492	504	516	528	540	552	564	576
Tests and Assessments[1]																
Physical Examination		X		X		X		X		X		X		X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	See Section 4.5															
Blood Chemistry		X		X		X		X		X		X		X		X
[redacted]																
Urine Pregnancy Test[2]		X		X		X		X		X		X		X		X
Urinalysis		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]
Brain MRI[4] Scan ± Gd[5]	Scheduled MRI scans were performed in protocol versions 1 through 6.															
EDSS		X		X		X		X		X		X		X		X
Visual Function Test		X		X		X		X		X		X		X		X
SF-36 and EQ-5D				X				X				X				X
Dispense Study Treatment (BG00012)[76]																
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6															
AE/SAE Reporting	Monitor and record throughout the study as per Section 15															

AE = adverse event; CRF = case report form; [redacted]; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol EQ-5D Health Survey; Gd = gadolinium; MRI = magnetic resonance imaging; [redacted]; SAE = serious adverse event; SF-36 = Short-form 36 Health Survey.

1. Tests and assessments must be completed prior to BG00012 distribution.
2. For women of childbearing potential. Results must be known prior to BG00012 distribution.
3. If urinalysis is abnormal, see Section 11.2.
4. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.
5. MRI must not be performed within 30 days of receiving a course of steroids.
6. The date and Study Visit/Week at which subjects are switched to open-label treatment should be recorded on the dosing CRF.

4.5. Study Activities (Hematology [redacted] Analysis: Year 4 Through End of Treatment Visits)

Tests and Assessments	Subjects With Lymphocyte Count ≥LLN	Subjects With Lymphocyte Count <LLN to ≥500/mm^3	Subjects With Lymphocyte Count <500/mm^3
Hematology	Every 12 weeks	Every 12 weeks	Every 4 or 12 weeks per Table 3
[redacted]			
Bone Marrow Biopsy (optional)	Not applicable	Not applicable	Optional procedure[6]

[redacted]; LLN = lower limit of normal; [redacted]

6. See Section 11.3 for further details.

4.6. Study Activities (Unscheduled and Post-Treatment Visits)

Tests and Assessments	End of Study Visit[1]	Unscheduled Relapse Assessment Visit[2]	Premature Study Treatment Withdrawal Visit[3]	Lymphocyte Follow-Up (Up to 96 Weeks After Last Dose)[4]
Physical Examination		X	X	
Vital Signs	X	X	X	X
Hematology	X[3]	X	X[3]	X
Blood Chemistry	X	X	X	
Urine Pregnancy Test[5]	X	X	X	
Urinalysis	X[6]	X[6]	X[6]	
Brain MRI[7] Scan ± Gd[8]	Scheduled MRI scans were performed in protocol versions 1 through 6.			
EDSS		X	X	
Visual Function Test		X	X	
SF-36 and EQ-5D		X	X	
Relapse Assessment		X		
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6			
AE/SAE Reporting	Monitor and record throughout the study as per Section 15			

AE = adverse event; EDSS = Expanded Disability Status Scale; EQ-5D = EuroQol EQ-5D Health Survey; Gd = gadolinium; LLN = lower limit of normal; MRI = magnetic resonance imaging; SAE = serious adverse event; SF-36 = Short-form 36 Health Survey.

1. For subjects who have already completed Visit 36 or beyond, an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled).
2. Unscheduled Relapse Assessment Visit is to be carried out within 5 days of suspected relapse.
3. Subjects who permanently discontinue BG00012 prior to Week 384 (Visit 36) should complete a Premature Study Treatment Withdrawal Visit within 4 weeks of their last dose. The Premature Study Treatment Withdrawal Visit will serve as the End of Study Visit..
4. Lymphocyte follow-up as per Section 11.3.
5. For women of childbearing potential.
6. If urinalysis is abnormal, see Section 11.2.
7. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.
8. MRI must not be performed within 30 days of receiving a course of steroid.

5. INTRODUCTION

5.1. Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects approximately 400,000 persons in North America and 365,000 persons in Europe. It is predominantly a disease of young adults, primarily women, with disease onset typically occurring between the ages of 20 and 40.

In most cases, subjects with relapsing-remitting MS (RRMS) experience discrete episodes of neurologic dysfunction (referred to as relapses, exacerbations, or attacks), each lasting several days to several weeks, which occur intermittently over many years. Symptoms of such relapses include loss of vision or double vision, numbness or tingling sensation in the extremities, muscle weakness, slurred speech, difficulty with coordination, and bladder dysfunction. Early in the course of this phase of the disease, these symptoms tend to subside completely after each attack. Over time, recovery from attacks tends to be incomplete, leading to the accumulation of functional disability. The majority of patients eventually develop the secondary progressive form of MS, which is characterized by the progressive accumulation of disability, with or without occasional relapses, minor remissions, and plateaus. Approximately half of all MS patients will be unable to walk without assistance within 15 years of their initial diagnosis [Weinshenker 1989].

MS primarily affects myelinated fiber tracts. Histologically, it is characterized by focal areas of demyelination, astrogliosis, the relative preservation of axons, and varying degrees of inflammation.

Although the etiology of MS is uncertain, there is evidence that autoimmunity to myelin constituents plays a central role in the development of the MS lesion. First, myelin breakdown products can be detected in macrophages in the MS lesion and in the cerebrospinal fluid (CSF) [Cohen 1976; Prineas 1990]. Second, the MS lesion has many features of a delayed-type hypersensitivity reaction [Traugott and Lebon 1988; Traugott 1983]. Lymphokines and cytokines (interferon [IFN]-gamma, tumor necrosis factor [TNF]-alpha, IL-1), activated cluster of differentiation (CD)4+ and CD8+ T cells, mononuclear phagocytes (macrophages, microglia, and monocytes) expressing variable levels of class II major histocompatibility complex antigens, and upregulation of leukocyte and vascular cell adhesion molecules have all been demonstrated within lesions [Ffrench-Constant 1994; Hartung 1995]. Third, CSF from MS patients shows intrathecal synthesis of immunoglobulins with restricted heterogeneity [Walsh and Tourtellotte 1986] and an increased frequency of autoreactive T cells secreting IFN-gamma in response to myelin proteins [Soderstrom 1993]. Fourth, agents with immunomodulatory properties, such as IFN-beta have been shown to impede the accumulation of lesions, decrease the frequency of relapses, and slow the progression of disability in MS.

5.2. Profile of Previous Experience with Fumarates

Biogen is evaluating BG00012 for the treatment of MS. BG00012 is a drug product formulated as enteric-coated microtablets in gelatin capsules (blue and white) for oral administration. Each

capsule contains 120 mg dimethyl fumarate (DMF). DMF is an odorless, white, crystalline powder.

Fumaric acid and fumaric acid derivatives have been used for over 30 years as topical and oral long-term treatments for psoriasis. Early oral therapies using fumaric acid derivatives were based on unapproved formulations. Doses and modes of preparation varied among pharmacies. Clinical studies have demonstrated the efficacy and relative safety of fumaric acid esters (FAEs). Two open-label, long-term trials showed significant improvement in psoriasis treated with FAEs, including FUMADERM®, for up to 3 years [Balasubramaniam 2004]. In 1994, Fumapharm AG gained approval in Germany for marketing of the oral compound, FUMADERM®, containing DMF and ethyl hydrogen fumarate formulated as an enteric-coated, unit-size tablet. Since then, FUMADERM® has become widely used as a systemic anti-psoriatic agent in Germany.

Treatment with FAEs would appear from the trials to be relatively safe compared with the risks known to be associated with other systemic treatments for psoriasis [Balasubramaniam 2004]. The most common side effects observed with FUMADERM® are flushing and gastrointestinal (GI) disorders. Changes in liver enzymes and serum creatinine have only rarely been reported [Balasubramaniam 2004]. To develop a monosubstance FAE and to potentially improve on the overall tolerability versus FUMADERM®, Fumapharm AG developed a new formulation of the drug, BG00012. BG00012 is formulated for oral administration as enteric-coated microtablets comprising 120 mg DMF contained in a gelatin capsule.

Function of DMF

The exact mechanism of action by which DMF exerts its effects in MS and psoriasis is still unclear. Nevertheless, the effectiveness of FAEs may be attributed to the following actions of DMF and monomethyl fumarate (MMF), its primary metabolite. FAEs may have both anti-inflammatory and neuroprotective effects. In vitro experiments have shown that FAEs can influence the expression of cytokines and adhesion molecules that are thought to be involved in the inflammatory cascade (including IL-4, IL-2, TNF-alpha, E-selectin, etc.). In addition, preliminary data have also implicated DMF in the regulation of a novel pathway for MS therapeutics: induction of the expression of Phase II detoxifying enzymes. This pathway is central to protection of cells from metabolic and inflammatory stress.

Clinical Safety in Healthy Volunteers

In Phase 1 clinical studies with FUMADERM® and BG00012, the most common adverse events (AEs) were flushing, pruritus, GI disturbance (diarrhea and stomach pain), myalgia, dizziness, and headache. BG00012 produced significantly less GI disturbance than FUMADERM®; this improvement was attributed to the formulation of BG00012. In other clinical studies of BG00012, co-administration with food was shown to delay the maximum concentration of MMF from approximately 2 hours (fasting) to approximately 5 hours (non-fasting). The overall exposures (area under the curve) remained equivalent.

Clinical Safety in Multiple Sclerosis

BG00012 has been developed as an oral treatment for MS and was previously studied in psoriasis and rheumatoid arthritis. As of September 2013, data were available for reporting from 2513 subjects with MS who participated in the controlled and/or uncontrolled Phase 2 and 3

safety and efficacy studies (Studies C-1900, 109MS301, 109MS302, and 109MS303) and were exposed to BG00012 accounting for approximately 6100 subject-years of exposure.

In a Phase 2, randomized, placebo-controlled study of BG00012 in RRMS (Study C-1900), subjects received BG00012 (120 mg once daily [QD] to 240 mg 3 times a day [TID]) or placebo for 24 weeks in Part 1 of the study. In the Part 2 extension phase of the study, subjects who received placebo in Part 1 received BG00012 240 mg TID. Overall, the most commonly observed events were flushing, MS relapse, nasopharyngitis, headache, nausea, diarrhea, fatigue, pruritus, upper abdominal pain, influenza, and hot flush.

Study 109MS301 was a Phase 3, double-blind, placebo-controlled, dose-comparison study designed to determine the efficacy and safety of BG00012 in subjects with RRMS. Subjects were randomized at a 1:1:1 ratio to receive BG00012 240 mg twice a day (BID; 2 × 120 mg BID and 2 placebo capsules QD), BG00012 240 mg TID (2 × 120 mg capsules TID), or placebo (2 capsules TID).

Study 109MS302 was a Phase 3, double-blind, placebo-controlled, dose comparison, active reference comparator study in subjects with RRMS. A total of 1430 subjects were randomized at a 1:1:1:1 ratio at 200 sites in 28 countries worldwide, and 363, 359, 345, and 350 subjects received at least 1 dose of placebo, BG00012 BID, BG00012 TID, and glatiramer acetate (GA), respectively.

The duration of BG00012 administration in both studies was 96 weeks. Clinic visits occurred every 4 weeks, with the End of Study Visit at Week 96 for subjects who chose to enroll in this protocol and at Week 100 for subjects who chose not to enroll in this protocol. The safety profile of BG00012 was similar in Studies 109MS301 and 109MS302. Across both studies, the commonly reported AEs in the BG00012 BID group included flushing and hot flush, GI events (diarrhea, nausea, abdominal pain upper, abdominal pain, vomiting, and dyspepsia), skin events (pruritus, rash, and erythema), albumin urine present, aspartate transaminase (AST) increased, and lymphopenia.

Clinical Efficacy in Multiple Sclerosis

An open-label, investigator-initiated, pilot study of FUMADERM® in 10 subjects with RRMS demonstrated a robust reduction of the median number of gadolinium (Gd)-enhancing lesions on T1 brain magnetic resonance imaging (MRI) from 8 to 2 ($p<0.05$) at Week 18 of therapy (equivalent DMF dose of 720 mg per day). Pharmacodynamic measures of T-cell function in this study demonstrated alterations in T_H1/T_H2 cytokine ratios and circulating TNF. All AEs were reported as mild and reversible.

In Study C-1900, subjects treated with 240 mg TID of BG00012 had a 69% reduction in the mean number of new Gd-enhancing lesions versus placebo as measured monthly from Weeks 12 to 24 of the study. In addition, subjects treated with BG00012 240 mg TID had a 44% reduction in the mean number of new Gd+ lesions versus placebo as measured monthly from Weeks 4 to 24 of the study. Subjects treated with BG00012 240 mg TID also demonstrated treatment advantages over placebo for other MRI parameters: a 48% reduction in the mean number of new or newly enlarging T2-hyperintense lesions versus placebo as measured at Week 24 of the study; a 53% reduction in the mean number of new T1-hypointense lesions versus placebo as measured at Week 24 of the study. Although the study was not powered to evaluate the effects of

BG00012 on clinical measures, clinical efficacy endpoints of the intent-to-treat population were evaluated as exploratory measures. There was a trend towards a reduction in annualized relapse rate (ARR) in the BG00012 240 mg TID group with a 32% reduction in the ARR (240 mg TID vs. placebo: 0.44 vs. 0.65, which was not statistically significant [the study was not powered to detect a difference]). This corresponded to a 24% reduction on the proportion of relapsing subjects, but this also failed to reach statistical significance (19% vs. 25%, p=0.524).

A post hoc analysis of the evolution of new Gd-enhancing lesions at Weeks 4, 8, and 12 evolving into T1-hypointense lesions on the post-Gd Week 24 scan was performed and showed a reduced probability of conversion of Gd lesions into T1-hypointense lesions comparing BG00012 240 mg TID with placebo (odds ratio 0.51; 95% CI 0.43–0.61; p<0.0001).

In the placebo-controlled Phase 3 clinical study, Study 109MS301, treatment with BG00012 240 mg BID and TID over 2 years significantly reduced the occurrence of clinical exacerbations, reduced the risk of confirmed (12-week) disability progression, and improved nearly all MRI measures of MS disease activity, compared with placebo. In Study 109MS302, treatment with BG00012, administered as 240 mg BID or TID, significantly reduced clinical relapses over the 2-year treatment period (as assessed by the ARR, the proportion of subjects relapsed, and the time to first relapse) and improved nearly all MRI measures of disease activity, compared with placebo. A clinically meaningful, non-statistically significant reduction in disability progression was observed in both the BG00012 BID and TID groups, with reductions in the risk of confirmed disability progression (as measured by Expanded Disability Status Scale [EDSS] score). BG00012 showed efficacy across all prespecified subgroups. The efficacy of GA treatment was consistent with its approved labeling and the results described in the published literature [Fox 2012].

Additional information on BG00012 is found in the BG00012 Investigator's Brochure and in the TECFIDERA prescribing information (where commercially available).

5.3. Study Rationale

This study will extend BG00012 therapy from Biogen Studies 109MS301 and 109MS302. This extension study will further evaluate the long-term safety and efficacy profile of BG00012 monotherapy.

5.4. Dose Rationale

The initial BG00012 dosage for the extension study (240 mg BID or 240 mg TID) was the same as that used in the Phase 3 Studies 109MS301 and 109MS302. Subsequent to the initiation of this study, BG00012 was approved in several countries for the treatment of MS at a dose of 240 mg BID. For this reason, all subjects continuing in this extension study are currently receiving the currently marketed dose of 240 mg BID. Subjects randomized to BG00012 240 mg TID were switched to BID dosing following BG00012 approval.

6. OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety profile of BG00012.

6.2. Additional Objectives

Secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of BG00012 using clinical endpoints (including relapse and ARR) and disability progression (EDSS).
- To evaluate further the long-term effects of BG00012 on MS brain lesions on MRI scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of Gd-enhancing lesions, number of new or newly-enlarging T2 lesions and volume of total T2 lesions, number of new T1 hypointense lesions and volume of T1 hypointense lesions, brain atrophy, and magnetization transfer ratio (MTR).
- To evaluate the long-term effects of BG00012 on health economics assessments and the visual function test. The endpoints are the Short-form 36 Health Survey (SF-36®) and EuroQol EQ-5D Health Survey (EQ-5D) quality of life questionnaire, and the visual function test scores.

Exploratory objectives of this study are as follows:

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

7. STUDY DESIGN

7.1. Study Overview

This first phase of this extension study is a multicenter, parallel-group, randomized, dose-blind, dose-comparison. The second phase of the study is an open-label phase during which all subjects receive BG00012 at a dose of 240 mg BID. Approximately 1700 subjects have been enrolled at approximately 375 sites in North America, Europe, and the rest of the world.

It is intended that eligible subjects from Studies 109MS301 and 109MS302 will be followed for at least 8 years in this extension study, assuming BG00012 continues to have a positive benefit-risk ratio. At enrollment into the study, all subjects received either:

- BG00012 240 mg BID (2 capsules [120 mg each] twice a day and 2 placebo capsules once a day).

  OR

- BG00012 240 mg TID (2 capsules [120 mg each] 3 times a day).

Subjects randomized to BG00012 in Study 109MS301 or 109MS302 continued on the same BG00012 dose in this extension study.

Subjects randomized to placebo in Study 109MS301 or 109MS302 or to GA in Study 109MS302 were randomized to BG00012 240 mg BID or 240 mg TID at a 1:1 ratio in this extension study.

Subjects who switched to an alternate approved MS therapy in Study 109MS301 or 109MS302 were randomized in this extension study as outlined above according to their original treatment group in Study 109MS301 or 109MS302.

All subjects continuing in this extension study are currently receiving the currently marketed dose of BG00012 240 mg BID (2 capsules [120 mg each] BID). Subjects randomized to BG00012 240 mg TID were switched to BID dosing (2 capsules [120 mg each] BID) following BG00012 approval.

Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count less than the lower limit of normal (<LLN) should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

7.2. Overall Study Duration and Follow-Up

7.2.1. Baseline

Eligible subjects will be enrolled at Week 96 (Visit 24) of their previous BG00012 study (109MS301 or 109MS302), which will serve as the Baseline Visit for this extension study. If the Baseline Visit cannot be combined with Visit 24 of their previous BG00012 study, subjects may be randomized within 6 months of Visit 24, provided that they are still eligible for enrollment. Baseline Visit assessments may need to be repeated if there is a gap in BG00012.

7.2.2. Treatment Period

Subjects will report to the study site every 4 weeks for the first 24 weeks (Visit 1 through Visit 6) and every 12 weeks thereafter.

Premature Study Treatment Withdrawal Visits and Unscheduled Relapse Assessment Visits will be performed as necessary. All efforts should be made to keep the subjects' visit schedule relative to their Baseline Visit (Day 1). Unscheduled Relapse Assessment Visits should not modify or replace their regular visit schedule.

7.2.3. Post-Treatment Period

Subjects who complete the Week 384 visit (Visit 36), regardless of further need to monitor lymphocytes on study, will complete an End of Study Visit at Week 388 ± 7 days. For subjects who have already completed Visit 36, an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study. Subjects who permanently discontinue BG00012 prior to Week 384, regardless of further need to monitor lymphocytes on study, will complete a Premature Study Treatment Withdrawal Visit within 4 weeks after their last dose of BG00012. Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

7.3. Relapses

Suspected relapses during this study will be reviewed and confirmed according to the protocol by the *treating neurologist*. Relapses are defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the *treating neurologist*. The subject must have objective signs on the *treating neurologist's* examination confirming the event. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse, and should not be treated with steroids. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse should be considered part of the same relapse and would not be treated with corticosteroid therapy within the protocol.

Subjects who experience new neurologic symptoms must contact the *treating nurse* or *treating neurologist* within 48 hours of the onset of symptoms to schedule an Unscheduled Relapse Assessment Visit. The subject will then be evaluated in person by the *treating neurologist* within 5 days of the onset of the potential relapse. The *treating neurologist* is to perform a relapse assessment and obtain an EDSS score. New objective findings on neurological examination performed by the *treating neurologist* are required to determine if a protocol-defined relapse has occurred. Subjects may not begin corticosteroid treatment of the relapse per protocol until the *treating neurologist* has examined them.

Treatment of an acute event of relapse as described in Section 11.6.1 may proceed at the discretion of the *treating neurologist* and will not affect the subject's eligibility to continue in the study.

7.4. Disability Progression

Disability progression can only be assessed from the EDSS scores performed as per the protocol-defined schedule of assessments at regular visits. The study staff must evaluate EDSS scores to determine if a subject experiences at least a 1.0 point increase on the EDSS from a baseline EDSS ≥1.0 that is sustained for 24 weeks or a 1.5 point increase on the EDSS from a baseline EDSS = 0 that is sustained for 24 weeks. In either case, the subject must be informed they have experienced a worsening of physical disability.

7.5. Study Stopping Rules

Biogen MA Inc. may terminate this study, after informing Investigators, at any time. Investigators will be notified by Biogen or designee if the study is placed on hold, completed, or closed.

7.6. End of Study

The end of study is defined as the Last Patient, Last Visit for final collection of data for the primary outcome.

8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of the Baseline Visit:

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
2. Subjects who participated in and completed as per protocol previous BG00012 clinical studies 109MS301 or 109MS302, including those subjects who received an open-label, approved MS therapy, and completed the modified visit schedule.
3. All male subjects and female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of BG00012. For further details of contraceptive requirements for this study, please refer to Section 15.5.3.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of the Baseline Visit:

1. Any significant change in medical history in subjects from 109MS301 or 109MS302, including laboratory tests, or current clinically significant condition that in the opinion of the Investigator would have excluded the subjects' participation from their previous study. The Investigator must re-review the subject's medical fitness for participation and consider any diseases that would preclude treatment.
2. Subjects from 109MS301 or 109MS302 who discontinued BG00012 due to an AE or due to reasons other than protocol-defined relapse/disability progression.
3. Subjects from 109MS301 or 109MS302 who discontinued BG00012 due to disability progression or relapses and did not follow the modified visit schedule up to Week 96.
4. History of malignancy.
5. History of severe allergic or anaphylactic reactions.
6. Alanine transaminase (ALT), AST, or gamma-glutamyl-transferase (GGT) >3 times the upper limit of normal (ULN).
7. Female subjects considering becoming pregnant while in the study, currently pregnant, or breast feeding.
8. Previous participation in this study (109MS303).
9. Unwillingness or inability to comply with the requirements of the protocol including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the protocol.

10. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

9. ENROLLMENT AND RANDOMIZATION PROCEDURES

9.1. Enrollment Procedures

Once the investigational site has been activated for study participation, subjects may be enrolled if they have met the inclusion and exclusion criteria. Subjects will be enrolled at Week 96 (Visit 24) of their previous BG00012 study, which will serve as the Baseline Visit for this extension study.

9.2. Randomization and Registration Procedures

Subjects were randomized after the Investigator verified they were eligible per criteria in Sections 8.1 and 8.2. Subjects who were randomized to BG00012 in Study 109MS301 or 109MS302 continued in the same dose group for this extension study. Subjects who were randomized to placebo in Study 109MS301 or 109MS302 or to GA in Study 109MS302 were randomized in this extension study as outlined in Section 7.1 according to their original treatment group in Study 109MS301 or 109MS302.

Each subject retained the subject identification number assigned to him/her in the previous BG00012 study. The subject's identification number was used on all of that subject's case report forms (CRFs).

9.3. Blinding Procedures

As sites still had subjects participating in the Phase 3 studies when subjects began to enroll in this extension study, measures were taken to preserve the blind for the Phase 3 studies during the dose-blind phase of the extension study. All subjects were to take 1 capsule TID for the first week of the extension study and 2 capsules TID from Day 8.

During the dose-blind phase, all study staff and subjects were blinded to subject treatment group, except when a subject experienced a medical emergency that required dose unblinding of the subject's randomized treatment assignment.

In addition, separate study personnel were designated to conduct efficacy assessments and to treat subjects in order to protect against perceived dose unblinding of treatment assignment. Roles and responsibilities of study personnel are described in Section 14.1.

All subjects continuing in this extension study are to receive open-label BG00012 240 mg BID. Consequently, subjects and study staff are no longer blinded to dose assignment but will remain blinded to the BG00012 dose that subjects were receiving before the open-label treatment, as well as to the treatment arm of the subject in the parent study.

10. BG00012 DESCRIPTION AND ALLOCATION

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

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, simeticone, sodium laurilsulfate, and polysorbate 80. Excipients for the manufacturing of the capsule shell include gelatin, titanium dioxide, and indigotine.

The label will include conditions for storage, lot number, and other pertinent information such as manufacturer, batch/lot number, and caution statement. Depending on country requirements, the Investigator's name may also appear on the label.

BG00012 is to be stored at 15 to 25°C in a secure location, preferably a monitored, locked cabinet. Accountability for BG00012 is the responsibility of the Investigator. More details concerning this responsibility are included in Section 10.2.

Study site staff should refer to the Directions for Handling and Administration (DHA) located in the Study Reference Guide for specific instructions on the handling and administration of BG00012. The individual dispensing BG00012 should first carefully review the instructions provided in the DHA, which supersedes all other references (e.g., Investigator's Brochure or commercial product prescribing information).

BG00012 must only be dispensed by qualified study staff and is to be dispensed only to subjects enrolled in this study. Do not use BG00012 after the expiration date unless a written notification of an expiration date extension is provided by Biogen. Once BG00012 is dispensed to a subject, it can only be taken by that subject.

10.1. BG00012 Packaging

The qualified study staff will dispense to subjects at least a 4-week supply of BG00012 at the Baseline Visit and at each subsequent study visit (excluding the End of Study Visit, Premature Study Treatment Withdrawal Visit, and the Unscheduled Relapse Assessment Visit).

BG00012 is provided in drug wallets identified by kit numbers supplied from an Interactive Voice and Web Response System (IXRS) at specific timepoints during the study.

During the dose-blind phase, BG00012 kits included 6 capsules per day (2 capsules each for the morning, noon, and evening doses). During the open-label treatment, the noon dose is eliminated, and the new kit will include 4 capsules per day (2 capsules each for the morning and evening doses).

10.2. BG00012 Accountability

The study site must maintain accurate records demonstrating dates and amount of BG00012 received, to whom dispensed (subject-by-subject accounting), amount returned by subject, and

accounts of any BG00012 accidentally or deliberately destroyed. The date (Study Visit/Week) that each subject switched to open-label treatment with 240 mg BID should also be recorded in the CRF.

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

The Investigator must return all unused capsules of BG00012 as instructed by Biogen. If any BG00012 supplies are to be destroyed at the site, the institution/Principal Investigator(s) must obtain prior approval by Biogen. After such destruction, the institution/Principal Investigator(s) must notify Biogen, in writing, of the method of destruction, the date of destruction, and the location of destruction.

11. TREATMENT

11.1. Treatment Schedule

At enrollment into the study, all subjects received either:

- BG00012 240 mg BID (2 capsules [120 mg each] twice a day and 2 placebo capsules once a day).

  OR

- BG00012 240 mg TID (2 capsules [120 mg each] 3 times a day).

Subjects randomized to BG00012 in Study 109MS301 or 109MS302 continued on the same BG00012 dose in this extension study.

Subjects randomized to placebo in Study 109MS301 or 109MS302 or to GA in Study 109MS302 were randomized to BG00012 240 mg BID or 240 mg TID at a 1:1 ratio in this extension study.

Subjects who switched to an alternate approved MS therapy in Study 109MS301 or 109MS302 were randomized in this extension study as outlined above according to their original treatment group in Study 109MS301 or 109MS302.

All subjects continuing in the extension study are currently receiving the currently marketed dose of BG00012 240 mg BID (2 capsules [120 mg each] BID). Subjects randomized to BG00012 240 mg TID were switched to BID dosing (2 capsules [120 mg each] BID) following BG00012 approval.

Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

11.2. Modification of Treatment Schedule

11.2.1. Abnormal Laboratory Values: Dosing Interruption and Management

BG00012 must be temporarily withheld when any of the following laboratory values meet the criteria defined in Table 1. Subjects are required to have additional evaluation when any of the following laboratory values meet the threshold limits defined in Table 2.

Table 1: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of BG00012

Laboratory Parameter	Laboratory Result	Required Action
AST or ALT	>3×ULN	The Investigator should repeat the test as soon as possible. If re-test value confirms AST or ALT >3×ULN, BG00012 must be withheld. If the value remains >3×ULN for ≥4 weeks after discontinuation of BG00012, then the subject **must *permanently* discontinue** BG00012**.**
Lymphocyte counts	<500/mm^3	See Table 3.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

While dosing is withheld, subjects will continue tests and assessments according to the schedule defined in the protocol (Section 4), and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice. Subjects who have abnormal laboratory results other than described in Table 1 must repeat the tests within 2 weeks (repeat tests will be run at the central laboratory). Abnormal laboratory results confirmed on repeat tests should be managed per the Investigator's standard practice.

Subjects who subsequently develop the same abnormal laboratory value at any other time during the study must permanently discontinue dosing with BG00012, i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality (see Table 1). However, subjects who subsequently experience a different laboratory abnormality can have BG00012 withheld again, allowing. 2 dosing interruptions for each subject. Any subject who experiences abnormal laboratory results that require temporary withholding as defined in Table 1 on a third occasion must permanently discontinue dosing.

Subjects who complete BG00012 or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN will be followed according to Section 11.3.

Table 2: Laboratory Analyses That Require Additional Evaluation

Laboratory Parameter	Laboratory Result	Required Action
Urinalysis	Urinary casts (other than hyaline casts)	Repeat test 2 weeks later; if the abnormality persists on re-testing, the subject should be followed as per standard of care.
Urinalysis	Glycosuria (trace or greater)	If occurring in the setting of normal serum glucose, repeat test 2 weeks later; if the abnormality persists on re-testing, the subject should be followed as per standard of care.

Laboratory Parameter	Laboratory Result	Required Action
Urinalysis	Proteinuria 1+	Subjects who demonstrate 1+ proteinuria (and do not have a documented history of benign proteinuria) should be re-tested within 2 weeks of initial abnormal finding. If the abnormality persists on re-testing, the subject should be followed as per standard of care.

11.2.2. Dosage Reductions

Dosage reduction will be allowed only for subjects who are unable to tolerate BG00012 *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 Section 11.2.1). Subjects who do not tolerate BG00012 will reduce their dosage by taking one 120-mg capsule BID for 4 weeks. After 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg (two 120 mg capsules) BID. If the subject is still unable to tolerate BG00012, the subject must discontinue BG00012 and be withdrawn from the study as described in Section 11.2.

11.2.3. Resumption of BG00012 Dosing

Subjects who have temporarily withheld BG00012 due to lymphopenia may resume BG00012 according to Section 11.3.

Subjects who are allowed to resume BG00012 dosing following a 2- to 4-week interruption due to *flushing and/or GI disturbances* will restart dosing at a reduced dosage for 1 week. Subjects will take one 120 mg capsule BID for 1 week. After 1 week at the reduced dose, subjects will resume taking two 120 mg capsules BID.

11.3. Monitoring and Management for Subjects with Abnormal Lymphocyte Count

Subjects who have a lymphocyte count <500/mm^3 at any time should be monitored and managed according to Table 3.

All subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason other than those specified in Table 3, and who have a lymphocyte count <LLN, will be monitored every 12 weeks until their lymphocyte count is ≥LLN OR for 48 weeks after their last dose, whichever is earlier.

Table 3: Lymphocyte Monitoring and Management for Subjects Who Have a Lymphocyte Count <500/mm^3

For subjects who have a lymphocyte count <500/mm^3, the Investigator should repeat the test as soon as possible. If re-test confirms that the lymphocyte count remains <500/mm^3, lymphocyte counts should be monitored every 4 weeks while on BG00012.

If subject has lymphocyte counts <500/mm^3 for ≥24 weeks, subject meets the **Temporary Withholding Rule** and BG00012 will be temporarily withheld. If the Temporary Withholding Rule is not met, the subject will be monitored every 12 weeks.

Lymphocyte Monitoring for Subjects Meeting the Temporary Withholding Rule	Management for Subjects Meeting the Temporary Withholding Rule
The subject will be monitored every 4 weeks for 24 weeks, then every 12 weeks until the lymphocyte count is ≥LLN OR for 96 weeks after their last dose, whichever is earlier. However, if a subject reaches the end of study and their lymphocyte count remains <LLN, the subject will be monitored every 12 weeks until the lymphocyte count is ≥LLN OR for 48 weeks after their last dose, whichever is earlier.	• If lymphocyte count remains **<500/mm^3 for 24 weeks** after temporary withdrawal, BG00012 must be permanently discontinued. • If lymphocyte count is between **≥500/mm^3 and ≤800/mm^3**, then BG00012 will continue to be temporarily withheld. • If lymphocyte count recovers to **>800/mm^3** (confirmed by 2 tests, at least 4 weeks apart), the physician/patient has the option to restart BG00012. If, upon resumption of BG00012, the lymphocyte count is <500/mm^3 on 1 occasion (confirmed by repeat testing), then BG00012 must be permanently discontinued. • Alternative disease-modifying treatment[a] may be considered, at the discretion of the treating physician as per standard of care. Subjects treated with alternative disease-modifying treatment will not have the option to restart BG00012.

AE = adverse event; CRF = case report form; LLN = lower limit of normal.
[a] The use of concomitant therapies as defined above must be recorded on the subject's CRF, according to instructions for CRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate CRF.

Optional hematology consult and/or bone marrow biopsy may be considered for subjects meeting the Temporary Withholding Rule at the discretion of the Investigator. Earlier hematology consult and/or bone marrow biopsy may be considered in consultation with the Medical Monitor.

11.4. Removal of Subjects from Treatment and Withdrawal from Study

Unless otherwise indicated, a subject *must* permanently discontinue BG00012 and be withdrawn from the study for any of the following reasons:

- The subject becomes pregnant. Treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.5.4.
- The subject desires to discontinue treatment and/or to discontinue participation under this protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.

- The subject develops >3×ULN elevations in ALT or AST that are sustained for 4 consecutive weeks after BG00012 has been withheld.
- The subject experiences more than one 1 deviation of the same laboratory parameter that requires temporary withholding as defined in Table 1 at any time during the study.
- The subject experiences more than 2 different deviations of laboratory parameters that require temporary withholding as defined in Table 1 at any time during the study. On a third occasion, the subject must permanently discontinue dosing.
- The subject cannot tolerate BG00012.
- The subject receives any of the disallowed concomitant medications described in Section 11.6.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons or for noncompliance.

NOTE: Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any of the aforementioned reasons and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

The date(s) and reason(s) for discontinuation of treatment and withdrawal from the study must be recorded in the subject's CRF. Subjects who permanently discontinue BG00012 prior to Week 384, regardless of further need to monitor lymphocytes on study, will complete a Premature Study Treatment Withdrawal Visit within 4 weeks of their last dose.

11.5. Treatment 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

A concomitant therapy is any drug or substance administered from the time of the subject's written consent until the subject's End of Study Visit.

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study until the subject's End of Study Visit, unless the subject is being followed for study-related toxicity.

Concomitant treatment with any of the following is *not* allowed unless otherwise described in this protocol:

- 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-beta, IFN-alpha, GA, natalizumab, fingolimod, teriflunomide, cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products, etc.), with the exception of acute management of protocol-defined relapse (as

described below) and subjects with prolonged lymphopenia (as described in Section 11.3).

- 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 intravenous methylprednisolone (IVMP), except for protocol-defined treatment of relapses as described below. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) or systemic steroid therapy for limited, short-term treatment of general medical conditions are allowed.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, intravenous immunoglobulin, plasmapheresis, or cytapheresis.

Subjects who receive any of these restricted medications will be required to discontinue permanently BG00012 and will be withdrawn from the study unless otherwise described in this protocol as outlined in Section 11.2.

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 non-prescribed drugs.

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

11.6.1. Treatment of Relapses on Scheduled or Unscheduled Visits

The protocol-approved treatment for relapse in this study is either 3 to 5 days with IVMP at doses of up to 1000 mg/day or a full dose regimen of oral corticosteroids for up to 14 days. Oral corticosteroid taper regimens are not permitted. IVMP or oral corticosteroids can be given once a day or in divided doses. Subjects may also refuse relapse treatment. BG00012 dosing is to continue uninterrupted during steroid treatment. New or recurrent neurologic symptoms that occur <30 days after the onset of a protocol-defined relapse should be considered part of the same relapse and should not be treated with steroid within the protocol. Steroid retreatment of the same relapse is not allowed unless approved by the Medical Monitor.

12. EFFICACY ASSESSMENTS

12.1. Clinical Efficacy Assessments

The following clinical tests/assessments will be performed to assess the efficacy of BG00012:

- Relapse assessment
- EDSS [Kurtzke 1983]
- Visual function test [Balcer 2000]: the low-contrast Sloan letter charts (contrast sensitivity)

12.2. Laboratory Efficacy Assessments

The following laboratory tests/assessments will be performed to assess the efficacy of BG00012:

- Brain MRI scan with and without Gd parameters (only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6).

12.4. Additional Assessments

- The SF-36 is one of the most widely accepted generic health status measures. It is a brief (36-item) scale developed by Steward, Hayes, and Ware. The SF-36 will be available for all subjects for whom a validated translation in the local language is available.
- EQ-5D: a self-administered questionnaire consisting of 5 sets of 3 questions pertaining to specific health states (i.e., mobility, self-care, pain, usual activities, and anxiety), a health status rating scale, and demographic questions.

13. SAFETY ASSESSMENTS

13.1. Clinical Safety Assessments

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

- Physical examination
- Vital signs (heart rate, blood pressure, and temperature)
- AE monitoring (see Section 15)

13.2. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of BG00012:

- Hematology: hemoglobin, hematocrit, red blood cell count, WBC count (with differential), and platelet count.
- Blood chemistry: sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, lactate dehydrogenase, GGT, blood urea nitrogen, creatinine, bicarbonate, calcium, magnesium, phosphate, uric acid, and glucose.
- Urinalysis: color, specific gravity, pH, protein, glucose, blood, ketones, and microscopy.
- Urine cytology

14. SCHEDULE OF EVENTS

A written, signed informed consent form (ICF) and all authorizations required by local law (e.g., PHI in North America) must be obtained prior to performing any tests or assessments under this protocol. All tests and assessments scheduled for a particular visit must be completed before BG00012 is distributed.

14.1. Site Personnel

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

- A primary and backup *treating neurologist*; NOTE: to preserve the blind prior to open-label treatment, an *examining neurologist* from a Phase 3 study (Study 109MS301 or 109MS302) could not serve as the *treating neurologist* for this extension study (109MS303).
- An *examining neurologist (*if the *treating neurologist* designates EDSS examinations)
- A *treating nurse* (or study coordinator)
- An *examining technician* (if the *treating neurologist* designates visual function test examinations)
- An *MRI technician* (only at sites that had MRI scans as part of Study 109MS301 or 109MS302 and in 109MS303 up through and including Amendment 6)

The *treating **and examining** neurologist* must have a minimum of 2 years of neurology specialty training and be able to make at least a 1-year commitment to the study.

Where specified, evaluations described in this section must be performed only by the personnel indicated.

The primary *treating neurologist* will be responsible for:

- Management of the routine neurological care of the subject.
- Assessment (including assignment of causality) and treatment of AEs and MS relapses.
- Review of selected hematology and blood chemistry results from the central laboratory to assess whether the subject's BG00012 should be temporarily withheld or permanently discontinued as per the criteria detailed in Sections 11.2 and 11.3.
- Obtaining an EDSS score based on a detailed neurological examination at the scheduled timepoints required in the protocol.
- Obtaining an EDSS score at every Unscheduled Relapse Assessment Visit when there is the possibility of a relapse.

The *treating neurologist* may designate other medical personnel (i.e., the backup *treating neurologist, examining neurologist* or the *treating nurse*) at the investigational site to perform

some of the tests and evaluations listed under "*treating neurologist*." If there is more than 1 *treating neurologist* available at a given site such that each one is assigned to particular subjects, then these *treating neurologists* may act as backup for each other. All sites, however, should attempt to maintain the same *treating neurologist* for a given subject throughout the study. The same holds true for the *treating* nurses. The backup *treating neurologist* will conduct subject evaluations ONLY if the primary *treating neurologist* is unavailable due to illness, vacation, or travel. Hematology and blood chemistry data will be sent to the investigational sites to aid in management of the subject.

The *examining neurologist* (if designated by the *treating neurologist*) will be responsible for:

- Obtaining an EDSS score based on a detailed neurological examination at the required clinical evaluation visits, at the Unscheduled Relapse Assessment Visit, and at the Premature Study Treatment Withdrawal Visit.

The primary *treating nurse* (or *study coordinator*) will be responsible for:

- Assisting the *treating neurologist* in subject management, including the treatment of AEs, the treatment and assessment of disease relapses, and the recording of AEs and concomitant medications.
- Monitoring the EDSS scores (as determined by the *treating neurologist*) and informing the *treating neurologist* if a subject experiences a 1.0 point increase on the EDSS from a baseline EDSS ≥1.0 that is sustained for 24 weeks or a 1.5 point increase on the EDSS from a baseline EDSS = 0 that is sustained for 24 weeks.

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

- Administering the visual function test at each scheduled clinical evaluation visit and at the End of Study or Premature Study Treatment Withdrawal Visit.

It is not necessary for the *examining technician* to be a health care professional as long as he/she is qualified, in the opinion of the Principal Investigator, to administer the visual function test.

The *MRI technician* (only at sites participating in MRI sub-study) will be responsible for:

- Performing a brain MRI scan with and without Gd at all protocol-required time points up through and including Amendment 6 of this protocol. Study-specific MRI scan procedures and protocols will be provided prior to study start and must be followed.

14.2. Subject Management

Male subjects and female subjects of childbearing potential must practice effective contraception during the study and continue contraception for 30 days after their last dose of BG00012. If a female subject becomes pregnant, BG00012 must be discontinued immediately. For detailed information on contraception requirements and pregnancy, please refer to Sections 15.5.3 and 15.5.4, respectively.

Other than the BG00012 dosing requirements and concomitant medication restrictions described in Sections 11.1, 11.2, and 11.6, there are no special subject management procedures. There are no restrictions regarding diet, alcohol use, or activity during this study.

Subjects should not donate blood until 4 weeks after their last dose of BG00012 in this study.

14.3. Tests and Assessments

14.3.1. Year 1

14.3.1.1. Baseline Visit (Day 1)

Eligible subjects will be enrolled at Week 96 (Visit 24) of their previous BG00012 study (109MS301 or 109MS302), which will serve as the Baseline Visit for this extension study. All tests and procedures of the Baseline Visit that are performed at Visit 24 of 109MS301 or 109MS302 protocol should be performed by the respective personnel of the parent study, unless there is a gap in treatment.

Designated Personnel

- Randomization by IXRS

Treating Neurologist

- Informed consent
- Eligibility criteria
- Medical history update including review of cardiovascular risk factors
- Physical examination
- EDSS (If there is a gap in treatment and an *examining neurologist* is not designated, otherwise this exam should be performed by the *examining neurologist* of the parent study.)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- BG00012 distribution
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.1.2. Visit 1 (Week 4 ±5 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.3. Visit 2 (Week 8 ±5 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.4. Visit 3 (Week 12 ±5 Days)

*Treating/**Examining** Neurologist*

- Monitoring of AEs (*treating neurologist*)

- EDSS (To be performed only for subjects who at the Week 96 visit [Visit 24] in 109MS301 or 109MS302 had a 1.0 point increase in their EDSS score from a baseline EDSS ≥1.0 or a 1.5 point increase in their EDSS from a baseline EDSS = 0. Since this is to confirm disability progression at the Week 96 visit, this should be performed by the *examining neurologist* of the parent study.)

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.5. Visit 4 (Week 16 ±5 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.6. Visit 5 (Week 20 ±5 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution

- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.7. Visit 6 (Week 24 ±5 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.1.8. Visit 7 (Week 36 ±7 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

14.3.1.9. Visit 8 (Week 48 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- BG00012 distribution
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. MRI must not be performed within 30 days of receiving a course of steroids.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.2. Years 2 and 3 Treatment Visits

14.3.2.1. Visits 9, 10, 11, 13, 14, and 15 (Weeks 60, 72, 84, 108, 120, and 132 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry

- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.2.2. Visits 12 and 16 (Weeks 96 and 144 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- BG00012 distribution
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. MRI must not be performed within 30 days of receiving a course of steroids.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.3. Years 4 through 8 Treatment Visits

14.3.3.1. Visits 17, 19, 21, 23, 25, 27, 29, 31, 33, and 35 (Weeks 156, 180, 204, 228, 252, 276, 300, 324, 348, and 372 ±7 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis
- BG00012 distribution (record the Visit/Week at which subjects are switched to BID dosing and/or open-label treatment on the dosing CRF)
- Recording concomitant medication and AEs

14.3.3.2. Visits 18, 22, 26, 30, and 34 (Weeks 168, 216, 264, 312, and 360 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- BG00012 distribution
- Recording concomitant medication and AEs

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.3.3. Visits 20, 24, 28, 32, and 36 (Weeks 192, 240, 288, 336, and 384 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis

- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- BG00012 distribution (except at Visit 36)
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. MRI must not be performed within 30 days of receiving a course of steroids.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.4. Study Activities for Subjects Who Already Completed Visit 36

For subjects who have already completed Visit 36 (or beyond), an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study. For subjects who have not completed Visit 36 prior to Protocol Version 8, Visit 36 will serve as the last scheduled Visit and an End of Study Visit should be completed 4 weeks after their next Visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study.

14.3.4.1. Visits 37, 39, 41, 43, 45, 47, 49, and 51 (Weeks 396, 420, 444, 468, 492, 516, 540, and 564 ±7 Days)

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis
- Recording concomitant medication and AEs

14.3.4.2. Visits 38, 42, 46, and 50 (Weeks 408, 456, 504, and 552 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential; results must be known prior to BG00012 distribution
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- Recording concomitant medication and AEs

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.4.3. Visits 40, 44, 48, and 52 (Weeks 432, 480, 528, and 576 ±7 Days)

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. MRI must not be performed within 30 days of receiving a course of steroids.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.5. End of Study Visit

NOTE: Subjects will complete an End of Study Visit 4 weeks following their last study visit. For subjects who have already completed Visit 36 (Week 384) or beyond, an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled). For subjects who complete a Premature Study Treatment Withdrawal Visit, this will also be used as the End of Study Visit.

Treating Neurologist

- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis. If lymphocyte count is <LLN, see Section 11.3.
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis.
- Recording concomitant medication and AEs

14.3.6. Unscheduled Relapse Assessment Visit

Unscheduled Relapse Assessment Visit to be carried out within 5 days of suspected relapse.

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Relapse assessment
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis. If urinalysis is abnormal, see Section 11.2.
- SF-36 and EQ-5D
- Recording concomitant medication and AEs

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.7. Premature Study Treatment Withdrawal Visit

Subjects who permanently discontinue BG00012 prior to Week 384, regardless of further need to monitor lymphocytes on study, will complete a Premature Study Treatment Withdrawal Visit within 4 weeks of their last dose.

Treating Neurologist

- Physical examination
- EDSS (may be performed by the *examining neurologist*)
- Monitoring of AEs

Treating Nurse

- Vital signs
- Collection of blood for hematology and lymphocyte analysis. If lymphocyte count is <LLN, see Section 11.3.
- Collection of blood for blood chemistry
- Collection of urine for urine pregnancy test in women of childbearing potential
- Collection of urine for urinalysis.
- SF-36 and EQ-5D
- Recording concomitant medication and AEs

MRI Technician

- Brain MRI scan with and without Gd in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. MRI must not be performed within 30 days of receiving a course of steroids.

Examining Technician (if designated by *treating neurologist*)

- Visual function test

14.3.8. Lymphocyte Follow-Up

Treating Nurse

- Vital signs
- Collection of blood for hematology as defined in Section 11.3.
- Recording concomitant medication and AEs

15. SAFETY DEFINITIONS, MONITORING, AND REPORTING

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.

15.1.2. Serious Adverse Event

A serious AE (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 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.

15.2. Monitoring and Recording Events

15.2.1. Adverse Events

Any AE experienced by the subject from the time of first dose of BG00012 until the final study visit (including, but not limited to, the lymphocyte follow-up visits [for applicable subjects]) is to be recorded on the CRF, regardless of the severity of the event or its relationship to BG00012.

15.2.2. Serious Adverse Events

Any SAE experienced by the subject from the time of the first dose of BG00012 until the final study visit is to be recorded on an SAE Form, regardless of the severity of the event or its relationship to BG00012. SAEs must be reported to Biogen or designee as detailed in Section 15.2.4.

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

15.2.3. All 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 BG00012 as defined in Section 15.3.1.
- The severity of the event as defined in Section 15.3.2.

Cardiac events: subjects who report symptoms suggestive of an underlying cardiac disease or condition should be promptly evaluated by the Investigator to determine if further investigations are required (e.g., 12-lead electrocardiogram), or whether a referral to a cardiologist may be necessary. For all cardiac SAEs, the Investigator should make every attempt to obtain the full details of all relevant investigations and the final diagnosis of the event. All cardiac SAEs should be followed up until the event has been resolved, stabilized, or returned to baseline.

15.2.4. 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 from the time that the subject has signed the ICF until the final study visit must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of the event.

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 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 to the following:

Please refer to the Investigator Site File or Study Reference Manual for complete information.

15.2.4.1. Death

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. Safety Classifications

15.3.1. 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	
Unrelated	Any event that does not follow a reasonable temporal sequence from administration of study treatment *AND* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Unlikely	Any event that does not follow a reasonable temporal sequence from administration of study treatment *OR* that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Possibly	Any reaction that follows a reasonable temporal sequence from administration of study treatment *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Related	Any reaction that follows a reasonable temporal sequence from administration of study treatment *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

15.3.2. Severity of Events

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

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

15.3.3. Expectedness of Events

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

15.4. 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 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.

15.5. Procedures for Handling Special Situations

15.5.1. Overdose

An overdose is any dose of BG00012 given to a subject or taken by a subject that exceeds the dose described in the protocol. Overdoses are not considered AEs, however all overdoses should be recorded on an Overdose form and faxed to Biogen or designee within 24 hours of the site becoming aware of the overdose. An overdose should be recorded even if it does not result in an AE. Overdoses do not need to be recorded in the CRF.

15.5.2. Medical Emergency

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

15.5.3. Contraception Requirements

All male and female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of BG00012.

For the purposes of the study, effective contraception is defined as follows:

For females:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), intrauterine contraception/device, hormonal contraception, or any 2 barrier methods (a combination of male or female condom with spermicide; diaphragm, sponge, and cervical cap).
- Abstinence can be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

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

- Post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 weeks post-surgical bilateral oophorectomy.

  OR

- Post-hysterectomy.

For males:

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

15.5.4. Reporting Pregnancy

If a female subject becomes pregnant, BG00012 must be discontinued immediately.

The Investigator must report the pregnancy by faxing the appropriate form to Biogen or designee within 24 hours of the study site staff becoming aware of the pregnancy.

The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee.

Please note that congenital abnormalities/birth defects in the offspring of male or female subjects should be reported as SAEs when conception occurred during the BG00012 period.

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

If the partner of a male subject receiving BG00012 becomes pregnant at any time during the study, the Investigator should follow the pregnancy outcome and report any congenital anomaly or birth defects as an SAE to Biogen or designee.

15.5.5. Dose Unblinding for Medical Emergencies

While BG00012 assignment was blinded prior to open-label treatment, emergency decoding was made available to the Investigator and designated personnel at Biogen or designee through IXRS.

During open-label treatment, all subjects will receive the same dose of BG00012, BG00012 240 mg BID. While study staff are no longer blinded to dose assignment, they will remain blinded to the BG00012 dose subjects were receiving before the open-label treatment, as well as to the treatment arm of the subject in the parent study.

15.5.6. Regulatory Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

SUSARs will be reported to the appropriate authorities and central ethics committees by appropriate personnel in Biogen Drug Safety Risk Management (or designee). A report will be sent to all Investigators. The subject may remain in the study and continue to receive BG00012 at the Investigator's discretion.

15.6. Investigator Responsibilities

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.
- Report SAEs to local ethics committees, as required by local law.

15.7. Biogen Responsibilities

Biogen's responsibilities include the following:

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

16. STATISTICAL STATEMENT AND ANALYTICAL PLAN

16.1. Description of Objectives and Endpoints

16.1.1. Primary Objective and Endpoint

The primary objective of the study is to evaluate the long-term safety profile of BG00012.

16.1.2. Additional Objectives and Endpoints

Secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of BG00012 using clinical endpoints (including relapse and ARR) and disability progression (EDSS).
- To evaluate further the long-term effects of BG00012 on MS brain lesions on MRI scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 and in 109MS303 up through and including Amendment 6. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of Gd-enhancing lesions, number of new or newly-enlarging T2 lesions and volume of total T2 lesions, number of new T1 hypointense lesions and volume of T1 hypointense lesions, brain atrophy, and MTR.
- To evaluate the long-term effects of BG00012 on health economics assessments and the visual function test. The endpoints are the SF-36 and EQ-5D quality of life questionnaire, and the visual function test scores.

Exploratory objectives of this study are as follows:

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

16.2. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized for each treatment group by presenting summary statistics, or frequency distribution.

16.3. Efficacy Data

16.3.1. Analysis Population

The efficacy population is defined as all subjects who received at least 1 dose of BG00012 in the study and have at least 1 post-baseline assessment of the efficacy parameter being analyzed.

16.3.2. Methods of Analysis

Annualized Relapse Rate

Relapse rate will be summarized for the extension phase as well as starting from the original baseline of the Phase 3 studies (109MS301 and 109MS302). Relapse rate will be presented for each of the treatment groups separately (i.e., original 240 mg BID, original 240 mg TID, placebo or GA later randomized to 240 mg BID, or placebo or GA later randomized to 240 mg TID). The following statistical comparisons may be made:

- The 2-year ARR in the original Phase 3 studies and the ARR in the extension study in the placebo later randomized to 240 mg BID group, and in the placebo later randomized to 240 mg TID group.
- The ARR in the extension study between the original 240 mg BID and the original 240 mg TID group.
- The ARR in the original Phase 3 studies and the extension study between the original 240 mg BID and the original 240 mg TID group.
- The ARR in the original Phase 3 studies and the extension study between the original 240 mg BID and the placebo later randomized to 240 mg BID, and the original 240 mg TID and the placebo later randomized to 240 mg TID.

A negative binomial regression model will be used for the analysis of ARR endpoints.

In addition to the ARR endpoint, proportion of subjects relapsed will also be analyzed, using the Cox proportional hazards model.

Disability Progression

- Progression of disability is defined as at least a 1.0 point increase on the EDSS from baseline EDSS 1.0 that is sustained for 24 weeks or at least a 1.5 point increase on the EDSS from baseline EDSS =0 that is sustained for 24 weeks. Progression will be assessed relative to the baseline EDSS scores in the extension study, as well as from the baseline scores in the previous study. The Cox proportional hazards model will be used to analyze disability progression.

MRI Endpoints

MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans up to and including Amendment 6 of this protocol.

- Number and volume of Gd-enhancing lesions
- Number of new or newly-enlarging T2 lesions and volume of total T2 lesions
- Number of new T1 hypointense lesions and volume of T1 hypointense lesions
- Brain atrophy
- MTR

The number of new lesions (Gd-enhancing, T2 or T1 hypointense) will be summarized by treatment groups. Comparison between the treatment groups will be made using multiple logit regression.

The change in the volume of lesions will be compared between the treatment groups using an analysis of covariance (ANCOVA) model.

The actual value and change from baseline in brain atrophy will be compared between the treatment groups using ANCOVA.

MTR will be compared between treatment groups using ANCOVA.

Health Economics Endpoints: EQ-5D and SF-36

Actual scores and change from baseline in EQ-5D and SF-36 will be summarized for the treatment groups separately. An ANCOVA model will be used to analyze the data.

Visual Function Test

Actual scores and change from baseline in the visual function test scores will be analyzed by an ANCOVA model.

16.4. Safety Data

16.4.1. Analysis Population

The safety population is defined as subjects who have received at least 1 dose of BG00012 in the extension study.

16.4.2. Methods of Analysis

All AEs, laboratory abnormalities, and vital signs will be evaluated for safety. Safety analysis will focus on the safety data in the extension study. For subjects who were dosed with BG00012 in the previous study, long-term safety data (extension study + 2 years in the previous Phase 3 studies) may also be summarized.

Clinical Adverse Events

Only treatment-emergent AEs will be presented in the summary tables. Treatment-emergent is defined as having onset date which is on or after start of study treatment, or that is worsened after the start of study treatment.

The incidence of treatment-emergent AEs will be summarized by treatment group, overall, by severity, and by relationship to study treatment. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class.

Laboratory Data

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be

presented for each laboratory test by treatment group. In addition, summary of laboratory values categorized based on Common Toxicity Criteria grade will also be made. Summary statistics for actual values and change from baseline will also be presented, for quantitative laboratory data. Additionally, lymphocyte count over time post-treatment [redacted] will be descriptively summarized for subjects who develop decreases in lymphocyte count (<LLN).

Vital Sign Data

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities will be presented by treatment group. The criteria for clinically relevant post-baseline abnormalities are shown in Table 4. Summary statistics for actual values and change from baseline will also be presented.

Table 4: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

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

[redacted]

16.6. Interim Analyses

Interim analyses maybe performed as needed.

16.7. Sample Size Considerations

There is no formal sample size calculation. The number of subjects eligible for this study is determined by the number of subjects who participated in Studies 109MS301 and 109MS302.

17. ETHICAL REQUIREMENTS

Biogen, the contract research organizations (CROs), and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (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

The Investigator, Biogen, and the CROs must adhere to the principles set forth by the Declaration of Helsinki dated October 2013.

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 will submit documents on behalf of the investigational sites in Europe.

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 Investigator(s) 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 any testing under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject 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., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Biogen, its partner(s) and designee(s), 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.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not enroll any subjects prior to completion of a study initiation visit, conducted by Biogen or designee. This initiation visit will be conducted during a routine Phase 3 monitoring visit and will include a 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 on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

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

The Clinical Monitor(s) will visit the Investigator(s) 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.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, BG00012 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 contract(s) between the institution, Investigator, and Biogen.

18.5. Publications

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

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Interactive Voice and Web Response System

For this study, an IXRS supplier will be used. Before subjects are enrolled, the IXRS will provide each study site with appropriate training and a user manual.

19.1.2. Contract Research Organizations

A CRO will be responsible for all administrative aspects of the study including, but not limited to, study initiation, monitoring and management of AE/SAE reporting. Prior to enrollment of the first subject at each site, the CRO will review study responsibilities with the Investigators and other site personnel, as appropriate. [redacted] has been selected by Biogen as the Data Coordinating Center (DCC) for this study. The DCC will be responsible for all aspects of data management.

19.1.3. Central Laboratories for Laboratory Assessments

[redacted], Switzerland has been selected by Biogen to analyze all hematology, blood chemistry, urine cytology, and urinalysis samples collected for this study.

19.1.4. Central Facility for Other Assessments

MRI Reading Centers

All of the MRI scans with and without Gd will be evaluated at the central MRI reading center.

Original MRI films and digital data on compact disc, DAT tape, or magnetic optical disk are to be sent by courier to the respective MRI Reading Center for review (the Clinical Monitor will provide specific MRI shipping instructions prior to the start of enrollment at each site).

Additional and more detailed MRI scans with and without Gd procedures and instructions are included in the study MRI manual (to be provided under separate cover prior to start of the substudy).

19.2. Advisory Committee

An Advisory Committee will be formed to provide scientific and medical advice on key decisions for the study, including: 1) subsequent study protocol amendments; 2) conduct of the study, including subject retention and follow-up measures; and 3) review and interpretation of key data and implications for patient management.

The Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees) and participating Investigators, as well as clinical experts who are not participating as Investigators in 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 Sections 17.2 and 17.3).

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, "A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy 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)

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

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

AMENDMENT SUMMARY

Biogen Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 8

Date: 5 February 2018

EUDRA CT Number: 2008-004753-14

Version 8 of the protocol has been prepared for this amendment, which supersedes Version 7.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 109MS303 is as follows:

- To change the length of the study from 12 years to 8 years

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

Section 7.1, Study Overview

Now reads:

It is intended that ~~E~~eligible subjects from Studies 109MS301 and 109MS302 will be followed for ~~up t~~ at least ~~12~~ 8 years in this extension study, assuming BG00012 continues to have a positive benefit-risk ratio. At enrollment into the study, all subjects received either:

Rationale:

After careful analysis, and agreement with the European Medicines Agency (EMA), it is apparent that continuing the study beyond 8 years will not generate additional information about the safety and efficacy profile of BG00012 (dimethyl fumarate; DMF). Importantly, the safety and efficacy profile of BG00012 has demonstrated a positive benefit/risk profile throughout the duration of the trial thus far, up to 12.5 years follow-up, including the parent studies 109MS301 and 109MS302. The data suggest that long-term exposure to DMF is not associated with any change in the known safety profile of DMF.

[redacted] Subjects in Study 109MS303 (ENDORSE) who discontinue treatment for any reason and have an ALC <LLN will continue to have follow-up post-treatment until lymphocyte counts return to LLN, or for at least 48 weeks (whichever is sooner).

This change also affects Section 4.4 Study Activities for Subjects Who Already Completed Visit 36; Section 4.5, Study Activities (Hematology and Lymphocyte Analysis: Year 4 Through End of Treatment Visits); Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 7.1, Study Overview; Section 7.2.2, Treatment Period; Section 7.2.3, Post-Treatment Period; Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study; Section 14.3.4, Study Activities for Subjects Who Already Completed Visit 36; Section 14.3.5, End of Study Visit; Section 14.3.7, Premature Study Treatment Withdrawal Visit; Section 16.3.2, Methods of Analysis; and Section 16.4.2, Methods of Analysis.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 7.2.3, Post-Treatment Period

Change: A sentence was added to clarify the end of study for those subjects who already have completed Visit 36.

Now reads:

Subjects who complete the Week **384** ~~576~~ visit (Visit 36 ~~52~~), regardless of further need to monitor lymphocytes on study, will complete an End of Study Visit at Week **388** ~~580~~ ± 7 days. **For subjects who have already completed Visit 36, an End of Study Visit should be completed 4 weeks after their next visit (scheduled or unscheduled), regardless of further need to monitor lymphocytes on study.** Subjects who permanently discontinue BG00012 prior to Week **384** ~~576~~, regardless of further need to monitor lymphocytes on study, will complete a Premature Study Treatment Withdrawal Visit within 4 weeks after their last dose of BG00012. Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

Rationale: Some subjects have already completed Visit 36; thus, this statement explains how sites should address end of study for those subjects.

This change also affects Section 4.3, Study Activities (Years 4 Through 8 Treatment Visits); Section 4.4, Study Activities for Subjects Who Already Completed Visit 36); Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 7.2.3, Post-treatment Period, Section 14.3.4, Study Activities for Subjects Who Already Completed Visit 36; Section 14.3.5, and End of Study Visit.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- Updated the version number, date, and contact information as appropriate throughout the protocol.
- Corrected any typographical errors and formatting issues.
- In Section 1.1, added the name of the Biogen European Union Qualified Person for Pharmacovigilance to the applicable Signature Page.
- Updated the name of the medical signatory.
- Clarified Footnote 2 in Section 4.6 to state that a Premature Study Treatment Withdrawal Visit serves as the End of Study Visit.
- In Section 16, stated that the analyses would be conducted on the entirety of the extension study as well as all time from start of original Phase 3 studies.
- Updated the Biogen United States address.

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

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

AMENDMENT SUMMARY

Biogen Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 7

Date: 07 November 2016

EUDRA CT Number: 2008-004753-14

Version 7 of the protocol has been prepared for this amendment, which supersedes Version 6.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 109MS303 are as follows:

- To remove the discontinuation criteria of elevated serum creatinine (either >1.2 × baseline serum creatinine or >1.2 × upper limit of normal [ULN]), positive urinalysis, and low white blood cell (WBC) count.

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

Section 11.2.1, Abnormal Laboratory Values: Dosing Interruption and Management

Change: Removed withdrawal criteria of elevated serum creatinine, positive urinalysis, and low WBC count from Table 1.

Table 1: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of BG00012

Laboratory Parameter	**Laboratory Result**	**Required Action**
AST or ALT	>3×ULN	The Investigator should repeat the test as soon as possible. If re-test value confirms AST or ALT >3×ULN, BG00012 must be withheld. If the value remains >3×ULN for ≥4 weeks after discontinuation of BG00012, then the subject **must *permanently* discontinue** BG00012**.**
Lymphocyte counts	<500/mm^3	See Table 3.
~~Serum creatinine~~	~~>1.2 Baseline serum ————~~	~~———— test value confirms that creatinine >1.2 BSCr ———— remains >1.2 BSCr for ≥4 weeks after discontinuation of BG00012 **must discontinue** BG00012.~~
~~————~~	~~———— ——~~	~~———— ———— ———— ———— **must** ———— ———— ————~~

Laboratory Parameter	Laboratory Result	Required Action
~~_____~~	~~_____~~ ~~_____~~ ~~_____~~	~~_____~~ ~~_____~~ ~~_____~~ ~~_____~~ ~~_____~~ ~~_____~~ **must discontinue** BG00012.~~_____~~ ~~_____~~ ~~_____~~
~~WBC~~	~~<2000/mm^3~~	~~_____~~ ~~test value confirms that WBC <2000/mm^3 remains <2000/mm^3 for ≥4 weeks after discontinuation~~ **must discontinue** ~~BG00012.~~

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal~~; WBC = white blood cell~~.

Rationale: The removal of elevated serum creatinine from the withdrawal criteria was determined through analyses of all 1738 subjects, their laboratory values, renal adverse events, and medical interpretation of causation. The review and analyses of subject data demonstrated that an increase in serum creatinine, whether above baseline serum creatinine or above the upper limit of normal, were not predictors of a clinical event.

In addition, removal of elevated serum creatinine, positive urinalysis and low WBC from the withdrawal criteria was to align with the guidance provided in the Tecfidera investigator's brochure and all reference safety information for BG00012 where there is no recommendation to discontinue treatment based on this criteria. Elevated creatinine, positive urinalysis and low WBC (excluding ALC) were withdrawal criteria during the clinical development of BG00012, but no data (i.e., related safety signals) from the clinical studies or in the post-marketing setting provide evidence that these should remain as criteria for discontinuation of BG00012. As of April 2015, approximately 5,100 subjects had been treated with BG00012 in completed and ongoing clinical studies (see Tecfidera IB, version 10). As of June 2016, over 215,000 patients have been treated with Tecfidera (BG00012) worldwide (in clinical trials and post-marketing), representing 285,694 patient-years of exposure (see Fox 2016, ECTRIMS abstract). It should be noted that although low WBC is being removed from the withdrawal criteria within the protocol, the monitoring of ALC and withdrawal criteria remains. Additionally, although the automatic withdrawal criteria was removed for elevated serum creatinine, low WBC (excluding low ALC) and positive urinalyses, the measurement of all safety parameters (short- and long-term) will continue and remains an integral part of the protocol to ensure patient safety.

To date, there is no clinical evidence to suggest an increase incidence of adverse events requiring treatment withdrawal as a result of elevated serum creatinine, positive urinalysis, or low WBC.

This change also affects Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Multiple sections

Change: Removed requirement for magnetic resonance imaging (MRI) assessments after Version 6 of the protocol.

16.1.2 Additional Objectives and Endpoints

Secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of BG00012 using clinical endpoints (including relapse and ARR) and disability progression (EDSS).
- To evaluate further the long-term effects of BG00012 on MS brain lesions on MRI scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302 **and in 109MS303 up through and including Amendment 6**. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of Gd-enhancing lesions, number of new or newly-enlarging T2 lesions and volume of total T2 lesions, number of new T1 hypointense lesions and volume of T1 hypointense lesions, brain atrophy, and MTR.

Rationale: MRI assessments are removed from Study 109MS303 because interpretation of the data has become limited. The MRI assessments were performed in Study 109MS303 only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302. Because not all subjects in Studies 109MS301 and 109MS302 were part of the MRI assessment cohort, only a subpopulation of the 109MS303 had MRI assessments performed. After a median of approximately 7 years on study (2 years in Study 109MS301 or 109MS302 and approximately 5 years in Study 109MS303), the interpretation of MRI assessment data is considered limited because of the diminished number of subjects in the MRI cohort remaining on study. Additionally, long-term efficacy of BG00012 is well established by analyses of the data collected during these years.

The wording “up through and including Amendment 6” was added to multiple relevant sections throughout the protocol. The wording “Scheduled MRI scans were performed in protocol versions 1 through 6.” was added to multiple tables outlining study activities or schedule of assessments.

Additional sections affected include Section 14.1, Site Personnel, Section 16.1.2, Additional Objectives and Endpoints and Section 16.3.2, Methods of Analysis.

Section 11.2.1, Abnormal Laboratory Values: Dosing Interruption and Management

Change: Removed an invalid example and changed an incorrect cross-reference.

Subjects who subsequently develop the same abnormal laboratory value at any other time during the study must permanently discontinue dosing with BG00012, i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality (see **Table 1**~~Section 11.4~~). However, subjects who subsequently experience a different laboratory abnormality can have BG00012 withheld again**, allowing** 2 dosing interruptions ~~are allowed~~ for each subject. Any subject who experiences abnormal laboratory results that require temporary withholding as defined in Table 1 on a third occasion must permanently discontinue dosing.

Rationale: The example and cross-reference were no longer valid with the removal of WBC count from the withdrawal/dose interruption criteria.

Section 11.2.1, Abnormal Laboratory Values: Dosing Interruption and Management

Change: Changed nonspecific text under "Required Action" in Table 2 to "followed as per standard of care."

Table 2: Laboratory Analyses That Require Additional Evaluation

Laboratory Parameter	**Laboratory Result**	**Required Action**
Urinalysis	Urinary casts (other than hyaline casts)	Repeat test 2 weeks later; if the abnormality persists on re-testing, the subject should be **followed as per standard of care**.
Urinalysis	~~g~~**G**lycosuria (trace or greater)	If occurring in the setting of normal serum glucose, repeat test 2 weeks later; if the abnormality persists on re-testing, the subject should **followed as per standard of care**.
Urinalysis	~~p~~**P**roteinuria 1+	Subjects who demonstrate 1+ proteinuria ~~on a urine~~ (and do not have a documented history of benign proteinuria) **should be re-tested within 2**

Laboratory Parameter	Laboratory Result	Required Action
		weeks of initial abnormal finding~~.~~ ~~**If the abnormality persists on re-testing**, the subject should be **followed as per standard of care.** for~~

Rationale: Modified text to specify standard of care in the country in which the assessment is performed rather than recommendations that may not be accessible as next steps in the clinical care of a subject.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number, date, and contact information were updated as appropriate throughout the protocol.
- Typographical errors and formatting were corrected.
- In Section 1.1, updated the name of one of the Study Medical Directors.
- Throughout the protocol, multiple cross-references to Section 11.4 were changed to Section 11.2 to reflect changes to discontinuation/withdrawal criteria of elevated serum creatinine, positive urinalysis, and low WBC count.

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

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

AMENDMENT SUMMARY

Biogen Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 6

Date: 21 January 2016

EUDRA CT Number: 2008-004753-14

Version 6 of the protocol has been prepared for this amendment, which supersedes Version 5.

PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 109MS303 include the following:

- To extend the study duration by an additional 4 years to collect data on long-term efficacy and safety of BG00012.
- To increase the minimal duration of follow-up for lymphopenic subjects upon discontinuation of treatment with BG00012, per Committee for Medicinal Products for Human Use (CHMP) recommendations.

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

Section 7.1, Study Overview

Now reads:

[...]

Eligible subjects from Studies 109MS301 and 109MS302 will be followed for up to ~~8~~**12** years in this extension study, assuming BG00012 continues to have a positive benefit-risk ratio.

[...]

Rationale: The purpose of the 4-year extension is to collect data on the long-term efficacy and safety of BG00012. The purpose of the longer minimum time of follow-up is to fulfill CHMP recommendation. Study 109MS303 is an important source of data [redacted], as it is the only large clinical study with ~1000 ongoing patients having more than 4 years of follow-up (up to 6 years for patients continuously treated with BG00012) up to 2015. Extending the study for 4 more years (14-year data on continuously treated patients and 12-year data on patients who switched from placebo) provides an important point of differentiation for BG00012.

This change also affects Section 3, Synopsis; Section 4.4, Study Activities (Years 9 Through 12 Treatment Visits); Section 4.5, Study Activities (Hematology and Lymphocyte Analysis: Years 4 Through 12 Treatment Visits); Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); include Section 7.2.2, Treatment Period; Section 14.3.4, Years 9 through 12 Treatment Visits; Section 14.3.5, End of Study Visit (Week 580 ± 7 Days); Section 16.3.2, Methods of Analysis; and Section 16.4.2, Methods of Analysis.

Section 11.3, Monitoring and Management for Subjects with Abnormal Lymphocyte Count

Now reads:

Section 11.3 ~~Treatment Schedule~~ **Monitoring and Management** for Subjects with Abnormal Lymphocyte Count

~~11.3.1 ^{3}**LLN**~~

~~must~~
~~meets the threshold limit defined in Table 2~~ **Subjects who have a lymphocyte count <500/mm^3 at any time should be monitored and managed according to Table 3.**

All subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason other than those specified in Table 3 and who have a lymphocyte count <LLN, will be monitored every 12 weeks until their lymphocyte count is ≥LLN OR for 48 weeks after their last dose, whichever is earlier.

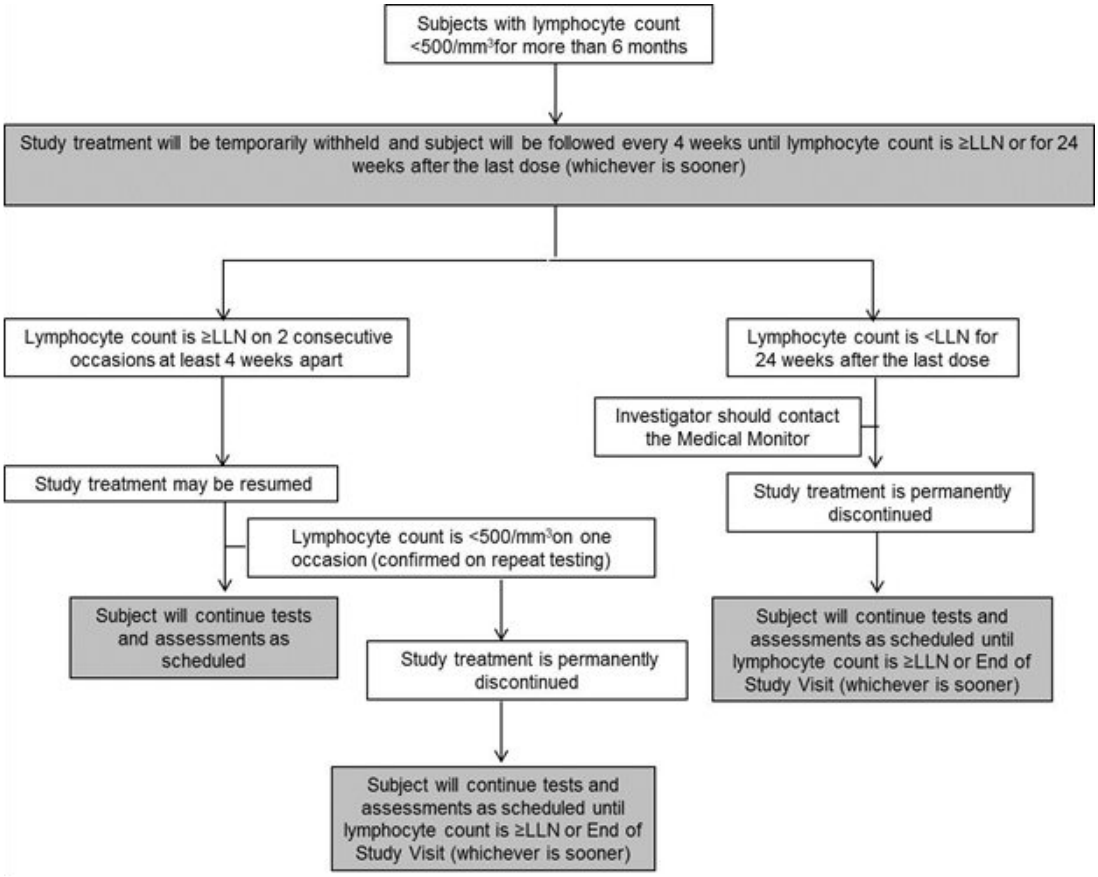
~~Table 2:~~

	~~<500/mm^3~~	~~The Inves~~ ~~<500/mm^3~~ ~~is <500/mm^3~~

~~Section 4.5 ^{3} for 24 weeks aft~~

~~described in Table 2~~
~~count is <500/mm^3~~
~~must~~ ~~ects who discontinue~~
~~^{3} should continue tests and assessments~~
~~4~~

~~See 1 ^{3}.~~
~~^{3}~~



~~11.3.2~~ ~~3~~

~~3~~

~~the schedule defined in Section 4~~

~~11.3.3.~~

Table 3: Lymphocyte Monitoring and Management for Subjects Who Have a Lymphocyte Count <500/mm^3

For subjects who have a lymphocyte count <500/mm^3, the Investigator should repeat the test as soon as possible. If re-test confirms that the lymphocyte count remains <500/mm^3, lymphocyte counts should be monitored every 4 weeks while on BG00012.

If subject has lymphocyte counts <500/mm^3 for ≥24 weeks, subject meets the Temporary Withholding Rule and BG00012 will be temporarily withheld. If the Temporary Withholding Rule is not met, the subject will be monitored every 12 weeks.

Lymphocyte Monitoring for Subjects Meeting the Temporary Withholding Rule	Patient Management for Subjects Meeting the Temporary Withholding Rule
The subject will be monitored every 4 weeks for 24 weeks, then every 12 weeks until the lymphocyte count is ≥LLN OR for 96 weeks after their last dose, whichever is earlier. However, if a subject reaches the end of study and their lymphocyte count remains <LLN, the subject will be monitored every 12 weeks until the lymphocyte count is ≥LLN OR for 48 weeks after their last dose, whichever is earlier.	• **If lymphocyte count remains <500/mm^3 for 24 weeks after temporary withdrawal, BG00012 must be permanently discontinued.** • **If lymphocyte count is between ≥500/mm^3 and ≤800/mm^3, then BG00012 will continue to be temporarily withheld.** • **If lymphocyte count recovers to >800/mm^3 (confirmed by 2 tests, at least 4 weeks apart), the physician/patient has the option to restart BG00012. If, upon resumption of BG00012, the lymphocyte count is <500/mm^3 on 1 occasion (confirmed by repeat testing), then BG00012 must be permanently discontinued.** • **Alternative disease-modifying treatment[a] may be considered, at the discretion of the treating physician as per standard of care. Subjects treated with alternative disease-modifying treatment will not have the option to restart BG00012.**

AE = adverse event; CRF = case report form; LLN = lower limit of normal.

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

Optional hematology consult and/or bone marrow biopsy may be considered for subjects meeting the Temporary Withholding Rule and whose lymphocyte counts remain <LLN for ≥48 weeks after discontinuation of BG00012, at the discretion of the Investigator. Earlier hematology consult and/or bone marrow biopsy may be considered in consultation with the Medical Monitor.

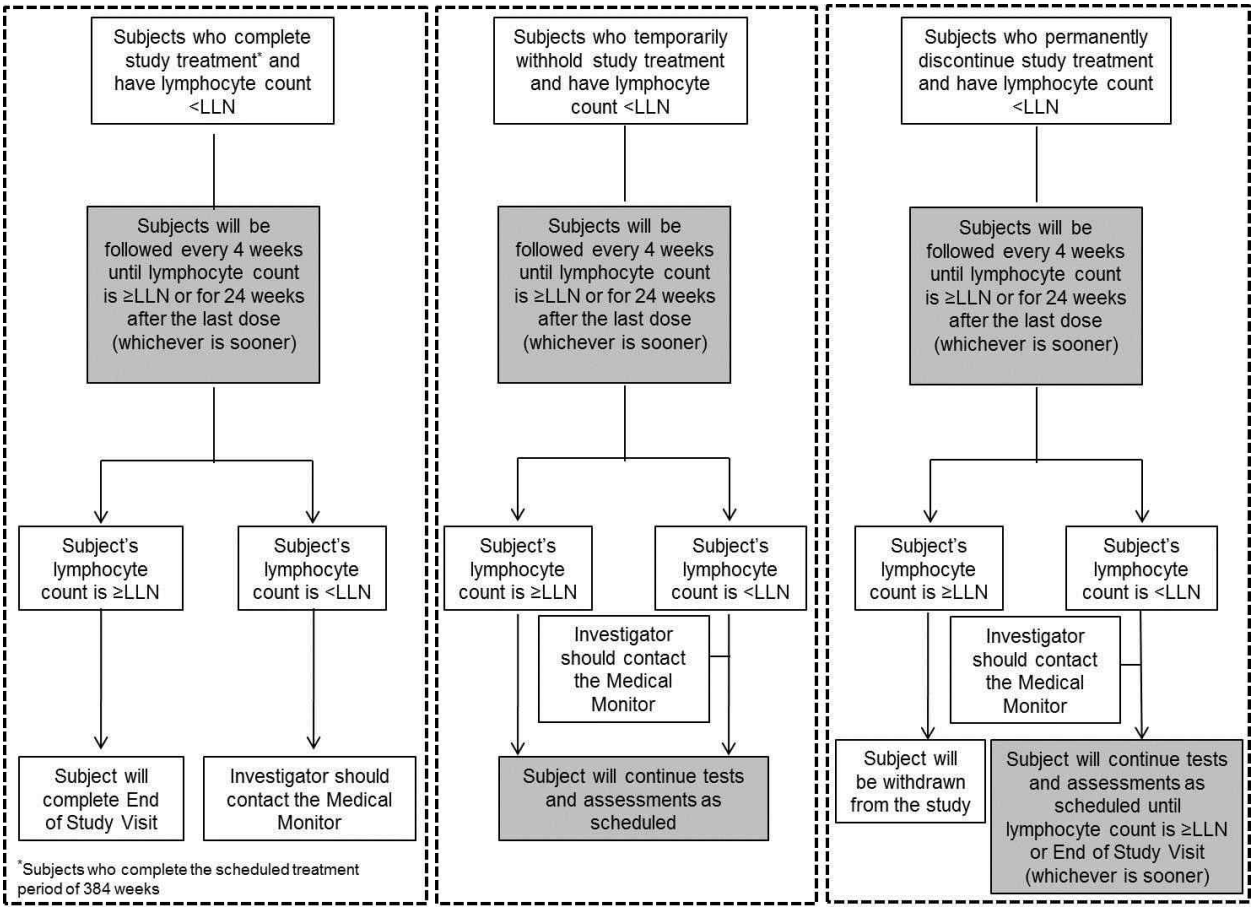
~~Section 11.3.3~~
~~Discontinue~~

~~11.2 count <LLN will be followed every~~
~~4~~

~~defined in Section 4 until the~~

~~See~~

~~<LLN~~



Rationale: As a safety measure, management of lymphocyte count is revised to ensure subjects with lymphopenia are followed-up for longer than 6 months after drug discontinuation, as preliminary evidence suggests full recovery of lymphocyte count to >LLN may take longer than 6 months following treatment cessation. Optional hematology consult and/or bone marrow biopsy will provide additional safety measures to facilitate patient management.

This change also affects Section 4.5, Study Activities (Hematology and Lymphocyte Analysis: Years 4 Through 12 Treatment Visits); Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 7.1, Study Overview; Section 7.2.3, Post-Treatment Period;

Section 11.2, Modification of Treatment Schedule; Section 11.2.1, Abnormal Laboratory Values: Dosing Interruption and Management; Section 11.2.2, Resumption of BG00012 Dosing; and Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 6.2, Additional Objectives

Change: The secondary objective was revised to be relevant to magnetic resonance imaging scans.

Now reads:

To evaluate further the long-term effects of BG00012 on MS brain lesions on MRI scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of Gd-enhancing lesions, number ~~and volume~~ of new or newly-enlarging T2 lesions **and volume of total T2 lesions**, number **of new T1 hypointense lesions** and volume of T1 ——————— lesions, brain atrophy, and magnetization transfer ratio (MTR).

Rationale: The revision was made to enable measurement of the accumulated burden of the disease rather than interval activity.

This change also affects Section 16.1.2, Additional Objectives and Endpoints and Section 16.3.2, Methods of Analysis.

Section 7.2.2, Treatment Period

Change: The name of the study visit was updated.

Now reads:

Subjects will report to the study site every 4 weeks for the first 24 weeks (Visit 1 through Visit 6) and every 12 weeks thereafter for up to 12 years.

Premature Study **Treatment** Withdrawal Visits and Unscheduled Relapse Assessment Visits will be performed as necessary. ——————————————————————————————————— ~~treatment dose.~~ All efforts should be made to keep the subjects' visit schedule relative to their Baseline

Visit (Day 1). Unscheduled Relapse Assessment Visits should not modify or replace their regular visit schedule.

Rationale: The name of the visit was updated to clarify that it is referring to the visit that occurs after premature withdrawal of study treatment and not after early withdrawal from the study.

This change also affects Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 7.2.3, Post-Treatment Period; Section 10.1, BG00012 Packaging; Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study; Section 14.1, Site Personnel; Section 14.3.7, Premature Study Treatment Withdrawal Visit.

Section 9.3, Blinding Procedures

Change: Added a phrase to specify blinding status during the extension study.

Now reads:

All subjects continuing in this study are to receive open-label BG00012 240 mg BID. Consequently, subjects and study staff are no longer blinded to dose assignment but will remain blinded to the BG00012 dose that subjects were receiving before the open-label treatment**, as well as to the treatment arm of the subject in the parent study**.

Rationale: This change will provide clarification regarding blinding during the study.

This change also affects Section 15.5.5, Dose Unblinding for Medical Emergencies.

Section 11.2, Modification of Treatment Schedule

Change: Changed the heading of Section 11.2.1 for clarification. In Table 1, rows were reordered to be alphabetical, a row was added for lymphocyte count, clarification was provided to indicate that creatinine was to be measured using serum, urine cytology was changed to urinalysis (to detect hematuria and proteinuria), and language pertaining to monitoring and management was updated. Section 11.2.4, Abnormal Urinalyses that Require Additional Evaluation, was removed; the contents of this section were captured in a new table, Table 2, which was added to Section 11.2.1. Section 11.2.3, Subsequent Development of Additional Laboratory Abnormalities, was removed and captured in the new text added to Section 11.2.2. Dosage Reduction was moved up as Section 11.2.2, prior to Resumption of BG00012 Dosing (now Section 11.2.3).

Now reads:

11.2.1 Abnormal Laboratory Values**: Dosing Interruption and Management**

BG00012 must be temporarily withheld when any of the following laboratory values meet the ~~threshold limits~~**criteria** defined in Table 1 ~~11.4~~.

Subjects are required to have additional evaluation when any of the following laboratory values meet the threshold limits defined in Table 2.

Table 1: Laboratory Criteria Requiring Withholding or Permanent Discontinuation of **BG00012**

Laboratory Parameter	**Laboratory Result**	**Required Action**
AST or ALT	>3×ULN	The Investigator should repeat the test as soon as possible. If re-test value confirms AST or ALT >3×ULN, the **BG00012** must be withheld. If the value remains >3×ULN for ≥4 weeks after discontinuation of **BG00012**, then the subject must *permanently* discontinue ~~treatment~~ **BG00012.**
Lymphocyte counts	**<500/mm^3**	**See Table 3.**
Serum ~~C~~creatinine	>1.2 × ~~ULN~~ **Baseline serum creatinine (BSCr)**	The Investigator should repeat the test as soon as possible. If re-test value confirms that creatinine >1.2 × ~~ULN~~ **BSCr**, **BG00012** must be withheld. If the value remains >1.2 × ~~ULN~~ **BSCr** for ≥4 weeks after discontinuation of **BG00012**, then the subject must *permanently* discontinue **BG00012**.
	~~Positive~~	~~has he consecutive~~
Urinalysis	**Dipstick proteinuria (≥2+)**	**The Investigator should repeat the test as soon as possible. If re-test confirms proteinuria ≥2+ without known etiology, BG00012 must be withheld. If proteinuria ≥2+ persists for ≥4 weeks after discontinuation, then the subject must *permanently* discontinue BG00012. Subjects should be referred to a nephrologist for further investigation.**

Laboratory Parameter	Laboratory Result	Required Action
Urinalysis	**Positive dipstick hematuria (≥1+) on microscopy**	**The Investigator should repeat the test as soon as possible. If re-test confirms microscopic hematuria ≥1+ without known etiology, BG00012 must be withheld and urine cytology must be performed. If hematuria persists for ≥4 weeks after discontinuation or if cytology is positive, then the subject must *permanently* discontinue BG00012. Subjects should be referred to a nephrologist for further investigation.**
WBC	**<2000/mm3**	**The Investigator should repeat the test as soon as possible. If re-test value confirms that WBC <2000/mm^3, BG00012must be withheld. If the value remains <2000/mm^3 for ≥4 weeks after discontinuation of study treatment BG00012, then the subject must permanently discontinue study treatment BG00012.**

ALT = alanine transaminase; AST = aspartate 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 the protocol (Section 4), and may also undergo additional assessments to evaluate the laboratory abnormality as per the Investigator's standard practice. ~~In~~ **Subjects who** have ~~the~~ abnormal laboratory result**s other than described in Table 1 must repeat the tests** ~~rechecked at~~ **within** 2 weeks (~~checks~~ **repeat tests** will be run at the central laboratory). **Abnormal laboratory results confirmed on repeat tests** should **be managed per the investigator's standard practice**.

Subjects who subsequently develop the same abnormal laboratory value at any other time during the study must permanently discontinue dosing with BG00012, i.e., only 1 dosing interruption is allowed for each subject for the same laboratory abnormality (see Section 11.4). However, subjects who subsequently experience a different laboratory abnormality can have BG00012 withheld again. For example, if a subject had dosing temporarily withheld for an abnormal ALT, then had dosing resume after ALT returned to acceptable limits, and subsequently developed abnormal white blood cells (WBCs), the subject may have BG00012 withheld again. However, only 2 dosing interruptions are allowed for each subject. Any subject who experiences abnormal laboratory results that require temporary withholding as defined in Table 1 on a third occasion must permanently discontinue dosing.

Subjects who complete **BG00012** ~~hhold,~~ or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN will be followed ~~until the for~~ **according to** Section 11.3.~~3~~.

Table 2: Laboratory Analyses That Require Additional Evaluation

Laboratory Parameter	Laboratory Result	Required Action
Urinalysis	**Urinary casts (other than hyaline casts)**	**Repeat test 2 weeks later; if the abnormality persists on retesting, the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist, if appropriate in the opinion of the Investigator.**
Urinalysis	**Dipstick glycosuria (trace or greater)**	**If occurring in the setting of normal serum glucose, repeat test 2 weeks later; if the abnormality persists on retesting, the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist, if appropriate in the opinion of the Investigator.**
Urinalysis	**Dipstick proteinuria 1+**	**Subjects who demonstrate 1+ proteinuria on a urine dipstick (and do not have a documented history of benign proteinuria) should have a spot protein/creatinine ratio (on morning void). If spot protein/creatinine ratio is >0.3 mg/mg, the subject should be fully investigated for possible causes and referred for evaluation by a nephrologist, if appropriate in the opinion of the Investigator.**

11.2.2 Dosage Reductions

Dosage reduction will be allowed only for subjects who are unable to tolerate BG00012 *due to flushing and/or GI disturbances* (dosage reductions will <u>not</u> be allowed for abnormal laboratory values; for management of abnormal laboratory values, refer to Section 11.2.1). Subjects who do not tolerate BG00012 will reduce their dosage by taking one 120 mg capsule BID for 4 weeks. After 4 weeks at the reduced dosage, subjects will resume taking the full dose of 240 mg (two 120 mg capsules) BID. If the subject is still unable to tolerate BG00012, the subject must discontinue BG00012 and be withdrawn from the study as described in Section 11.4.

11.2.3 Resumption of **BG00012** Dosing

~~with the Medical Monito~~

must per

Subjects who **have** temporarily **withheld BG00012** due to decreases in **lymphopenia** may resume **BG00012** when **according to** Section 11.3.

Subjects who are allowed to resume BG00012 dosing following a 2- to 4-week interruption due to *flushing and/or GI disturbances* will restart dosing at a reduced dosage for 1 week. Subjects will take one 120 mg capsule BID for 1 week. After 1 week at the reduced dose, subjects will resume taking two 120 mg capsules BID.

11.2.3

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Section 11.4

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criteri defined in Table 1 on a third occasion must

count <LLN will be followed every

[see Section .

11.2.4

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Rationale: These changes provide a more concise and specific set of guidelines for the monitoring and management of subjects who develop laboratory abnormalities that require dosing interruption.

This change also affects Section 4.1, Study Activities 109MS303 (Year 1 Visits); Section 4.2, Study Activities 109MS303 (Years 2 and 3 Treatment Visits); Section 4.3, Study Activities (Years 4 Through 8 Treatment Visits); Section 4.4, Study Activities (Years 9 Through 12 Treatment Visits); Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study; Section 14.3.1.1, Baseline Visit (Day 1); Section 14.3.1.2, Visit 1 (Week 4 ±5 Days); Section 14.3.1.3, Visit 2 (Week 8 ±5 Days); Section 14.3.1.4, Visit 3 (Week 12 ±5 Days); Section 14.3.1.5, Visit 4 (Week 16 ±5 Days); Section 14.3.1.6, Visit 5 (Week 20 ±5 Days); Section 14.3.1.7, Visit 6 (Week 24 ±5 Days); Section 14.3.1.8, Visit 7 (Week 36 ±7 Days); Section 14.3.1.9, Visit 8 (Week 48 ±7 Days); Section 14.3.2.1, Visits 9, 10, 11, 13, 14, and 15 (Weeks 60, 72, 84, 108, 120, and 132 ±7 Days); Section 14.3.2.2, Visits 12 and 16 (Weeks 96 and 144 ±7 Days); Section 14.3.3.2, Visits 18, 22, 26, 30, and 34 (Weeks 168, 216, 264, 312, and 360 ±7 Days); Section 14.3.3.3, Visits 20, 24, 28, 32, and 36 (Weeks 192, 240, 288, 336, and 384 ±7 Days); Section 14.3.4.2, Visits 38, 42, 46, and 50 (Weeks 408, 456, 504, and 552 ±7 Days); Section 14.3.4.3, Visits 40, 44, 48, and 52 (Weeks 432, 480, 528, and 576 ±7 Days); Section 14.3.5, End of Study Visit (Week 580 ± 7 Days); Section 14.3.6, Unscheduled Relapse Assessment Visit; and Section 14.3.7, Premature Study Withdrawal Visit.

<u>Section 11.6, Concomitant Therapy and Procedures</u>

Change: Specified the condition in which certain concomitant treatments would be allowed.

Now reads:

[...]

Concomitant treatment with any of the following is *not* allowed unless otherwise described in this protocol:

- 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-beta, IFN-alpha, GA, natalizumab, **fingolimod, teriflunomide,** cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products, etc.), with the exception of acute management of protocol-defined relapse **(as described below) and subjects with prolonged lymphopenia** (as described **in Section 11.3**).

- 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 as described below. Steroids that are administered by non-systemic routes (e.g., topical, inhaled) **or systemic steroid therapy for limited, short-term treatment of general medical conditions** are allowed**.**

[...]

Rationale: This change is to reflect [redacted] that study subject experiencing prolonged and severe lymphopenia in the absence of BG00012 treatment has a risk for relapse.

This change also affects Section 11.2.2, Resumption of BG00012 Dosing and Section 11.3, Treatment Schedule for Subjects with Abnormal Lymphocyte Count.

Section 11.6.1, Treatment of Relapses on Scheduled or Unscheduled Visits

Change: Added corticosteroid as allowed treatment for relapses

Now reads:

The ~~——~~ protocol-approved treatment for relapse in this study is either 3 ~~———~~ **to** 5 days with IVMP **at doses of up to** 1000 mg/day **or a full dose regimen of oral corticosteroids for up to 14 days. Oral corticosteroid taper regimens are not permitted**. IVMP **or oral corticosteroids** can be given once a day or in divided doses. Subjects may also refuse relapse treatment. ~~————————~~ **BG00012** dosing is to continue uninterrupted during ~~IVMP~~ **steroid** treatment. **New or recurrent neurologic symptoms that occur less than 30 days after the onset of a protocol-defined relapse should be considered part of the same relapse and should not be treated with ~~IVMP~~steroid within the protocol. Steroid retreatment of the same relapse is not allowed unless approved by the Medical Monitor.**

Rationale: Oral corticosteroids were added to provide the Neurologist with the option of treating relapses with oral corticosteroids and not just intravenous methylprednisolone.

This change also affects Section 7.3, Relapses.

Section 14.3.8, Telephone Follow-Up (12 Weeks After Last Study Visit)

Change: Removed the section and text pertaining to telephone follow-up

Now reads:

~~14.3.8.~~

~~withdrawal.~~

~~*Treating Nurse*~~

~~•~~

Rationale: Telephone follow-up is no longer necessary, given the longer follow-up planned for lymphocytes.

This change also affects Section 4.6, Study Activities (Unscheduled and Post-Treatment Visits); Section 10.1, BG00012 Packaging; Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study; and Section 15.2.1, Adverse Events.

Section 19.1.4, Central Facility for Other Assessments

Change: Removed text pertaining to the parent studies.

Now reads:

MRI Reading Centers

All of the MRI scans with and without Gd will be evaluated at the central MRI reading center ~~used for the s~~.

Original MRI films and digital data on compact disc, DAT tape, or magnetic optical disk are to be sent by courier to the respective MRI Reading Center for review (the Clinical Monitor will provide specific MRI shipping instructions prior to the start of enrollment at each site).

Rationale: Due to the extended duration of the study, the update was made to allow flexibility in central MRI reading center.

Section 19.2, Advisory Committee

Change: Revised the information on the advisory committee and deleted all references to Data Safety Monitoring Committee.

Now reads:

19.2. ~~——~~ **Advisory** Committee~~–~~

~~19.2.1 Advi~~

An Advisory Committee will be formed to provide scientific and medical **advice on key decisions** ~~direction~~ for the study~~——————————————~~**, including: 1) subsequent study protocol amendments; 2) conduct of the study, including subject retention and follow-up measures; and 3) review and interpretation of key data and implications for patient management.** ~~——————————~~
~~————————————————————~~
~~————————————————————~~
~~————————~~

The Advisory Committee will include the Medical Director, Clinical Trial Manager, and Project Statistician from Biogen (and/or their designees) and participating Investigators, as well as clinical experts who are not participating as Investigators in this study. ~~————————~~
~~————————————————————and this individual will also~~
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~~19.2.2 ——————————————~~

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Rationale: This change is to seek and integrate expert advice as part of decision-making during the conduct of this trial.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number, date, Biogen logo, company name and address, and contact information were updated as appropriate throughout the protocol.
- Typographical errors and formatting were corrected.
- All signature pages were deleted in keeping with the current Biogen approval process; the Signature page will be added separately.
- Replaced the words “study treatment” with “BG00012” throughout the protocol and synopsis for clarity.
- Replaced the words “study treatment dose visit” with “study visit” throughout the protocol.
- Changed the number of global study locations in Section 3, Synopsis to more closely reflect the total number of sites that participated in the study across time.

Study Location:	Global; approximately ~~375~~ **300** sites

- Added the names of study medical directors to Section 1.1.
- There were minor text revisions in Section 5.4, Dose Rationale.

  The initial BG00012 dosage for the extension study (240 mg BID or 240 mg TID) was the same as that used in the Phase 3 Studies 109MS301 and 109MS302. Subsequent to the initiation of this study, BG00012 was approved in several countries for the treatment of MS at a dose of 240 mg BID. For this reason, all subjects continuing in this **extension** study ~~will receive~~ **are receiving** the currently marketed dose of 240 mg BID. Subjects ———————— **randomized to** BG00012 240 mg TID ~~will be~~ **were** switched to BID dosing ~~at their next scheduled visit~~ **following BG00012 approval**.

  This change also affects Section 7.1, Study Overview and Section 11.1, Treatment Schedule.

- Changed the timepoint mentioned in Section 6.2, Additional Objectives from “months” to “weeks”.

[redacted]

This change also affects Section 16.1.2, Additional Objectives and Endpoints.

- Added a sentence to Section 7.1, Study Overview referring to Section 11.3 for lymphocyte monitoring and management.

  Subjects who complete BG00012 treatment or permanently discontinue BG00012 for any reason and who have a lymphocyte count <LLN should not be withdrawn from the study. These subjects will be followed according to Section 11.3.

  This change also affects Section 7.2.3, Post-Treatment Period; Section 11.1, Treatment Schedule; and Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study.

- Added the word "serum" prior to the word creatinine in Section 11.4, Removal of Subjects from Treatment and Withdrawal from Study for clarity.

  The subject develops >1.2×ULN elevation in **serum** creatinine that is sustained for 4 consecutive weeks after ———————— **BG00012** has been withheld.

Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

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

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 5

Date: 16 November 2014

EUDRA CT Number: 2008-004753-14

Version 5 of the protocol has been prepared for this amendment, which supersedes Version 4.

PRIMARY REASON FOR AMENDMENT

Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. Severe, prolonged lymphopenia is a known risk factor for PML. In the controlled and uncontrolled BG00012 clinical studies, 2% of subjects experienced lymphocyte counts <0.5 x 10^9/L for at least six months. In these subjects, the majority of lymphocyte counts remained <0.5 x 10^9/L with continued therapy. The study protocol is being amended to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects.

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

Section 11.3, Treatment Schedule for Subjects with Abnormal Lymphocyte Count

Now reads:

11.3.1 Schedule of Subjects with Lymphocyte Count <500/mm^3

Table 2: Lymphocyte Count Requiring Withholding of Study Treatment

Laboratory Parameter	Laboratory Result	Required Action
Lymphocyte count	**<500/mm^3**	**The Investigator should repeat the test as soon as possible. If re-test confirms that lymphocyte count is <500/mm^3, lymphocyte count should be closely monitored (at least every 4 weeks). If lymphocyte count is <500/mm^3 for more than 6 months, study treatment must be temporarily withheld.**

While dosing is withheld, subjects will be followed every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner) [see Lymphocyte Follow-up in Section 4.5]. If lymphocyte count remains <500/mm^3 for 24 weeks after the last dose, then study treatment must be permanently discontinued.

Subjects who temporarily withhold study treatment due to decreases in lymphocyte count as described in Table 2, may resume study treatment when lymphocyte counts recover (defined as a lymphocyte count ≥LLN on two consecutive occasions at least 4 weeks apart). If the lymphocyte count is <500/mm^3 on one 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/mm^3 should continue tests and assessments according to the schedule defined in Section 4 until the lymphocyte count recovers or until the End of Study Visit (whichever is sooner).

See Figure1 for the treatment schedule of subjects with lymphocyte counts <500/mm^3.

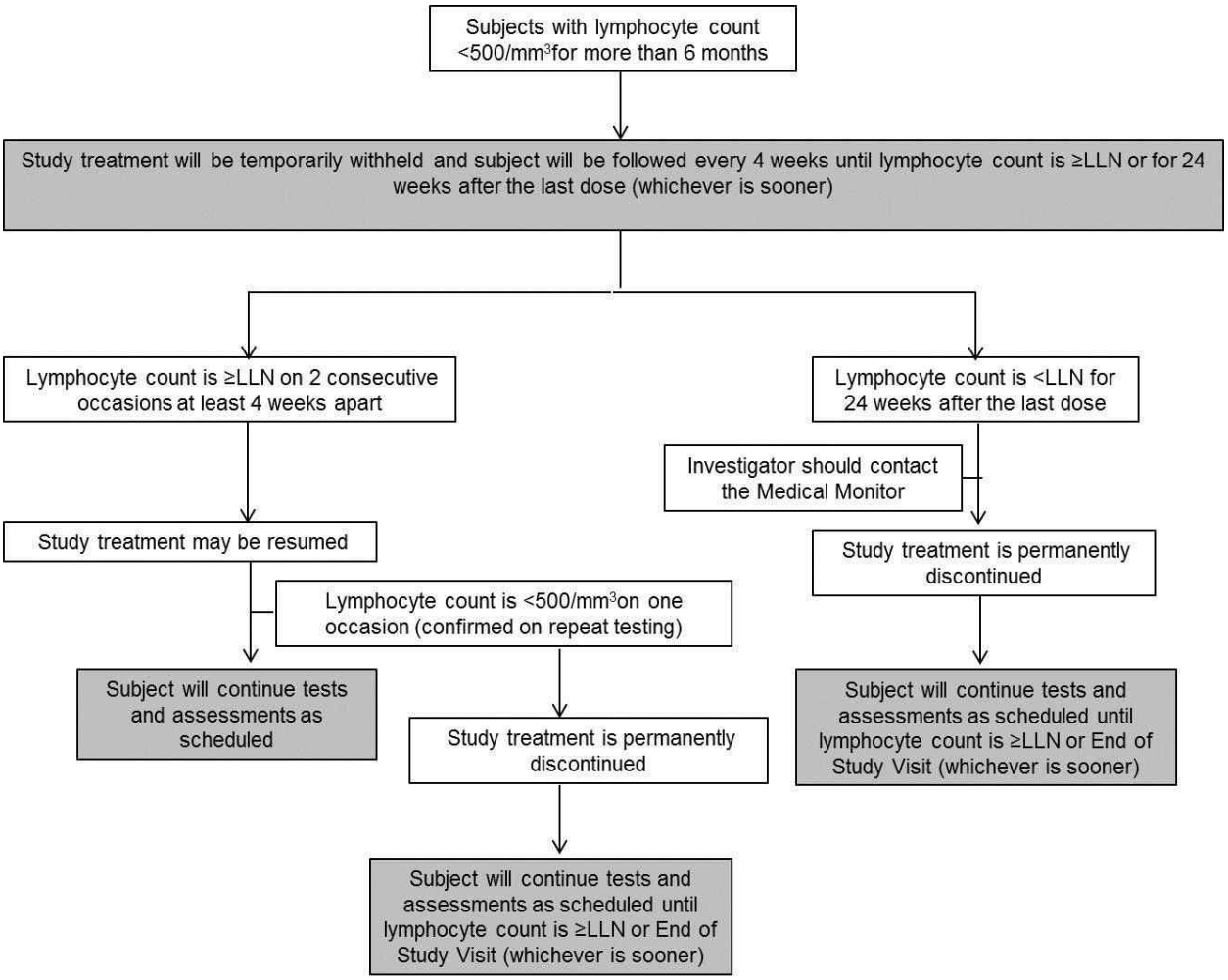

Figure 1: Schedule for Subjects with Lymphocyte Count <500/mm^3

11.3.2 Schedule for Subjects with Lymphocyte Count <LLN to >500/mm^3

Subjects with lymphocyte count <LLN to ≥500/mm^3 will have tests and assessments according to the schedule defined in Section 4 (blood draw for hematology and lymphocyte analysis every 12 weeks). 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 Also Have Lymphocyte Count <LLN

Subjects who complete, temporarily withhold, or permanently discontinue BG00012 for any other reason (see Section 11.2) and who have a lymphocyte count <LLN will be followed every 4 weeks until the lymphocyte count is ≥LLN or for 24 weeks after the last dose (whichever is sooner). Subjects who permanently discontinue study treatment and

have lymphocyte count <LLN should continue tests and assessments according to the schedule defined in Section 4 until the lymphocyte count recovers or until the End of Study Visit (whichever is sooner).

See Figure 2 for a schedule of subjects who complete, temporarily withhold or permanently discontinue BG00012 for any other reason and who have a lymphocyte count <LLN.

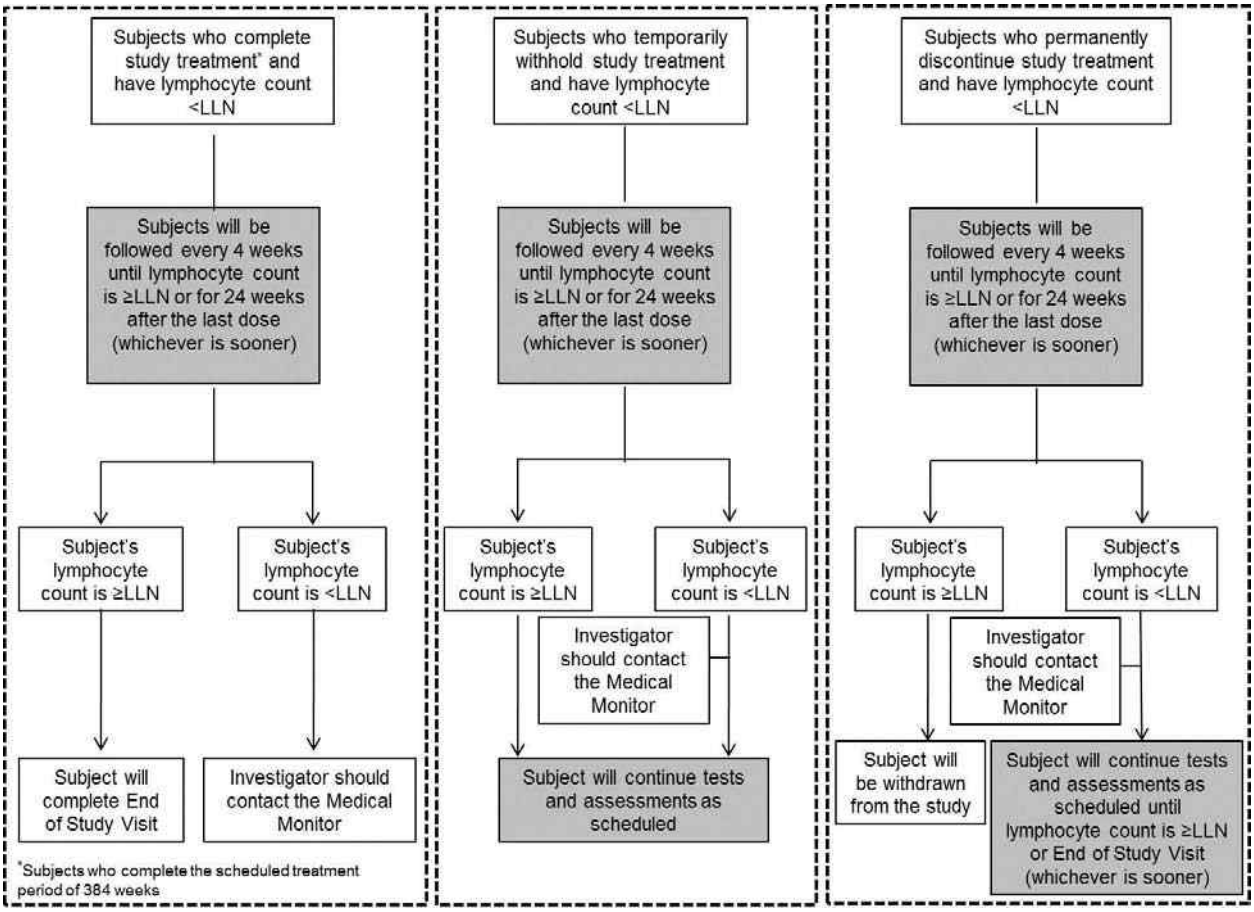

Figure 2: Schedule for Subjects Who Complete, Temporarily Withhold or Permanently Discontinue Study Treatment Due to Any Reason and Have Lymphocyte Count <LLN

Rationale: Severe, prolonged lymphopenia is a known risk factor for PML. The rationale for this change is to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on when study treatment should be temporarily withheld in these subjects.

This change also affects Section 7.2.3, Post-Treatment Period; Section 11.2.1, Dosing Interruption for Abnormal Laboratory Values; Section 11.2.2, Resumption of Study Treatment

Dosing; Section 11.2.3, Subsequent Development of Additional Laboratory Abnormalities; and Section 11.4 Removal of Subjects from Treatment and Withdrawal from Study.

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 4.3, Study Activities (Years 4 through 8 Treatment Visits)

Change: Additional tests and assessments have been included.

Now reads:

Year	Year 4				Year 5				Year 6				Year 7				Year 8			
Visit	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Study Week (±7 days)	156	168	180	192	204	216	228	240	252	264	276	288	300	312	324	336	348	360	372	384
Tests and Assessments[1]																				
Physical Exam ination		X		X		X		X		X		X		X		X		X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	**See Section 4.4**																			
Blood Chemistry		X		X		X		X		X		X		X		X		X		X
[redacted]																				
Urine Pregnancy Test[2]		X		X		X		X		X		X		X		X		X		X
Urinalysis		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]
Brain MRI[4] Scan ± Gd				X[5]				X[5]				X[5]				X[5]				X[5]
EDSS		X		X		X		X		X		X		X		X		X		X
Visual Function Test		X		X		X		X		X		X		X		X		X		X
SF-36 and EQ-5D				X				X				X				X				X
Dispense Study Treatment[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.6
AE/SAE Reporting	Monitor and record throughout the study as per Section 15

1. Tests and assessments must be completed prior to study treatment distribution.
2. For women of childbearing potential. Results must be known prior to study treatment distribution.
3. Urine cytology must be performed if subject experiences hematuria (of unknown etiology) on 2 consecutive tests. If urine cytology is positive during the treatment period, subject must permanently discontinue study treatment (see Section 11.4).
4. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302.
5. MRI must not be performed within 30 days of receiving a course of steroids.
6. The date and Study Visit/Week at which subjects are switched to open-label treatment should be recorded on the dosing CRF.

Rationale: As additional safety measures, more frequent hematology tests (complete blood count with differential, including [redacted]) have been added. [redacted]

This change also affects Section 14.3.3, Years 4 through 8 Treatment Visits.

Section 4.4, Study Activities (Hematology [redacted] Analysis, Years 4 Through 8 Treatment Visits)

Change: A table has been added.

Now reads:

Tests and Assessments	Subjects with lymphocyte count ≥LLN	Subjects with lymphocyte count <LLN to ≥500/mm^3	Subjects with lymphocyte count <500/mm^3
Hematology	**Every 24 weeks**	**Every 12 weeks**	**Every 4 weeks**
[redacted]			

Rationale: The table has been added to provide guidance on the frequency of collection of blood samples for hematology and additional exploratory analyses.

Section 6.2, Additional Objectives

Change: Three exploratory objectives have been added.**Now reads:**

Secondary objectives of this study are as follows:

- To evaluate the long-term efficacy of BG00012 using clinical endpoints (including relapse and ARR) and disability progression (EDSS).
- To evaluate further the long-term effects of BG00012 on MS brain lesions on MRI scans in subjects who had MRI scans as part of Studies 109MS301 and 109MS302. The following MRI endpoints will be evaluated in the subset of subjects who participated in the MRI scans: number and volume of Gd-enhancing lesions, number and volume of new or newly-enlarging T2 lesions, number and volume of T1 hypointense lesions, brain atrophy, and magnetization transfer ratio (MTR).
- To evaluate the long-term effects of BG00012 on health economics assessments and the visual function test. The endpoints are the Short-form 36 Health Survey (SF-36®) and Euroqol EQ-5D Healthy Survey (EQ-5D) quality of life questionnaire, and the visual function test scores.

Exploratory objectives of this study are as follows:

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

Rationale:

[redacted]

This change also affects Section 12.3, [redacted]; Section 16.1.2, Additional Objectives and Endpoints; Section 16.4.2, Methods of Analysis; and Section 16.5, [redacted].

The following minor changes were made to the protocol:

- The version number and date were updated throughout the protocol.
- Signatory information was revised for alignment with current practice.
- The List of Abbreviations was updated.

Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

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

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 4

Date: 02 September 2014

EUDRA CT Number: 2008-004753-14

Version 4 of the protocol has been prepared for this amendment, which supersedes Version 3.

PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 109MS303 is to update the safety reporting information.

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

Section 15.2.4, Immediate Reporting of Serious Adverse Events

Now reads:

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify **Biogen Idec or designee** [redacted] 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 from the time that the subject has signed the ICF until the final study visit must be reported to **Biogen Idec or designee** [redacted] within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to **Biogen Idec or designee** [redacted] regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not 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 to the following:

[redacted]

[redacted]

Please refer to the **Investigator Site File or** Study Reference Manual for complete information.

Rationale: Study responsibilities for Study 109MS303 have been transferred from [redacted] to [redacted]. This revision reflects this change.

The change also affects Section 15.2.2, Serious Adverse Events; Section 15.2.4.1, Death; Section 15.5.1, Overdose; Section 15.5.4 Reporting Pregnancy; and Section 15.6, Investigator Responsibilities.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol:

- The version number and date were updated throughout the protocol.
- With the implementation of Version 4, references to Version 3 in the body text were deleted throughout the protocol.

Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

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

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 3

Date: 17 March 2014

EUDRA CT Number: 2008-004753-14

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

PRIMARY REASONS FOR AMENDMENT

The primary reasons for this amendment to Protocol 109MS303 are to extend the study duration for each subject from 5 years to 8 years and to change the dosing regimen from dose-blind dosing with BG00012 240 mg twice a day (BID) or three times a day (TID) to open-label dosing with BG00012 at a dose of 240 mg BID for all subjects.

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

Section 7.1, Study Overview

Now reads:

The first phase of this extension study ~~This~~ is a multicenter, parallel-group, randomized, dose-blind, dose-comparison study. **The second phase of the study, implemented with Protocol Version 3, is an open-label phase during which all subjects receive BG00012 at a dose of 240 mg BID.** Approximately 1700 subjects ~~will be randomized~~**have been enrolled** at approximately 375 sites in North America, Europe, and the rest of the world.

Eligible subjects from Studies 109MS301 and 109MS302 ~~will be enrolled in this extension study and~~ will be followed for up to ~~5~~**8** years **in this extension study**, assuming BG00012 continues to have a positive benefit~~-~~risk ratio. **At enrollment into the study, all subjects received either**:

- BG00012 240 mg BID (2 capsules [120 mg each] twice a day and 2 placebo capsules once a day).

  OR

- BG00012 240 mg TID (2 capsules [120 mg each] three times a day).

Subjects randomized to BG00012 in Study 109MS301 or 109MS302 ~~will continue~~**continued** on the same BG000012 dose in this extension study.

Subjects randomized to placebo in Study 109MS301 or 109MS302 or **to** ~~——————~~**GA** in Study 109MS302 ~~will be~~**were** randomized to BG00012 **240 mg BID or 240 mg TID** ~~in~~**at a 1:1 ratio** ~~————————~~

Subjects who switched to an alternate approved MS therapy in Study 109MS301 or 109MS302 ~~will be~~**were** randomized in this extension study as outlined above according to their original treatment group in **Study** 109MS301 or 109MS302.

~~If~~**Effective with** the ~~results~~**approval** ~~————~~**Version** ~~————————————~~ **of the protocol, all subjects are to receive the currently marketed dose of** ~~———~~ **(2 capsules [120 mg each] BID)**~~—~~ **Subjects who are receiving BG00012** ~~————————————————~~

~~extension study~~ will be switched to ~~that dose.~~**BID dosing (2 capsules [120 mg each] BID) at their next scheduled visit after the approval of Protocol Version 3**.

Rationale: The risk-benefit of BG00012 continues to be favorable, and treatment of subjects in this study for up to 8 years will allow evaluation of the longer-term safety and efficacy of BG00012. Subsequent to the initiation of this study, BG00012 has received marketing approval in several countries for the treatment of MS at a dose of 240 mg BID. For this reason, all subjects continuing in this study at the time Protocol Version 3 is implemented will receive the currently marketed dose of 240 mg BID. Subjects currently receiving BG00012 240 mg TID will be switched to BID dosing at their next scheduled visit following approval of Protocol Version 3. Because all subjects will receive the same dosing regimen, dosing is no longer blinded; however, subjects and study personnel will remain blinded to the dose regimen subjects were receiving prior to the open-label phase. The change related to the increase in study duration from 5 years to 8 years also affects the following sections:

- Sections 4.2, Study Activities 109MS303 (Years 2 and 3 Treatment Visits)
- Section, 4.3, Study Activities (Years 4 Through 8 Treatment Visits Effective with Protocol Version 3)
- Section 7.2.2, Treatment Period
- Section 11.1, Treatment Schedule
- Section 14.3.2, Years 2 and 3 Treatment Visits
- Section 14.3.3, Years 4 Through 8 Treatment Visits
- Section 14.3.4, End of Study Visit (Week 388 ±7 Days)
- Section 16.3.2, Methods of Analysis
- Section 16.4.2, Methods of Analysis

The change related to the switch to open-label dosing with 240 mg BID also affects the following sections:

- Section 5.4, Dose Rationale
- Section 9.3, Blinding Procedures
- Section 10.1, Study Treatment Packaging

- Section 11.2.2, Resumption of Study Treatment Dosing
- Section 11.2.5, Dosage Reductions
- Section 14.1, Site Personnel
- Section 15.5.5, Dose Unblinding for Medical Emergencies

SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

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

Section 3, Synopsis

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

Section 4.3

Change: The frequency of some study procedures (clinical chemistry, hematology, urinalysis, physical examination, and urine pregnancy testing) was decreased from every 12 weeks to every 24 weeks during Year 4 through 8 of the treatment period. The study activities chart (Chart 2 of 2) was revised and new study activities charts for Years 2 and 3, Years 4 through 8, and post-treatment and unscheduled visits were created to reflect the new schedule of assessments as well as the extended duration of the study.

Now reads:

~~4.2 Study Activities 109MS303 (Chart 2 of 2)~~

~~Tests and Assessments[1]~~	~~Visit 9, 13, 17, 21 (Week 60, 108, 156, 204 ±7d)~~	~~Visit 10, 14, 18, 22 (Week 72, 120, 168, 216 ±7d)~~	~~Visit 11, 15, 19, 23 (Week 84, 132, 180, 228 ±7d)~~	~~Visit 12, 16, 20 (Week 96, 144, 192 ±7d)~~	~~Visit 24 (Week 240 ±7d)~~	~~End of Study Visit[8] (Week 100 244 ±7d)~~	~~Unscheduled Relapse Assessment Visit[8]~~	~~Premature Study Withdrawal Visit[9]~~	~~Telephone Follow-Up (12 Weeks after Last Dose)[10]~~
~~Physical Examination~~		~~X~~		~~X~~	~~X~~		~~X~~	~~X~~	
~~Vital Signs~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
~~Hematology~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
~~Blood Chemistry~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
~~Urine Pregnancy Test[2]~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	
~~Urinalysis~~	~~X[5]~~	~~X[5]~~	~~X[5]~~	~~X[5]~~	~~X[5]~~	~~X[5]~~	~~X~~	~~X[5]~~	
~~Brain MRI[3] Scan ± Gd~~				~~X[6]~~	~~X[6]~~			~~X[6]~~	
~~EDSS~~		~~X~~		~~X~~	~~X~~		~~X~~	~~X~~	
~~Visual Function Test~~		~~X~~		~~X~~	~~X~~		~~X~~	~~X~~	
~~SF-36 and EQ-5D~~				~~X~~	~~X~~		~~X~~	~~X~~	
~~Relapse Assessment~~							~~X~~		
~~Dispense Study Treatment~~	~~X~~	~~X~~	~~X~~	~~X~~					
~~Concomitant Therapy and Procedures Recording~~	~~Monitor and record throughout the study as per Section 11.5~~								~~X~~
~~AE/SAE Reporting~~	~~Monitor and record throughout the study as per Section 15~~								~~X~~

1. ~~Tests and assessments must be completed prior to study treatment distribution.~~
2. ~~For females of child-bearing potential. Results must be known prior to study treatment distribution.~~
3. ~~Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302.~~
4. ~~The Week 96 visit (Visit 24) for 109MS301 and 109MS302 will serve as the Baseline Visit for this extension study.~~
5. ~~Urine cytology must be performed if subject experiences hematuria (of unknown etiology) at 2 consecutive visits or is present at the End of Study Visit. If urine cytology is positive, subject must permanently discontinue study treatment (see Section 11.3).~~
6. ~~MRI must not be performed within 30 days of receiving a course of steroids.~~
7. ~~To be performed only for subjects who at the Week 96 visit (Visit 24) in 109MS301 or 109MS302 had a 1.0 point increase in their EDSS score from a baseline EDSS ≥1.0 or a 1.5 point increase in their EDSS from a baseline EDSS = 0.~~
8. ~~Unscheduled Relapse Assessment Visit to be carried out within 5 days of suspected relapse.~~
9. ~~To be performed within 4 weeks of the subject's last study treatment dose.~~

~~10. Required for all subjects regardless of premature study withdrawal.~~

4.2 Study Activities 109MS303 (Years 2 and 3 Treatment Visits)

Year	Year 2				Year 3			
Visit	9	10	11	12	13	14	15	16
Study Week (±7 days)	60	72	84	96	108	120	132	144
Tests and Assessments[1]								
Physical Examination	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Blood Chemistry	X	X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X
Urinalysis	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Brain MRI[4] **Scan ± Gd**				X[5]				X[5]
EDSS	X	X	X	X	X	X	X	X
Visual Function Test	X	X	X	X	X	X	X	X
SF-36 and EQ-5D				X				X
Dispense Study Treatment	X	X	X	X	X	X	X	X
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.5							
AE/SAE Reporting	Monitor and record throughout the study as per Section 15							

1. Tests and assessments must be completed prior to study treatment distribution.
2. For women of childbearing potential. Results must be known prior to study treatment distribution.
3. Urine cytology must be performed if subject experiences hematuria (of unknown etiology) on 2 consecutive tests. If urine cytology is positive, subject must permanently discontinue study treatment (see Section 11.3).
4. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302.
5. MRI must not be performed within 30 days of receiving a course of steroids.

4.3 Study Activities (Years 4 Through 8 Treatment Visits Effective with Protocol Version 3)

Year	Year 4				Year 5				Year 6				Year 7				Year 8			
Visit	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Study Week (±7 days)	156	168	180	192	204	216	228	240	252	264	276	288	300	312	324	336	348	360	372	384
Tests and Assessments[1]																				
Physical Examination		X		X		X		X		X		X		X		X		X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X		X		X		X		X		X		X		X		X		X
Blood Chemistry		X		X		X		X		X		X		X		X		X		X
Urine Pregnancy Test[2]		X		X		X		X		X		X		X		X		X		X
Urinalysis		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]
Brain MRI[4] Scan ± Gd				X[5]				X[5]				X[5]				X[5]				X[5]
EDSS		X		X		X		X		X		X		X		X		X		X
Visual Function Test		X		X		X		X		X		X		X		X		X		X
SF-36 and EQ-5D				X				X				X				X				X
Dispense Study Treatment[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.5																			
AE/SAE Reporting	Monitor and record throughout the study as per Section 15																			

1. Tests and assessments must be completed prior to study treatment distribution.
2. For women of childbearing potential. Results must be known prior to study treatment distribution.
3. Urine cytology must be performed if subject experiences hematuria (of unknown etiology) on 2 consecutive tests. If urine cytology is positive during the treatment period, subject must permanently discontinue study treatment (see Section 11.3).
4. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302.
5. MRI must not be performed within 30 days of receiving a course of steroids.
6. The date and Study Visit/Week at which subjects are switched to open-label treatment should be recorded on the dosing CRF.

4.4 Study Activities (Unscheduled and Post-Treatment Visits)

Tests and Assessments	End of Study Visit[1] (Week 388 ± 7 days)	Unscheduled Relapse Assessment Visit[2]	Premature Study Withdrawal Visit[1]	Telephone Follow-Up (12 Weeks After Last Dose)[3]	[redacted] Follow-Up (up to 24 Weeks After Last Dose)[4]
Physical Examination		X	X		
Vital Signs	X	X	X		X
Hematology	X	X	X		X
Blood Chemistry	X	X	X		
Urine Pregnancy Test[5]	X	X	X		
Urinalysis	X[6]	X	X[6]		
Brain MRI[7] Scan ± Gd			X[8]		
EDSS		X	X		
Visual Function Test		X	X		
SF-36 and EQ-5D		X	X		
Relapse Assessment		X			
Concomitant Therapy and Procedures Recording	Monitor and record throughout the study as per Section 11.5				
AE/SAE Reporting	Monitor and record throughout the study as per Section 15				

1. To be performed within 4 weeks of the subject's last study treatment dose.
2. Unscheduled Relapse Assessment Visit is to be carried out within 5 days of suspected relapse.
3. Required for all subjects regardless of premature study withdrawal.
4. Effective with Protocol Version 3, subjects who complete or discontinue BG00012 for any reason and have a lymphocyte count less than the LLN will be followed every 4 weeks until the lymphocyte count is ≥LLN OR until 24 weeks after the last dose (whichever is sooner).
5. For women of childbearing potential.
6. Urine cytology must be performed if subject experiences hematuria (of unknown etiology) on 2 consecutive tests or is present at the End of Study Visit or Premature Study Withdrawal Visit.
7. Only in subjects who had MRI scans as part of Studies 109MS301 and 109MS302.
8. MRI must not be performed within 30 days of receiving a course of steroids.

Rationale: Because the safety of BG00012 is well established and the dose of BG00012 240 mg BID is now approved in several countries, it is considered that the decrease in the frequency of certain safety assessments from every 12 weeks to every 24 weeks will be less burdensome for subjects while remaining adequate to monitor subject safety. Subjects will continue to visit the clinical site every 12 weeks throughout the study for study drug dispensing and will undergo vital signs assessments at these visits. Monitoring for adverse events and concomitant medications continues throughout the study.

This change also affects the following sections:

- Section 14.3.2, Years 2 and 3 Treatment Visits
- Section 14.3.3, Years 4 Through 8 Treatment Visits
- Section 14.3.4, End of Study Visit (Week 388 ±7 Days)

Section 7.2.3, Post-Treatment Period

Change: Follow-up for subjects with low lymphocyte count at completion or early termination of treatment was added.

Now reads:

Subjects will complete an End of Study Visit 4 weeks following their last treatment visit. Subjects will receive a follow-up telephone call 12 weeks after the last dose of study treatment regardless of whether they prematurely withdrew from the study. **Subjects who complete or discontinue BG00012 for any reason and have a lymphocyte count less than the lower limit of normal (LLN) will be followed every 4 weeks until the lymphocyte count is ≥LLN or until 24 weeks after the last dose (whichever is sooner; see Section 14.3.8).**

Rationale: Lymphopenia is a known effect of BG00012 treatment. Additional follow-up of subjects with low lymphocyte counts after the completion or early termination of study treatment will provide information regarding the time required for decreased lymphocyte counts to resolve following treatment withdrawal.

This change also affects the following sections:

- Section 4.4, Study Activities (Unscheduled and Post-Treatment Visits)
- Section 11.2.1, Dosing Interruption for Abnormal Laboratory Values
- Section 11.2.3, Subsequent Development of Additional Laboratory Abnormalities
- Section 11.3, Removal of Subjects from Treatment and Withdrawal from Study
- Section 14.3.8, Lymphocyte Follow-Up

Section 11.2.2, Resumption of Study Treatment Dosing

Change: Dosing regimen in the case of dosage interruption was updated.

Now reads:

Subjects who are allowed to resume study treatment dosing following a 2 to 4 week interruption will restart dosing at a reduced dosage for 1 week. Subjects will take ~~1~~**one 120 mg** capsule ~~TID~~**BID** for 1 week. After 1 week at the reduced dose, subjects will resume taking ~~2~~**two 120 mg** capsules ~~TID~~**BID**.

Rationale: The dosing regimen for BG00012 was changed so that all subjects will now receive 240 mg BID.

This change also affects Section 11.2.5, Dosage Reductions.

Section 11.2.4, Abnormal Urinalyses that Require Additional Evaluation

Change: Tests for urine beta 2-microglobulin and microalbumin and referral to a nephrologist for abnormal urinalysis values are no longer required.

Now Reads:

Subjects who develop any of the following abnormal urine laboratory values must have the test repeated 2 weeks later:

- Urinary casts (other than hyaline casts)
- Proteinuria (1+ or greater)
- _____
- _____
- Glycosuria (trace or greater) in the setting of normal serum glucose.

_____
_____
_____

Abnormalities detected on urinalysis should be managed as per the local standard of care.

Rationale: Abnormal beta 2-microglogulin and microalbumin values have been rarely reported, and BG00012 has not been associated with renal dysfunction. Follow-up as per local standard of care for abnormal urinalysis values is considered adequate to ensure patient safety and is consistent with other ongoing clinical studies of BG00012.

This change also affects the following sections:

- Section 11.3, Removal of Subjects from Treatment and Withdrawal from Study
- Section 13.2, Laboratory Safety Assessments.

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.
- Section 1.1, Biogen Idec Personnel, was updated.
- Section 2, List of Abbreviations, was updated.Section 5.2, Profile of Previous Experience with Fumarates, was updated with efficacy and safety results from recently completed studies.
- Section 11.6, Continuation of Treatment, was deleted as it no longer applies.
- Section 15.5.1, Overdose, was changed to indicate that overdoses are to be reported on an Overdose Form and faxed to [redacted].
- Section 15.5.4, Reporting Pregnancy, was changed for consistency with the protocol template and the procedures used in other ongoing BG00012 studies.
- Section 17, Ethical Requirements; Section 18, Administrative Procedures; and Section 19, Further Requirements and General Information, were updated for consistency with revisions to the Biogen Idec protocol template and other BG00012 protocols and to update information related to the roles and responsibilities of clinical research organizations and other vendors.
- Section 20, References, was updated to include a new reference.
- Minor editorial and formatting changes were made throughout the protocol.

Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142, USA

Biogen Idec Ltd.
Innovation House
70 Norden Road
Maidenhead Berkshire
SL6 4AY
United Kingdom

AMENDMENT SUMMARY

Biogen Idec Protocol 109MS303

A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Version 2

Date: 15 September, 2010

EUDRA CT Number: 2008-004753-14

Version 2 of the protocol has been prepared for this amendment, which supersedes Version 1.

PRIMARY REASON(S) FOR AMENDMENT

The primary reason for this amendment to Protocol 109MS303 is extension of the duration of the study from 2 years to 5 years or marketing authorization (if approved), whichever occurs first.

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

Section 7.1, Study Overview

Now reads:

This is a multicenter, parallel-group, randomized, dose-blind, dose-comparison study. Approximately 1700 subjects will be randomized at approximately 375 sites in North America, Europe, and the rest of the world.

Eligible subjects from Studies 109MS301 and 109MS302 will be enrolled in this extension study a ~~_____~~ **5 years,** assuming BG00012 continues to have a positive benefit/risk ratio.

Rationale:

Treatment of subjects in this study for up to 5 years or until marketing authorization, whichever occurs first, will allow evaluation of BG00012 for longer term safety and efficacy.

This change also affects Sections 3, Synopsis; 4.2, Study Activities 109MS303 (Chart 2 of 2); 7.2.2 Treatment Period; 7.2.3, Post-Treatment Period; 11.6, Continuation of Treatment; 14.3.13, Tests and Assessments; 16.3.2, Methods of Analysis (Efficacy Data); 16.4.2, Methods of Analysis (Safety Data).

SUMMARY OF MINOR CHANGES TO THE PROTOCOL

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

- The version number and date were updated throughout the protocol.

- It was clarified that the study personnel may include an examining neurologist to perform EDSS evaluations if the treating neurologist does not perform these assessments. This clarification affects Sections 14.1, Site Personnel; 14.3.1, Baseline Visit; 14.3.4, Visit 3; 14.3.7, Visit 6; 14.3.9, Visit 8; 14.3.11, Visit 10, 14, 18, 22; 14.3.12, Visit 12, 16, 20, 24; 14.3.14, Unscheduled Relapse Assessment Visit; 14.3.15, Premature Study Withdrawal Visit.

- It was clarified that the study personnel may include an examining technician if the treating neurologist designates visual function test examinations. This change affects Sections 14.1, Site Personnel; 14.3.1, Baseline Visit; 14.3.7, Visit 6; 14.3.9, Visit 8; 14.3.11, Visit 10, 14, 18, 22; 14.3.12, Visit 12, 16, 20, 24; 14.3.14, Unscheduled Relapse Assessment Visit; 14.3.15, Premature Study Withdrawal Visit.

- A window between Visit 24 of the 109MS301 or 109MS302 study and Baseline for the 109MS303 study will be allowed. If the Baseline Visit for 109MS303 cannot be combined with Visit 24 of the preceding study, subjects may be randomized within 6 months of Visit 24. Language that pertains to continuous dosing has been eliminated. This change affects Sections 3, Synopsis; 7.2.1, Baseline; 9.1, Enrollment Procedures; 14.3.1, Baseline Visit.

- It was clarified that all tests and procedures of Baseline Visit that are also included in the 109MS301 or 109MS302 protocol should be performed by the respective personnel of the parent study. This change affects Section 4.1, Study Activities 109MS303 (Chart 1 of 2); 14.3.1, Baseline Visit; 14.3.4, Visit 3.

- Sections 14.3.10 and 14.3.12 in Version 1 were identical; these are now consolidated into Section 14.3.10; Section 14.3.12 is deleted; headings have been re-numbered in Section 14.3. This also affects the Table of Contents.

- Drug Safety and Risk Management signatory updated, page 1.

- Section 1, Contact List, was updated.