CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204063Orig1s000

MEDICAL REVIEW(S)

MEMORANDUM

DATE: March 17, 2013

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 204063

SUBJECT: Recommendation for action on NDA 204063, for the use of Tecfidera (Dimethyl Fumarate) for the treatment of patients with Relapsing Remitting Multiple Sclerosis (RRMS)

NDA 204063, for the use of Tecfidera (Dimethyl Fumarate) as an oral treatment for patients with Relapsing Remitting Multiple Sclerosis (RRMS), was submitted by Biogen Idec Inc., on 2/27/12. A major amendment, addressing Agency questions related to the carcinogenic potential of the drug, was submitted on 10/5/12; as a result, the user fee goal date is 3/27/13.

The application contains the results of two randomized controlled trials purporting to provide substantial evidence of the drug's effect in the treatment of patients with RRMS. In addition, the application contains safety, non-clinical, clinical pharmacology, and chemistry and manufacturing control (CMC), data that the sponsor believes support the application's approval.

The application has been reviewed by Drs. David Claffey and Sarah Miksinski, Office of New Drug Quality Assessment (ONDQA); Michael Trehy and Anjanette Smith, Division of Pharmaceutical Analysis; Dr. Elsbeth Chikhale, ONDQA, Biopharmaceutics; Drs. Melissa Banks-Muckenfuss and Lois Freed, pharmacology/toxicology; Steve Thomson, Office of Translational Sciences, Office of Biostatistics; Dr. Jagan Parepally, Office of Clinical Pharmacology; Dr. Michael Skelly, Office of Scientific Investigations, Division of Bioequivalence and GLP Compliance; CDER QT Interdisciplinary Review Team; Dr. Heather Fitter, medical reviewer; Dr. Xiang Ling, Office of Biostatistics; Drs. Gerard Boehm and Sally Yasuda, safety team; Dr. Antoine El-Hage, Office of Scientific Investigations, Division of Good Clinical Practice Compliance; Drs. Carrie Ceresa and Nadia Hejazi, Pediatric and Maternal Health Staff; Dr. Alicja Lerner, Controlled Substance Staff; Dr. Andrew Fine, Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance I; Drs. Kendra Worthy and Julie Neshiewat, OSE, Office of Medication Error Prevention and Risk Management; Shawna Hutchins, Office of Medical Policy Initiatives, Division of Medical Policy Programs; Dr. Quynh-Van Tran, Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion; Dr. Meeta Patel, OPDP, Division of Consumer Drug Promotion; Elizabeth Donohoe, Study Endpoints and Labeling Development (SEALD); and Dr. Billy Dunn, neurology team leader and Cross Discipline Team Leader (CDTL).

The review team recommends that the application be approved, albeit with recommendations for the imposition of Post-Marketing Requirements (PMRs).

In this memo, I will briefly review the relevant data, and offer the rationale for the division's recommendations for action on the application.

Background

Dimethyl fumarate (DMF) is rapidly and essentially fully metabolized to the active metabolite monomethyl fumarate (MMF); subsequent metabolism is through the tricarboxylic acid (TCA) cycle, and the active moiety is primarily eliminated as CO_2. Although the precise mechanism of action is unknown, it is believed to activate the nuclear factor related factor 2 (Nrf2) antioxidant response pathway, a pathway believed to upregulate antioxidant response genes.

DMF is not marketed anywhere, but a closely related product, Fumaderm, a combination of DMF and other salts of monoethyl fumarate, has been marketed in Germany since 1994 for the treatment of moderate to severe psoriasis.

Effectiveness

As noted above, the sponsor has submitted the results of two randomized controlled trials of relatively similar design to support a finding of substantial evidence of effectiveness (Studies 301 and 302). In addition, they have submitted the results of another controlled trial (Study C-1900) that served as the basis for the choice of doses studied in Studies 301 and 302. I will briefly review the results of these studies.

C-1900

This was a double-blind, multiple fixed dose study in which patients with RRMS were randomized to receive either placebo, or DMF 120 mg qd, 120 mg tid, or 240 mg tid for 6 months. The primary outcome was the total number of new gadolinium-enhancing lesions measured at Weeks 12, 16, 20, and 24. New or newly enlarging T2 hyperintense lesions at Week 24 were also assessed, as were other MRI measures and annualized relapse rate. From 63-65 patients were randomized to each group.

The following chart displays the relevant results:

	Pbo	120 qd	120 tid	240 tid
Mean new Gd lesions				
Weeks 4-24	6.6	6.2	6.7	3.7
P-value		0.9	0.8	0.002
New enlarging T2				
Hyperintense lesions	4.2	3.8	4.1	2.2
P-value		0.9	0.8	0.0006
New enlarging T1				
Hyperintense lesions	1.7	1.3	1.5	0.8
P-value		0.7	0.8	0.01
Annualized relapse rate	0.65	0.42	0.78	0.44
P-value		0.2	0.6	0.3

Study 301

This was a double blind, multiple fixed dose, multi-center trial in which patients with RRMS were randomized to either placebo, DMF 240 mg BID, or DMF 240 mg TID. The trial duration was two years, and the primary outcome was the proportion of patients relapsing. The study personnel consisted of Primary and Backup Treating Neurologists, Primary and Backup Treating Nurses, and Primary and Backup Examining Neurologists. All study personnel were blinded to treatment assignment. According to Dr. Fitter's very clear explanation, the procedure for documenting that a relapse had occurred is described below:

Patients who experienced new neurologic symptoms were to contact the treating neurologist or nurse within 48 hours. They completed a phone questionnaire, and a determination was made whether an unscheduled relapse assessment visit was necessary. If so, the patient had to have been seen by the treating neurologist within 72 hours of the onset of symptoms, and by the examining neurologist within 5 days of the onset of symptoms. The examining neurologist performed a relapse assessment and an expanded disability severity score (EDSS). Based on the examining neurologist's examination, the treating neurologist determined if there were new objective findings.

If the treating neurologist determined (based on the examining neurologist's exam) that there were new objective findings, the treating neurologist referred the case to the Independent Neurologic Evaluation Committee (INEC), a body of three neurologists. The INEC reviewed the patients' records independently (they

did not meet to discuss the cases). If a majority of the INEC determined that a relapse occurred, it was counted as a relapse. Only INEC-declared relapses were considered in the analyses of relapses.

Subjects could be treated with intravenous methylprednisolone (IVMP) for an acute relapse only after they had been examined by the examining neurologist. If a patient had an INEC-confirmed relapse that occurred at or after Week 24, and had completed 48 weeks of study treatment, they had the following options:

1) remain on blinded treatment
2) switch to open-label alternative MS treatment and remain in the study
3) discontinue study treatment, decline alternative treatment, and remain in the study

Patients who experienced disability progression at any time during the study had the same options.

Other outcome measures included:

1) **Disability Progression**-defined as at least a 1 point increase in the EDSS from a baseline EDSS of at least 1.0 that was sustained for 12 weeks, or a 1.5 point increase in EDSS from a baseline EDSS of 0, sustained for 12 weeks.
2) **Annualized Relapse Rate (ARR)**-including only INEC-confirmed relapses that occurred before a patient received alternative MS treatments
3) **MS Functional Composite (MSFC) Scale**-a three part assessment consisting of a timed 25 foot walk, a 9-Hole Peg Test, and a paced auditory serial addition test 3 (PASAT 3, a cognitive test)
4) **Patient Reported Outcomes**, including:
    1) Global impression of well-being: A visual analogue scale (VAS) from 0-100
    2) SF-36 Health Survey-a 36 item questionnaire with 8 quality of life domains
    3) EQ-5D-consisting of 2 domains; the descriptive system (5 health dimensions) and a VAS

5) **MRI assessments**-

    MRI was assessed at only a subset of sites that had the appropriate facilities and expertise. All MRI scans were centrally read, and assessments were made at baseline and Weeks 24, 48, and 96. A partial list of measures included:

    1) New or enlarging T2 weighted lesion count
    2) T2 weighted lesion volume
    3) Gd-enhancing lesion count

4) Gd-enhancing lesion volume
5) T1 weighted lesion count
6) New T1 weighted non-enhancing hypointense lesion count
7) Percent brain volume change

Results

A total of 1237 patients were randomized at 198 sites in 28 countries. As noted by Dr. Ling, the highest enrolling countries, in descending order, were: US (203), Germany (172), Poland (132), and India (114). The following chart displays the patient disposition in the study:

	Pbo	240 BID	240 TID
Randomized	410	411	416
Pts dosed	408	410	416
Number completing study drug	265	284	289
Number discontinuing study drug:			
MS relapse	31	4	10
MS progression	14	7	7
Adverse event	22	61	56
Consent withdrawn	34	18	18
Number completing study	317	315	320
Number receiving alternative MS tx	53	25	21

The following chart displays the results of the primary analysis, Proportion of Patients Relapsing:

	Pbo	240 BID	240 TID
Number relapsing	171 (42%)	98 (24%)	95 (23%)
Proportion relapsed at 2 yrs	0.46	0.27	0.26
Hazard ratio		0.51	0.50
Percentage reduction		48.5	49.5
P-value		<0.0001	<0.0001

Several worst-case analyses were performed by Agency reviewers, including counting all relapses, including those that occurred after the use of alternative MS treatments in the DMF-treated patients but including only those relapses that occurred prior to such alternative use in the placebo patients, and also including all patients who had an unknown relapse status at 2 years (16%, 21%, and 20% in the placebo, BID, and TID groups, respectively) as having had a relapse if they discontinued study medication for MS relapse, lack of efficacy, or alternative MS therapy having been started. These sensitivity analyses were consistent with the primary analysis, including the lack of dose effect.

Annualized Relapse Rate (ARR)

The following chart displays the results of the annualized relapse rates. The primary analysis of ARR excluded relapses that occurred after the institution of alternative MS treatments. The ARR for a treatment group was calculated as the total number of INEC-confirmed relapses divided by the total patient-time in study (subtracting time of alternative MS treatments).

	Pbo	240 BID	240 TID
Adjusted ARR	0.364	0.172	0.189
Rate Ratio		0.473	0.521
Percentage Reduction		52.7%	47.9%
P-value		<0.0001	<0.0001

A worst case analysis in which relapses occurring after alternative MS treatments were started were included in the DMF groups, but not for the placebo group, yielded a similar outcome.

Disability Progression

The following chart displays the results of the analyses of disability progression:

	Pbo	240 BID	240 TID
Number progressed	89	57	62
Proportion progressed	0.27	0.16	0.177
Hazard ratio		0.62	0.66
Percent reduction		38.0	33.8
P-value		0.005	0.013

Dr. Ling performed two sensitivity analyses: one in which patients had to have had a 24 week sustained disability, and one in which patients who had met the protocol-definition of progression (sustained for 12 weeks) and in whom progression was sustained at the end of the study. The results are presented below:

	Pbo	240 BID	240 TID
24 week sustained			
Number progressed	57	44	41
Proportion progressed	0.17	0.13	0.12
Hazard ratio		0.77	0.69
Percent reduction		23.2	30.5
P-value		0.19	0.08

	Pbo	240 BID	240 TID
Sustained at study end			
Number progressed	54	36	35
Proportion progressed	0.18	0.10	0.1
Hazard ratio		0.66	0.62
Percent reduction		34.6	38.1
P-value		0.05	0.03

The following results were obtained for the analyses of the main MRI assessments, taken from Dr. Ling's Tables 8 and 9, page 19 of her review:

Number of New or Newly enlarging T2 lesions at 2 years:

	Pbo	240 BID	240 TID
N	165	152	152
Adjusted Mean	17.0	2.6	4.4
Percent reduction		-85	-74
P-value		<0.0001	<0.0001

The above results represent the protocol-specified analysis, which imputed missing data based on a constant-rate assumption. Dr. Ling performed various sensitivity analyses which used last observed data (the sponsor performed several sensitivity analyses that used only Week 96 data, but not earlier data if Week 96 data were missing). Dr. Ling performed analyses using the last

observed data only prior to institution of alternative MS treatments, and also using the last observed data including after switching to alternative therapies. These analyses were consistent with the primary analysis presented above.

Number of Gd-Enhancing Lesions at 2 years:

	Pbo	240 BID	240 TID
N	165	152	152
Mean	1.8	0.1	0.5
Odds ratio		0.10	0.5
P-value		<0.0001	<0.0001

Study 302

Study 302 was similar in design to Study 301, with one significant exception: This study also included an additional randomized arm, consisting of open-label glatiramer acetate, an approved injectable treatment for RRMS. Because this arm was open-label, I will not present the results for this arm. In addition, although similar outcomes were assessed and analyzed in both studies, in Study 302, the primary outcome was ARR, not proportion of patients who relapsed.

A further difference between the two studies was the rule for being eligible to receive alternative MS treatments. In Study 302, patients had the option to receive alternative MS treatments if they had completed 48 weeks of blinded treatment and had 2 INEC-confirmed relapses, or if they had significant disability progression at any time.

Results

A total of 1430 patients were enrolled at 200 sites in 28 countries. According to Dr. Ling, the highest enrolling countries, in descending order, were Poland (282), US (2670, India (107), and Ukraine (104).

The following chart displays patient disposition:

	Pbo	240 BID	240 TID
Randomized	363	362	345
Pts dosed	363	359	345
Number completing study drug	234	253	249
Number discontinuing study drug:			
MS relapse	28	8	6
MS progression	10	8	7
Adverse event	22	38	42
Consent withdrawn	12	8	10
Number completing study	278	284	273
Number receiving alternative MS tx	40	25	28

Annualized Relapse Rate (ARR)

The following chart displays the results of the annualized relapse rates. The primary analysis of ARR excluded relapses that occurred after the institution of alternative MS treatments. The ARR for a treatment group was calculated as the total number of INEC-confirmed relapses divided by the total patient-time in study (subtracting time of alternative MS treatments).

	Pbo	240 BID	240 TID
Adjusted ARR	0.401	0.224	0.198
Rate Ratio		0.560	0.495
Percentage Reduction		44.0%	50.5%
P-value		<0.0001	<0.0001

A worst case analysis in which relapses occurring after alternative MS treatments were started were included in the DMF groups, but not for the placebo group, yielded a similar outcome, including numerical superiority of the high dose compared to the low dose.

As in Study 301, analyses of the proportion of patients relapsing at 2 years was also performed:

	Pbo	240 BID	240 TID
Number relapsing	140 (39%)	93 (26%)	76 (22%)
Proportion relapsed at 2 yrs	0.41	0.29	0.24
Hazard ratio		0.66	0.55
Percentage reduction		34.0	44.6
P-value		0.002	<0.0001

Disability Progression

The following chart displays the results of the analyses of disability progression:

	Pbo	240 BID	240 TID
Number progressed	52	40	38
Proportion progressed	0.17	0.13	0.13
Hazard ratio		0.79	0.76
P-value		0.25	0.20

As for Study 301, Dr. Ling performed two sensitivity analyses: one in which patients had to have had a 24 week sustained disability, and one in which patients met the protocol-definition of progression (sustained for 12 weeks) and in whom progression was sustained at the end of the study. The results are presented below:

	Pbo	240 BID	240 TID
24 week sustained			
Number progressed	52	40	38
Proportion progressed	0.13	0.08	0.12
Hazard ratio		0.77	0.09
P-value		0.06	0.12

	Pbo	240 BID	240 TID
Sustained at study end			
Number progressed	37	20	26
Proportion progressed	0.13	0.06	0.09
Hazard ratio		0.52	0.73
P-value		0.02	0.21

The following results were obtained for the analyses of the main MRI assessments, taken from Dr. Ling's Tables 14 and 15, page 23 of her review:

Number of New or Newly enlarging T2 lesions at 2 years:

	Pbo	240 BID	240 TID
N	139	140	140
Adjusted Mean	17.4	5.1	4.7
Percent reduction		-71	-73
P-value		<0.0001	<0.0001

The above results represent the protocol-specified analysis, which imputed missing data based on a constant-rate assumption. As for Study 301, Dr. Ling performed various sensitivity analyses which used last observed data (the sponsor performed several sensitivity analyses that used only Week 96 data, but not earlier data if Week 96 data were missing). Dr. Ling performed analyses using the last observed data only prior to institution of alternative MS treatments, and also using the last observed data including after switching to alternative therapies. These analyses were consistent with the primary analysis presented above.

Number of New or Newly Enlarging T1 Lesions at 2 years:

	Pbo	240 BID	240 TID
N	139	140	140
Mean	7.0	3.0	2.4
Percent reduction		57	65
P-value		<0.0001	<0.0001

Number of Gd-Enhancing Lesions at 2 years:

	Pbo	240 BID	240 TID
N	167	169	170
Mean	2.0	0.5	0.4
Odds ratio		0.26	0.35
Percent reduction		74	65
P-value		<0.0001	<0.0001

Safety

The sponsor has submitted safety data for the total of 3,424 subjects/patients who received at least one dose of DMF. A total of 2,210 patients with MS received at least 6 months of treatment, 1,787 received at least 12 months of treatment, and 712 patients received at least 3 years of treatment. A total of 2,665 patients with MS were treated with DMF and 2,537 patients with MS received doses of at least 240 mg BID.

The sponsor also performed studies in patients with Psoriasis (N=320), in patients with Rheumatoid Arthritis (RA; N=101), and inn healthy subjects (N=338).

The sponsor submitted the safety data in various pools of patients:

Pool A-controlled MS trial data (Studies C-1900, 301, and 302; N=1,720)
Pool B-controlled and open-label MS studies (N=2,513)
Pool C-controlled trials in Psoriasis (Study 12/01, 3 months, same doses as C-1900, N=144; Study 01/02, 4 months, 240 mg TID, N=213)
Pool D-controlled and open-label Psoriasis studies (N=296)

The sponsor also submitted data from several other studies in MS patients, healthy subjects, and patients with RA.

The primary safety analyses were performed on Pool A, though, of course, Dr. Boehm has reviewed all safety data.

Deaths

There were a total of 11 deaths in the development program; 9 occurred in DMF-exposed patients (N=7 MS, N=2 Psoriasis). A total of 3 deaths occurred in MS controlled trials; 1 in the 240 mg BID group (though the death occurred during titration, while the patient received 120 mg BID) and 2 occurred in the 240 mg TID group. Dr. Boehm has reviewed the deaths in detail (pages 21-24 of his review). None of the deaths has any obvious or suspected relation to treatment.

Serious Adverse Events (SAEs)

In controlled MS trials, the incidence of SAEs was greater in the placebo group (21%) than in the combined DMF groups (16%) or in any DMF dose group (greatest incidence 18% in the 240 mg BID group). No individual AE occurred in at least 1% of DMF-treated patients and at a greater incidence than in the placebo group.

A total of 17% of DMF-treated MS patients experienced at least one SAE. Only MS Relapse occurred at an incidence of more than 1% (9%). Only Gastroenteritis (N=10), gastritis (N=8), Urinary Tract Infection (N=8), Falls (N=5), and Road Accident (N=5) occurred in at least 5 patients.

Dr. Boehm has identified several SAEs that he has characterized as being of potential concern. He includes in this list: hypersensitivity (N=2), anaphylactic and anaphylactoid reaction (N=1 each), Stevens Johnson Syndrome (SJS; N=1), allergic dermatitis (N=1), chronic hepatitis, hepatic failure, cholestatic hepatitis (N=1 each), rhabdomyolysis (N=1), increased Beta-2 microglobulin (N=1), proteinuria (N=1), and myopericarditis (N=1). Several of these will be discussed later in subsequent sections.

Regarding these events, there were plausible alternative explanations for the anaphylactic reaction (patient with nut allergy ate a nut); and SJS (patient was treated with carbamazepine, which was discontinued, and remained on DMF). The patient with hepatic failure took a fatal overdose of acetaminophen. The patient with rhabdomyolysis began a weight training program after having not done so in years.

The patient with myopericarditis was a 64 year old man with pain in the upper thorax and neck on Day 174 of treatment. EKG showed ST elevations in numerous leads, and angiography showed 60% stenosis of 2 vessels. He discontinued treatment on Day 178.

Discontinuations

The following table, based on Dr. Boehm's Table on pages 31-2 of his review, displays the incidence of adverse events that led to study discontinuation at a rate greater than placebo in any DMF dose group in the MS controlled studies:

Event	Pbo	240 mg BID	240 mg TID
N	836	769	823
Flushing	<1%	3%	2%
Diarrhea	<1%	<1%	2%
Nausea	0%	<1%	2%
Vomiting	0%	1%	1%
Abdominal pain	<1%	1%	2%
Skin disorders	<1%	2%	2%

A total of 11 patients discontinued treatment for events called Hypersensitivity. According to Dr. Boehm, they were not well described, but some included the terms: itching, edema of the lips/face, flushing, pruritis, shortness of breath, burning face; some patients were treated with steroids and antihistamines. Four of these occurred on the first day of dosing, 5 occurred within the first month, 2 occurred from about 3 and 4 months on treatment, and one occurred after about one year on treatment.

Common Adverse Events

The following table, adapted from Dr. Boehm's table on pages 75-6 of his review, displays the common adverse events that occurred in the MS controlled trials, and that occurred in any dose group at a rate of 1.5 times more frequent than in the placebo group.

Event	Pbo	240 mg BID	240 mg TID
Flushing	5%	34%	29%
Diarrhea	10%	14%	17%
Nausea	9%	12%	14%
Abdominal pain	4%	9%	8%
Pruritis	4%	8%	8%
Vomiting	5%	8%	7%
Rash	3%	8%	7%
Hot flush	2%	7%	7%
Erythema	1%	5%	7%
Urinary albumen	3%	6%	4%

Event	Pbo	240 mg BID	240 mg TID
AST increased	2%	4%	4%
Hyperhidrosis	1%	2%	3%

Laboratory Findings

DMF causes lymphopenia. In MS controlled trials, mean decreases in lymphocyte counts are seen at Week 4, at the first determination. Mean counts continue to decrease until Week 48, after which the counts stabilize. Specifically, the following values were seen:

Lymphocyte count (change from baseline; $x10^9$/L)

	Placebo	240 mg BID	240 mg TID
Week 4	0.04	-0.05	-0.10
Week 48	0.02	-0.63	-0.54
Week 96	0.02	-0.66	-0.58

These mean changes were accompanied by an increase in the number of patients who met outlier criteria for low lymphocyte counts:

Lymphocytes ($x10^9$/L)	Pbo	240 BID	240 TID
<0.8	3%	28%	21%
<0.5	<1%	6%	3%

The data are suggestive that, at 4 weeks post discontinuation of dosing, the lymphocyte count continues to approach baseline, though does not return to baseline.

Similar, though smaller, changes were seen for total WBC, neutrophils, hemoglobin, hematocrit, and platelets (see Dr. Boehm's table, page 79-80).

There was a slight increase in Eosinophil count at Week 4 that resolved at later time points:

Eosinophil count (change from baseline; $x10^9$/L)

	Placebo	240 mg BID	240 mg TID
Week 4	0.00	0.19	0.15
Week 8	0.00	0.02	0.01

Dr. Boehm has examined the incidence of patients who had eosinophil counts at least 2 x ULN at Weeks 4, 8, and 12:

Week	Placebo	240 mg BID	240 mg TID
4	<1%	5.5%	3.9%
8	<1%	<1%	<1%
12	0	<1%	0

Other chemistries

DMF caused small mean decreases in serum chloride and triglycerides, and small mean increases in serum bicarbonate compared to baseline, as shown below:

		Chloride	
Week	Placebo	240 mg BID	240 mg TID
Week 12	0.13	-0.33	-0.23
Week 96	-0.03	-0.29	-0.25
		Bicarbonate	
Week 4	0.17	0.53	0.48
Week 24	0.03	0.55	0.63
Week 52	-1.48	-1.27	-1.08
Week 96	-0.29	-0.01	-0.06
		Trigylcerides	
Week 4	0.02	-0.16	-0.14
Week 96	0.05	-0.15	-0.14

There was a slight increase in the percent of patients on DMF who had bicarbonate levels > ULN-32 mmol/L (7%, 11%, and 11% for placebo, 240 BID and TID, respectively). There was also a higher percent of DMF-treated patients who had a shift in bicarbonate levels from normal at baseline to high (9%, 16%, and 15% for placebo, BID, and TID, respectively).

Parathyroid hormone (PTH) and Vitamin D

PTH was increased and Vitamin D levels were decreased in DMF treated patients compared to placebo. These differences were reflected in mean changes, as well as shifts compared to baseline and patients with values greater than baseline, as displayed below:

PTH

Week	Placebo	240 mg BID	240 mg TID
Week 48	-0.96	7.97	10.4
Week 96	3.07	12.02	15.4
Shift High	8%	19%	22%
>ULN	8.6%	19.8%	22.8%
>1.5 X ULN	0.9%	3.5%	4.6%

Vitamin D

Week 48	0.58	-18.31	-24.69
Week 96	-20.97	-31.92	-36.17
Shift Low	5%	8%	10%

Dr. Boehm has calculated the percent of patients who had both elevated PTH (>ULN) and decreased Vitamin D (<LLN) at both Weeks 48 and 96:

	Placebo	240 mg BID	240 mg TID
Week 48	10%	9.1%	7.9%
Week 96	6.7%	11.1%	13.0%

There were no changes in measures of serum Calcium (mean changes from baseline, shifts from baseline, or percent meeting outlier criteria).

Vital signs

There were no appreciable changes in vital signs in either of the treatment groups compared to placebo.

EKG

A thorough QT study was performed comparing the effects of single doses of DMF of 240 and 360 mg and 400 mg moxifloxacin and placebo. The study had adequate assay sensitivity (increase in the QT in the moxifloxacin group of 11 ms) and showed no effect on QT in either of the DMF groups.

Adverse Events of Special Interest

Flushing

DMF causes flushing in about 30% of DMF treated patients, compared to 5% in placebo patients; it appears not to be dose-related. Typically, flushing occurs early, occurring on the first day in about 45% of the patients who develop flushing, and in about 60% of patients within the first week. The incidence appears to drop considerably by the second month of treatment, though in some patients it does not resolve. In controlled trials, almost 70% of the episodes were considered mild, with about 4% considered severe.

The sponsor reported 4 events of flushing as being serious, but one was a hypersensitivity reaction, and one was an anaphylactoid reaction. None were life-threatening, though several of these events were treated with steroids and/or antihistamines.

The sponsor investigated pre-treatment with aspirin as a prophylaxis against flushing, but the number of patients treated was small, and the differences in incidence of flushing between the ASA-treated and non-ASA-treated patients was minimal. The sponsor performed a cross-over study comparing the rates of flushing when the drug was taken with or without food. A total of 96% of patients (34/36) experienced flushing when DMF was taken without food, compared to 68% (23/34) who experienced flushing when DMF was taken with food.

Liver injury

DMF caused a slight increase in the percent of patients who experienced at least one elevated transaminase compared to placebo (ALT: 35%, 48%, and 53%; AST 21%, 26%, and 31% for placebo, 240 mg BID, and 240 mg TID, respectively), but no appreciable differences in the percent of patients experiencing elevations equal to or greater than 3 X ULN. There were no differences between DMF- and placebo-treated patients in the percentages with elevated bilirubin, and no patient experienced an LFT elevation of at least 3 X ULN and bilirubin at least 2 X ULN.

A total of 3 events related to possible liver injury were reported as serious.

One was a patient who committed suicide by acetaminophen overdose.

One was a 29 year old woman with fluctuating transaminase levels during treatment with 240 mg BID in Study 301. Her levels were normal at the end of that study. She was off drug for the next 6 months, after which she entered an open-label extension; her LFTs were elevated at baseline for that phase, after having been off treatment for 6 months (ALT 110, AST 72). Her LFTs increased after 20 days of treatment (ALT 314, AST 264). Drug was discontinued, and a month later, her transaminases were still elevated (ALT 99, AST 59). Her LFTs remained elevated for about 4 months after discontinuation.

One patient, a 45 year old woman with a history of hyperbilirubinemia, developed elevated ALT and AST on Day 421 of treatment. Her bilirubin was elevated (28), but not above screening (29). On Day 444, her ALT and AST peaked (1276 and 827, respectively), as did her bilirubin (38). The drug was discontinued, and ALT and AST returned to essentially normal by Day 505; bilirubin was increased, but equal to screening.

Renal toxicity

Because DMF causes renal pathology in multiple animal species, the sponsor performed extensive monitoring of renal function in clinical trials, including measuring BUN, creatinine, routine urinalysis, urine microalbumin, Beta-2-microglobulin, and mandatory nephrologist consultations for patients who met certain thresholds on various renal function tests.

There were no appreciable differences in MS controlled trials in the incidence of adverse events related to renal toxicity. Rare renal adverse events were observed in open-label MS studies; two were considered SAEs:

1) a 51 year old woman had the onset of Nephrotic Syndrome on Day 369 of open label treatment, with symptoms and signs first observed on the day that she had an MRI with IV gadobutrol (foot edema, 2+ urinary protein, urine microalbumin of 168 mg/dL). Two weeks later, urinary protein was 3+, and urine microalbumin was 448 mg/dL. About one week later, drug was discontinued, and urinary protein was 3+ and microalbumin was 652 mg/dL. She was admitted to the hospital on Day 378, about a week after drug discontinuation. About 6 weeks later, after treatment (enalapril, spironolactone, furosemide), nephritic syndrome was reportedly resolved.
2) A 42 year old woman with elevated beta-2-microglobulin level about 6 months after starting treatment (1.08 mg/L; ULN of 0.3 mg/L). The level was still slightly elevated about 3 months later (0.53 mg/L) and microalbumin was elevated at 5 mg/dL. Subsequent levels were not elevated, and drug was not discontinued.

There were 16 discontinuations related to renal adverse events in MS trials, all but one in open-label studies. These were: proteinuria (6), hematuria, nephrolithiasis (2 each), and nephritic syndrome, chronic renal failure, renal impairment, renal pain, tubulointerstitial nephritis, and beta-2-microglobulin increased (one each). None of these events, save for the two previously described, were considered serious (Dr. Boehm has reviewed these cases in detail).

Renal laboratory abnormalities

There was a slight decrease in mean serum creatinine in MS controlled trials in DMF-treated patients compared to baseline, as can be seen in the table below:

Mean Change from Baseline in Creatinine (micromole/L)

Week	Placebo	240 mg BID	240 mg TID
Week 4	0.23	-4.50	-6.58
Week 96	1.96	-3.89	-5.68

There were no important differences in the number of patients who shifted to either high or low from baseline among the treatment groups.

In MS controlled trials, 5%, 21%, and 30% of placebo, 240 mg BID, and TID patients, respectively, had 2 consecutive urines positive for ketones. The incidences of patients who shifted to high/positive from normal baseline were consistent with these results (26%, 63%, and 68%, for placebo, 240 BID, and TID, respectively).

There were no appreciable differences among treatment groups in the mean changes from baseline in beta-2-microglobulin or microalbumin, or in the percent of patients who shifted from normal baseline to high for either of these urinary analytes.

GI Adverse Events

As shown above in the common adverse event table, DMF causes various GI adverse events . Serious GI AEs in MS controlled trials included vomiting (4), abdominal pain (3), and gastritis (3). About 9% and 6% of the DMF and placebo GI AEs in the MS controlled trials were rated as severe.

A total of 12 patients discontinued from MS controlled trials (<1%, 4%, and 6% of placebo, 240 mg BID, and TID patients, respectively). The common AEs were diarrhea, nausea, vomiting, and abdominal pain. These events were also the

most common AEs leading to temporary dose reductions (about 1-2% for each of these events in DMF-treated patients compared to <1% for each event in placebo patients).

The greatest incidence of GI AEs occurred in the first month of treatment (see Dr. Boehm's histogram, page 65 of his review).

Infections

There was no appreciable difference in the incidence of infections among the treatment groups in controlled trials.

Carcinogenicity

DMF causes renal tubular adenomas and carcinomas in male mice and renal tubular adenomas in female mice, and renal tubular adenomas in male rats and renal tubular carcinomas in female rats.

There were no differences in the frequency of malignancies among the treatment groups in MS controlled trials. In MS controlled and open-label experience, there were 19 malignancies in 18 patients. The rate (375.4/100,000 patient-years) was below the rate of all malignancies in the SEER database (456.7/100,000 patient-years).

As displayed by Dr. Boehm, the rates of kidney malignancies (per 100,000 patient-years) in the database exceed various background rates (including a Managed Care Database):

	DMF	SEER	(b) (4) Claims
Kidney (excluding pelvis)	44.10	14.5	(b) (4)
Renal pelvis	26.29	1.0	(b) (4)

These rates are based on 2 kidney malignancies and one renal pelvis malignancy.

Post-Marketing Events for Fumaderm

As noted above, Fumaderm is a combination that includes DMF. The sponsor estimates that, through 9/2011, there have been 159,000 patient-years of exposure in 159,000 patients.

The sponsor asserts, based on reports in the literature, that the most common

AEs with Fumaderm are flushing and GI AEs. In addition, Fumaderm causes decreased lymphocytes and neutrophils, and transient eosinophilia.

There have been few serious events reported (breast cancer, lymphopenia, renal failure, LFT increased, myocardial infarction, cirrhosis).

In addition, there have been 20 serious renal AEs, including renal failure/acute renal failure (8), increased creatinine (4), proteinuria (4), hematuria (3), tubulointerstitial nephritis (3), toxic nephropathy (2), osteomalacia (2), Fanconi syndrome, and glycosuria. Many of these reports did not have adequate information; the cases of tubulointerstitial nephritis and toxic nephropathy appeared to have been treated with fumaric acid formulations (fumaric acid, fumaric acid ointment, fumaric acid baths) that differed from Fumaderm. This was true also for the patient with Fanconi syndrome.

Of interest, the sponsor reports 3 cases of Progressive Multifocal Leukoencephalopathy (PML). In one case, the patient had been on Fumaderm for only 1 month. In another case, the patient had a history of melanoma, treatment with efalizumab, and decreased immunoglobulins of unknown etiology. In the third case, the patient had been treated with Fumaderm for 3 years; he had previously been treated for psoriasis with acitretine and methotrexate.

The sponsor also reported another case of PML who had been treated with compounded dimethyl fumarate and copper monoethyl fumarate for 6-7 years.

Pharmacology/Toxicology

DMF is toxic to the kidney in multiple species.

Renal pathology, including tubular basophilia, tubular dilatation, nephropathy, tubular hyaline droplets, tubular hypertrophy, and tubular regeneration were seen in the rat in 3 and/or 6 month studies with no No Adverse Effect Levels (NOAELs); similar findings were seen in the dog, in addition to cortical paranchymal atrophy and papillary urothelium hyperplasia, also with no NOAEL in an 11 month study. In a one year monkey study, tubular necrosis and regeneration were also seen, with a NOAEL of 5 mg/kg. In all species, BUN and creatinine were decreased.

DMF also caused tumors in rat and mouse, including renal tubular adenomas and carcinomas in male mice and renal tubular adenomas in female mice, and renal adenomas in male rat and renal carcinomas in female rat, though the sponsor’s expert re-reading of the rat data suggests no tumors in male rat and only 1/75 female rats at the high dose of 150 mg/kg with a renal carcinoma.

Comments and Recommendations

The sponsor has submitted two adequate and well-controlled clinical trials that clearly provide substantial evidence of effectiveness for Tecfidera in the treatment of patients with RRMS.

The studies clearly demonstrate a robust effect on preventing relapses at both doses of 240 mg BID and 240 mg TID. Study 302 showed a very slight numerical advantage of the higher dose compared to the lower dose on relapses, whereas there is very little difference between the doses in Study 301. Study 301 is clearly positive on standard measures of disease progression, whereas in Study 302, neither dose is statistically significantly superior to placebo on the protocol-specified primary analysis of disease progression, though both doses are numerically superior to placebo. Several additional analyses of disease progression in Study 302 suggest superiority of the low dose compared to the high dose, with these contrasts reaching, or almost reaching, nominal significance. A pooled analysis of both studies on disease progression reaches nominal significance for both doses.

Both studies provide robust evidence of effects of both doses on MRI measures that are routinely evaluated in studies of treatments for MS, again, with little difference between doses. At least one standard MRI measure, Number of Gd-Enhancing lesions at 2 years, numerically favors the low dose in Study 302.

Although the population studied was patients with RRMS, the division has recently concluded that such studies reasonably support granting a somewhat wider claim, a claim for patients with relapsing forms of MS. It is clear that data in patients with RRMS that demonstrates an effect on preventing relapses will have a similar effect on relapses in patients with relapsing forms of MS. Similarly, an effect on progression in patients with RRMS can reasonably be extrapolated to patients with relapsing forms of MS. Therefore, we conclude that Tecfidera should be considered to be effective in patients with relapsing forms of MS.

Should a claim be granted for Tecfidera for disease progression?

Although a statistically significant effect on disease progression was not demonstrated in Study 302, various analyses of disease progression did strongly suggest (at least at the lower dose) a real effect. Further, the very robust findings in Study 302 on relapse and MRI measures strongly argue that these effects will translate into an effect on disease progression, seen against the background of a clear effect on progression in Study 301. Finally, the pooled positive analysis adds further strength to the argument that these data, taken together, provide substantial evidence of an effect on disease progression (there is also precedent for granting a claim for progression on the basis of a pooled

analysis; these studies are typically not specifically powered to show a statistically significant effect on measures of disease progression).

Regarding safety, the drug clearly causes flushing and GI adverse events, as well as lymphopenia, and very minor mean increases in LFTs, bicarbonate, and PTH, and decreases in chloride, Vitamin D, and creatinine. These changes are typically unassociated with any clinical findings.

Because renal toxicity is so prominent in several animal species at exposures near or below to those achieved in humans, the sponsor performed fairly intensive monitoring of kidney function. Although there were some changes in urinary beta-2-microglobulin and microalbumin, there were no clear signals of renal toxicity, nor is there a credible signal of carcinogenicity.

It is, of course, possible, that renal toxicity is occurring, but that the measures used to assess for it are not sensitive to those changes, or that patients have not been exposed for sufficient durations for any possible toxicity to have appeared, as expressed by Dr., Banks-Muckenfuss. However, we do have fairly extensive experience for an NME (over 700 patients exposed for at least 3 years), and the current data are reassuring to date (but see below regarding post marketing studies).

There are no other safety issues that would preclude approval.

For these reasons, then, we recommend that the application be approved.

We do, however, believe that the sponsor must perform several additional studies, and these have been negotiated with the sponsor as Post Marketing Requirements (PMRs).

Specifically, the sponsor must perform a pediatric effectiveness trial in patients between the ages of 10-17 years old (this study is required under the Pediatric Research Equity Act [PREA]). In addition, the following studies must be performed:

1) A comprehensive in vitro receptor binding study of DMF and MMF
2) A non-clinical self administration study to assess abuse potential
3) A non-clinical discrimination study to assess abuse potential
4) A juvenile rat toxicology study
5) A prospective study in at least 5000 patients followed for at least 5 years to assess the risk of serious infections, malignancies, and other serious renal and hepatic adverse events

We have also come to an agreement with the sponsor on product labeling.

Importantly, the sponsor and the division have agreed that the recommended dose should be 240 mg BID. Although, as described above, in Study 302, the high dose seemed to be somewhat numerically superior to the low dose on some measures, these differences were very small, and this was clearly not the case in Study 301, and, indeed, some analyses of some measures in Study 302 favored the low dose (as did some in Study 301). And although the incidence of AEs seemed, in general, not to be dose-related, the general lack of superiority of the high dose compared to the low dose, and at least the potential for an increase in AEs at the high dose, argue for recommending the low dose.

For these reasons, then, we recommend that the application be approved, with the appended, agreed upon, labeling.

Russell Katz, M.D.

APPEARS THIS WAY ON ORIGINAL

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/s/

RUSSELL G KATZ
03/27/2013

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA:	204063
Drug:	Dimethyl fumarate (Tecfidera)
Route:	Oral
Indication:	Relapsing Multiple Sclerosis
Sponsor:	Biogen Idec
Review Date:	February 7, 2013
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Neurology Drug Products

1 Background

Dimethyl fumarate (DMF), also referred to as BG00012, is an orally administered fumarate ester. According to the Sponsor, its effect appears to be mediated through activation of the nuclear factor related factor 2 (Nrf2) pathway. The Sponsor is seeking approval for treatment of patients with relapsing MS. The proposed initial dose is 120 mg twice a day, and the dose is increased after 7 days to the maintenance dose of 240 mg twice a day. According to the Sponsor, after oral administration dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases to the active metabolite monomethyl fumarate (MMF). MMF is further metabolized through the tricarboxylic acid cycle with exhalation of CO2 as the primary route of elimination. The elimination half-life of MMF is approximately 1 hour. Dimethyl fumarate has not yet been approved by a regulatory agency although Fumaderm, a combination product containing dimethyl fumarate and other fumarate esters, has been approved in Germany for treatment of psoriasis since 1994.[1] Dimethyl fumarate has been used as a fungicide and a desiccant for furniture and is banned in several countries for use for this purpose due to allergic skin reactions.

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Boehm, of the Tecfidera NDA 204063.

2 Summary of Findings from the Safety Review

2.1 Integrated Review of Safety

The current submission summarizes safety data for 3,424 subjects from clinical trials in healthy volunteers and adults with MS, psoriasis, and rheumatoid arthritis. The primary focus was on safety data from MS clinical trials. MS pool A included the safety data from one Phase 2 and two Phase 3 placebo-controlled randomized controlled trials (RCTs). In that pool, C-1900 part 1 was a 6 month study that evaluated BG00012 120 mg qd, 120 mg tid, and 240 mg tid. MS301 and MS 302 were 2 year studies that both evaluated BG00012 240 mg BID and 240 mg TID. MS 302 also had a glatiramer acetate (GA) arm. MS Pool B includes data from the RCTs and their open label extensions. The

[1] The Sponsor estimates that 159,000 patients have been exposed to Fumaderm (p. 8627, Appendix 3, ISS).

sponsor also submitted analyses of pooled data from 2 RCTs in Psoriasis (Pool C) and the psoriasis RCTs and their open label extensions (Psoriasis Pool D) that included 296 DMF-exposed subjects. Data from the remaining trials were submitted as individual study reports. According to Dr. Boehm's review 2,210 MS subjects were exposed to BG00012 for at least 6 months, 1787 for at least 1 year, 1,198 for at least 2 years, and 712 for at least 3 years thru the 120 Day Safety Update. There were 2,537 MS patients who received doses ≥ 240 mg twice a day of whom 1,136 received the intended recommended dose of 240 mg twice daily. The Sponsor has met the ICH guidelines for exposure.

2.1.1 Deaths

According to Dr. Boehm's review, there were 11 deaths in the BG00012 clinical trials thru the 120 day safety update. Nine occurred in BG00012 exposed subjects in the integrated trials (7 MS, 2 Psoriasis), 1 occurred in a subject exposed to GA, and 1 occurred in a placebo subject. The reported causes of death in the MS trials for the BG00012 subjects were traumatic brain injury following bicycle accident, motor vehicle accident, complications of MS relapse, cardiopulmonary arrest/respiratory muscle weakness/MS relapse, sepsis/decubitus ulcers/respiratory arrest/aspiration pneumonia, mesothelioma[2], and suicide/paracetamol overdose with subsequent hepatic failure. The placebo death was due to ischemic stroke, and the GA patient's death was due to suicide. Of the deaths in the integrated psoriasis trials (2/296, 0.7%), one death was a sudden death in a patient with a history of untreated borderline hypertension, alcohol use (10 drinks of vodka per day), and cigarette smoking (20 cigarettes per day); the second death was from acute left heart failure, presumed due to acute MI as a consequence of documented coronary heart disease in a patient with a history of hyperlipidemia and borderline hypertension, myocardial ischemia, and cigarette smoking. I agree with Dr. Boehm that there does not appear to be a cluster of deaths due to unusual causes and that there does not appear to be a meaningful difference in mortality between BG0012 (3/1720, 0.2%), placebo (1/836, 0.1%), and GA (1/351, 0.3%) in the Pool A MS controlled trials.

2.1.2 Serious Adverse Events

Dr. Boehm finds that in the MS controlled trials (Pool A), serious adverse events (SAEs) occurred slightly more frequently in placebo patients (21%, 173/836) compared to BG00012 240 mg BID (18%, 135/769), 240 mg TID (15%, 126/823), and GA (17%, 60/351) treatment groups. There was no individual SAE reported by ≥1% in BG00012 and greater than placebo. In Pool B SAEs reported by at least 5 patients were gastroenteritis (n=10), gastritis (n=8), UTI (n=8), fall (n=5), and road accident (n=5). In the integrated controlled Psoriasis trials (Pool C), percentages of patients with SAEs were similar across BG00012 low dose (0/72), 240 mg TID (3%, 4/141), and placebo (2%, 2/106), and no individual preferred term occurred in at least 1% of BG00012 patients. In the Pool D psoriasis trials, 9% (27/296) experienced one or more SAEs; myocardial infarction (1%, 3/296) was the only SAE that occurred in at least 1%. In the non-

[2] The event leading to the death began on Day 340 of exposure to DMF in a 49 y.o. patient with no documented history of asbestos exposure or tobacco use. According to Dr. Boehm, the Sponsor noted that asbestos consumption has increased dramatically in India and is a major public health concern.

integrated clinical trials, there were no SAEs reported in BG00012 subjects in the Phase 1 trials. In an ongoing open label trial in MS, 3 patients experienced SAEs (1 epigastric abdominal pain with gastrointestinal chest pain, 1 muscular weakness and diabetes mellitus, 1 C. difficile infection).

Dr. Boehm has also summarized less frequent but potentially concerning SAEs. These included allergic reaction SAEs including hypersensitivity (n=2), 1 of which appeared to be asymptomatic hypereosinophilia that was not severe or life-threatening but resulted in discontinuation from the trial, and the other (354-301) that was fever, flushing, and skin redness but no angioedema, dyspnea, wheezing, or cardiovascular instability, 2 hours after the first dose, treated with methylprednisolone and recovered (study drug was discontinued); anaphylactic reaction (n=1) in a patient with a plausible alternative explanation and who continued in the trial without further recurrence; and anaphylactoid reaction (n=1) in subject 198-310 who experienced increased flushing and pruritus on day 1, erythema and pruritus on Day 8, and an anaphylactoid reaction on Day 13 with flushing and shortness of breath, but no cardiovascular or respiratory instability who was treated, and drug was stopped, and she recovered. There is not clear evidence of causality.

Two subjects had skin reaction SAEs, one with dermatitis allergic following initiation of amoxicillin/clavulanate and the other with biopsy diagnosed Stevens Johnson syndrome (SJS) who was taking carbamazepine at the time of the event and who remained on BG00012 throughout the event and for 1 month after without recurrence of SJS. I agree with Dr. Boehm that there are plausible non-BG00012-related alternative causes for these events.

Other SAEs were 3 hepatic SAEs (1 due to intentional acetaminophen overdose with subsequent hepatic failure mentioned under deaths; 1 chronic hepatitis and 1 cholestatic hepatitis discussed later under events of special interest; 1 proteinuria and 1 beta-2 microglobulin SAE discussed under renal injury events of special interest; and 1 case of rhabdomyolysis thought by the investigator to be due to excessive muscular activity on initiation of a weight training regimen. One patient had myopericarditis on Day 174 that resulted in withdrawal from the study on Day 178; viral infections are the most common causes of myopericarditis[3], and it is not possible to determine whether it could be drug-related in this case.

2.1.3 Dropouts and Other Significant Adverse Events

Adverse events (AEs) were the reason for discontinuation of study drug in approximately 16% of patients in the Pool B trials and in 14% of BG00012 subjects in MS Pool A. Discontinuations due to adverse events (AEs) in MS Pool A were more frequent in BG00012 than placebo subjects (9% in low dose, 14% of BID, and 14% of TID for BG00012 vs 11% for placebo). The most common AEs leading to discontinuation among BG00012 subjects in MS Pool B were flushing, diarrhea, nausea, vomiting, MS relapse, abdominal pain upper, and abdominal pain, all in ≤2% of

[3] Imazio, M and Trinchero R. Myopericarditis: Etiology, management, and prognosis. International Journal of Cardiology 2008; 127:17-26.

BG00012 treated patients. In MS Pool A the most common AEs leading to discontinuation and greater than placebo were flushing, diarrhea, nausea, vomiting, abdominal pain upper, and abdominal pain, all in ≤2% of BG00012 treated patients in any dose group. Temporary dose reductions and temporary dose interruption were allowed in MS Pool A trials, and occurred primarily due to GI events (7%, 113/1720) and flushing (2.6%, 45/1720) in BG00012 treated patients. One patient had dose reduction for lymphocyte count decreased and one for WBC count decreased, and other dose interruptions were for flush or hot flush (n=14), ALT increased (n=13), AST increased (n=10), and leucopenia (n=1). In Pool B trials no BG00012 MS patients discontinued for Stevens Johnson syndrome, toxic epidermal necrolysis, angioedema, rhabdomyolysis, aplastic anemia, or pancytopenia.

Eleven subjects experienced AEs of hypersensitivity and 1 experienced anaphylactoid reaction (3 of which were described under SAEs) that were identified as the reason for discontinuing study drug, and 1 RA subject discontinued for facial swelling on day 2 of treatment that resolved after discontinuation without other intervention.

In the Psoriasis clinical trials, investigators were not required to identify the specific AEs that led to treatment discontinuation and these were not presented by the Sponsor. In the non-integrated trials in healthy volunteers and in RA, AEs leading to discontinuation in the non-integrated trials were generally similar to those reported in the MS trials.

2.1.4 Submission Specific Primary Safety Concerns

Flushing and related symptoms

In Pool A MS trials, the frequency of flushing-related symptoms among BG00012 treated subjects was 45% for the BID group and 42% for the TID group compared to 9% for placebo and 5% for GA. BG00012 patients are at increased risk of experiencing transient eosinophilia, but I agree with Dr. Boehm flush does not appear to be related to eosinophilia as the percent of BG00012 patients with flushing that had elevated eosinophil counts was similar to the overall percentage of BG00012 patients with elevated eosinophil counts. In Pool A, the majority (67%) of flushing AEs were rated as mild; 30% were moderate, and 4% were severe. The severity of hot flush events was similarly distributed. Dr. Boehm shows on p. 37 of his review that the incidence of flushing related events was highest in the first month of treatment. In the 68% of patients for whom this information was available, the median duration was 17 days. Dr. Boehm notes, however, that for approximately 25% of patients, the reaction was ongoing. Results from a flushing symptom questionnaire in clinical pharmacology trial 109HV106 suggest that symptoms can begin as soon as 30 minutes following ingestion with median onset of 80 minutes following a dose. During that trial, severity was highest on the first treatment day, declined, and then plateaued. Flushing did not appear to vary by sex or by age (<40 vs ≥40 y.o.), although the age range was limited to 18-55 years.

Several factors have been evaluated as to whether they could mitigate flushing, including dose, aspirin pre-treatment, food, and dose interruption/reduction. With respect to <u>dose</u>, Dr. Boehm notes that during clinical pharmacology trial 109HV106, using small treatment groups of 6-8 subjects each, the 360 mg BID group had lower symptom scores

than the 240 mg BID or 240 mg TID groups, raising questions about the dose relationship and the usefulness of lowering doses for flushing (despite the allowance for that during the clinical trials). The study also evaluated pretreatment with non-enteric coated 325 mg aspirin. Considering only the 240 mg dose intended for marketing, 3/6 (50%) pre-treated with ASA experienced flushing compared to 5/6 (83%) without pre-treatment. Flushing severity scores were lower with aspirin pretreatment than when BG00012 was administered with placebo. The small study size limits application of the results. Aspirin was not routinely used for flushing symptoms in the MS Pool A trials and Dr. Boehm notes that less than 10% of patients in each dose group had recorded concomitant use of aspirin; the most commonly reported indications were cardiac disease prevention, pain, and fever, with flushing listed in 4 patients. A food effect study showed that flushing risk was 94% (34/36) in the fasting state vs 68% (23/34) during the fed state. In Pool A MS trials, investigators were allowed to hold or temporarily reduce the dose of study drug in patients with flushing. Although study drug was temporarily held in 0.8% and the dose temporarily reduced in 2.6% of BE00012-treated patients, it is unclear if these interventions improved tolerability. Based on the results of the food effect study, I agree with noting in the proposed label that food may reduce the incidence of flushing.

Hepatic disorders
Dr. Boehm finds that in the Pool A MS trials, dimethyl fumarate treated subjects were more likely than placebo patients to experience transaminases above ULN, but not > 3X, >5X, > 10X, or > 20X ULN. For >1X ULN, these rates were higher for BG00012 than for placebo or for GA. There was no difference in risk for elevated total bilirubin in the MS trials and no patients had transaminases ≥ULN concurrently with total bilirubin > 2X ULN in the MS trials or in any of the clinical trials. The findings from the Pool C Psoriasis trials were similar. There were 3 hepatic SAEs from BG00012 clinical trials including intentional acetaminophen overdose discussed with deaths. The other SAEs were chronic hepatitis and cholestatic hepatitis. The patient diagnosed with chronic hepatitis had elevations of ALT, AST, and GGT that fluctuated from normal to elevated (up to 4-5X ULN) to near normal in study MS 301, and remained elevated after 6 months off of study treatment. I agree with Dr. Boehm that a relationship to BG00012 seems unlikely in light of the fluctuations and lack of resolution over a 6 month period off study drug. Subject 505-303 was a patient with a history of hyperbilirubinemia with elevated total bilirubin and ALP at baseline. After 446 days of treatment she also had elevated ALT and AST, resulting in discontinuation of study medications. No other laboratories abnormalities were observed to show signs of liver dysfunction, and abdominal ultrasound was normal. Transaminase levels were reportedly normal within approximately 3 months after discontinuation of study drug. I agree with Dr. Boehm that this case did not clearly suggest a causal relationship with BG00012. I also agree that the transient increases in liver transaminases doe not appear to be associated with an increase in clinically significant liver disease.

Renal Toxicity
Nonclinical studies showed evidence of BG00012 related renal toxicity in multiple animal species. This included renal tubular and interstitial toxicity. As Dr. Boehm notes, because of these findings, in addition to the usually collected renal related lab data (BUN,

creatinine, urinalysis), the MS RCTs incorporated enhanced renal monitoring that included urine microalbumin and β2-microglobulin testing every 3 months (these are markers of tubular injury), requirements for renal consultations for patients with pre-specified abnormal results[4], and special study medication stopping rules. [5]

AEs - In Pool A, Dr. Boehm does not find notable differences in risk for AEs included under the Renal and Urinary Disorders SOC. In the 240 mg BID dose group, proteinuria was 9% vs 7% in placebo, microalbuminuria was 5% vs 3% in placebo, and albumin present in urine was 6% vs 3% in placebo.

In addition to those AEs, Dr. Boehm notes that 1 BG00012 patient in Pool A trials had an AE of *chronic renal failure* and 1 had an AE of *renal tubular acidosis* (and no placebo or GA subjects). Neither of these were SAEs. No BG00012 subjects had AEs of acute renal failure, tubulointerstitial nephropathy, acute interstitial nephritis, chronic tubulointerstitial nephropathy, acute tubular necrosis, nephrotic syndrome, or glomerulonephritis. Dr. Boehm reports 3 subjects had an AE of *renal failure chronic* in MS pool B, and that the following events were reported 1 time each: *renal tubular acidosis, tubulointerstitial nephritis, nephritic syndrome, and nephritis*; these were not SAEs. None of the above listed events were observed in the Psoriasis Trials Pool D. In the RA trial 109 RA 201, *hematuria* (1 in BG00012 and 1 placebo) and *microalbuminuria* (1 BG00012 and 1 placebo) were the only renal AEs reported. In the ongoing Phase 2 MS trial the only reported renal AEs were *glycosuria* (1 subject receiving BG00012+GA) and *neurogenic bladder* (1 subject receiving BG00012+INF). The only renal AEs reported in Phase 1 studies were *dysuria* (n=1) and *hematuria* (n=1). I agree with Dr. Boehm that isolated SAEs due to nephrotic syndrome or beta-2 microglobulin, or discontinuations due to proteinuria (n=3), hematuria (n=2), nephrolithiasis (n=2), nephrotic syndrome (n=1, same as SAE), renal failure chronic (n=1), renal impairment (n=1), renal pain (n=1), tubulointerstitial nephritis (n=1), beta-2 microglobulin increased (n=1), protein urine present (n=2), and albumin urine present (n=1) in which some of the abnormalities were either present at baseline, recurred off BG00012 or were present when the patient was taking placebo, and are not shown to be causally associated with BG00012.

Renal related lab results – Dr. Boehm shows that the mean change from baseline for BG00012 subjects was similar to the mean changes in placebo and GA subjects for *BUN*. BG00012 subjects experienced mean declines in *creatinine* (of 3.89 to 6.83 umol/L) [6] while placebo subjects experienced small mean increases of less than 2 umol/L. However, Dr. Boehm notes no notable difference for shifts from normal or low to at least

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[4] Dr. Boehm notes that the independent nephrologist felt that there was no evidence of drug-induced nephrotoxicity in any BG00012-treated subject.

[5] Subjects in Phase 2 trials who developed casts (other than hyaline casts), proteinuria, β2-microglobulinuria, urinary microalbuminuria, or glycosuria in the setting of normal serum glucose, confirmed on repeat testing, were referred for evaluation by a nephrologist. If the nephrologist determined there was evidence of renal dysfunction the subject was to discontinue study treatment. Data for all subjects referred to a nephrologist were collected for a secondary evaluation by a blinded, independent, external nephrologist.

[6] This is relative to the reference range for serum creatinine in MS 301 and in MS 032 for 18-50 y.o of 35.36-97.21 umol/L for females and of 44.2-106.08 umol/L for males.

one high (> ULN) result or from normal or high at baseline to at least 1 low (< LLN) result during treatment, across treatment groups. The mechanism for the decrease in creatinine and its significance is not clear. I agree with Dr. Boehm that urinalysis showed no remarkable difference in the percentage of patients who experienced 2 consecutively positive UAs for *protein* (placebo 47%, BG00012 BID 51%, BG00012 TID 53%, GA 56%) or for shift analysis to positive for urine protein (placebo 73%, BG00012 BID 79%, BG00012 TID 75%). It is not clear to me why the placebo rate is so high, but this is perhaps because of the multiple measurements made. There do not appear to be notable increases in mean change from baseline for β2-microglobulin or for microalbumin. A slightly higher percentage of BG00012 treated patients shifted to high for microalbumin but not for β 2 microglobulin.

Dr. Boehm identified a notable difference in the percentage of patients with 2 consecutive *positive urine ketone* results (5% of placebo subjects, 4% of GA subjects, 21% of BG00012 BID patients, and 30% of BG00012 TID patients in Pool A), and the incidence of shifts to high/positive showed similar differences. Dr. Boehm finds that these results were not associated with increased serum glucose and generally not associated with an increased anion gap. When asked, the Sponsor hypothesized that a pharmacodynamic effect may result in upregulation of glutathione synthesis by DMF and MMF and the free sulfhydryl group could react with the reagent for testing the urine for ketone bodies or that urinary metabolites may directly interfere. The sponsor also evaluated the possibility of an association between ketonuria and GI tolerability events that could result in decreased oral intake, diarrhea, and vomiting, and starvation ketosis, but did not find such an association as shown on p. 59 of Dr. Boehm's review. Upon request, the Sponsor addressed the potential safety related implications of elevated urinary ketones. I agree with Dr. Boehm that there do not appear to be meaningful differences in percentages of patients with AEs when comparing those with urinary ketones to those without. In addition, the Sponsor did not find that patients with diabetes or other metabolic conditions[7] were at greater risk for developing ketonuria from BG00012 compared to placebo, or were at greater risk for AEs or SAEs.

I agree with Dr. Boehm that, despite nonclinical evidence of BG00012 related renal toxicity in multiple animal species, the clinical trials did not suggest that BG00012 exposed patients were at increased risk of renal toxicity. I also agree that whether this is because humans are not similarly affected, or because longer exposure is required to develop toxicity than was provided for in the clinical studies, is unknown, although as previously noted there is exposure for at least 3 years in more than 700 patients. In the Clinical Overview (p. 47), the Sponsor states that they intend to "conduct a large, global, observational study with the primary objective of determining the nature and incidence of serious infections, malignancies, and other SAEs (e.g., serious renal and hepatic events) or other medically significant events with marketed use of BG00012. Approximately 5000 MS patients treated with BG00012 would be enrolled and followed for up to 5

[7] According to the Sponsor's submission of 7/30/12, on p. 241, in Pool A, there were 45 placebo patients, 35 BID BG00012 patients, and 55 TID BG00012 patients with diabetes or other metabolic conditions at baseline of whom 25 placebo patients, 17 BID BG00012 patients and 30 TID BG00012 patients had diabetes.

years, which would provide approximately 18,000 person-years of follow-up after accounting for treatment discontinuation and drop-out rates." I believe that such a study may be useful in evaluating the effects after longer term exposure; the Division should be involved in the development of the protocol for that study.

Gastrointestinal adverse events
In Pool A trials, 40% of BG00012 subjects experienced one or more GI AEs compared to 30% of placebo patients. Dr. Boehm notes that diarrhea, vomiting, and abdominal pain were the individual GI AEs that most commonly occurred in BG00012 patients and that occurred more frequently compared to placebo. Dr. Boehm notes that BG00012 patients had slightly greater frequency of GI SAEs (vomiting n=4, abdominal pain n=3, gastritis n=3) than placebo patients (vomiting n=1). BG00012 subjects discontinued more frequently for GI adverse events (4% of BG00012 BID, 6% of BG00012 TID, and < 1% of placebo and < 1% of GA subjects) in Pool A. In Pool A trials, investigators could temporarily reduce the BG00012 dose for subjects experiencing GI adverse events. In these trials 7% of BG00012 subjects had their dose reduced for AEs in the GI SOC vs 2% of placebo patients and 0 GA patients (not including subjects who subsequently discontinued); as Dr. Boehm notes, it is unclear whether this improved tolerability. BG00012 patients were more likely to have their GI AE rated as severe (9%) vs 6% for placebo and 0 for GA. The incidence was highest and demonstrated the greatest difference vs placebo during the first month of treatment, as shown on p. 65 of Dr. Boehm's review. Dr. Boehm finds that the relative risks of BG00012 for diarrhea and abdominal pain upper were higher for females. He does not find age-related differences for < 40 y.o. vs 40 ≥y.o. (limited by the age range of subjects in Pool A of 18-55 years). The food effect study previously described showed a slightly greater risk of nausea in the fasting state compared to the fed state (8% vs 6%), and a slightly greater risk of vomiting (6% in the fasting state compared to 0 in the fed state). I agree there is insufficient evidence to determine if taking BG00012 with food improved tolerability with respect to GI AEs.

Infections
BG00012 has a lymphocyte lowering effect as will be discussed under Laboratory Results. Despite this, there do not appear to be notable differences in risk for infections when comparing BG00012 to placebo in MS Pool A trials. This is shown on p. 67 of Dr. Boehm's review, where the infection AEs that occurred in ≥2% and more commonly among BG00012 subjects at any dose vs placebo are nasopharyngitis, UTI, URTI, sinusitis, and bronchitis, for which the risk is at most 3% higher on BG00012 than on placebo. Dr. Boehm specifically examined viral infection AEs, and did not find important differences in risk by treatment in the Pool A trials. Similarly, infection SAEs did not appear to vary markedly by treatment; Dr. Boehm found no reported herpes-related SAEs in Pool A/Pool B MS trials. There also was not a difference in the risk of discontinuation across treatment groups in Pool A MS trials for infections, and no single infection AE led to discontinuation of more than 1 BG00012 patient in Pool A MS trials. Dr. Boehm also notes that despite declining lymphocyte and WBC results, there did not appear to be increases in risk of infections over time. There appeared to be a slightly greater incidence of infections with minimum post-baseline lymphocyte count

<0.8x109/L compared to greater lymphocyte counts (62-67% vs 53-57%) and a slightly increased risk for the lowest post-baseline WBC counts, but no increased risk for Infection SAEs using these comparisons, although those event rates were much lower. A safety signal for opportunistic infections was not identified. I agree with Dr. Boehm who notes that these findings are somewhat reassuring. However, as he notes, the trials were performed in highly selected populations that were closely monitored. Excluded were patients with HIV, recent use of immune modulating treatments, and low WBC counts, and participants who developed low WBC were discontinued (although in Pool A only 1 patient discontinued for WBC decreased). I agree with Dr. Boehm that the generalizability to a real world population is unclear.

Cardiovascular disorders
Although cardiovascular AEs (including myocardial infarctions and coronary artery disease) were reported in small Psoriasis trials, evaluation of ischemic events did not appear to show evidence of increased risk for BG00012 vs placebo or GA in the MS trials safety database. Dr. Boehm notes that the Sponsor's consultant cardiologist felt that except for 1 case, the cases did not support a diagnosis of cardiac ischemia. There were few cerebrovascular events in the Pool A studies, and in those cases the BG00012 patients had underlying conditions that predisposed to ischemic events. An additional event in uncontrolled trial 303 was judged by the consultant cardiologist to be an ischemic event (acute MI).

Suicide and Depression
Dr. Boehm shows on p. 72 of his review that there are no notable differences in the frequencies of suicide and self-injury AE terms in the Pool A MS trials from BG0012, placebo, or GA. Dr. Boehm notes that the Pool B data are consistent with the data presented for Pool A.

2.1.5 Common Adverse Events

Overall the percentages of patients who experienced one or more AEs in the Pool A MS trials were similar when comparing placebo (92%), BG00012 at any dose (89% for low dose, 95% for 240 mg BID, 93% for 240 TID), and GA (87%) groups. In the Pool A MS trials, Dr. Boehm shows the adverse events occurring most commonly (≥2%). Those occurring ≥2% more frequently in any dose group compared to placebo include flushing and hot flush, diarrhea, nausea, abdominal pain, abdominal discomfort, dyspepsia, vomiting, rash, erythema, sinusitis, bronchitis, albumin urine, muscle spasms, microalbuminuria, AST increased, gastrointestinal disorder, hyperhydrosis, and influenza-like illness. Flushing was the most commonly reported AE in both MS Pool A and Pool B. For the Psoriasis Pool C trials, the percentages of patients who experienced one or more AEs were lower for placebo (66%) compared to BG00012 low dose (74%) and BG00012 240 mg TID (88%). The most commonly occurring AEs in that group (and greater than placebo) included flushing, nasopharyngitis, diarrhea, and headache, abdominal pain upper, nausea, and pruritus. The most common AEs in the nonintegrated trials were similar to those reported in the rest of the database.

2.1.6 Laboratory findings

The laboratory findings of concern to Dr. Boehm are lymphopenia, eosinophilia, and parathyroid hormone changes and are summarized below.

Hematology
Lymphopenia: Both the MS and Psoriasis controlled trials show that BG00012 causes declines in lymphocyte counts from baseline that were not seen in placebo patients, and BG00012 patients had greater percentages of low outliers for lymphocyte counts compared to placebo. In the MS Pool A trials, mean declines in WBCs were observed, driven by declining lymphocytes, with more modest decreases in neutrophils, hemoglobin, hematocrit, and platelets. Pool C trials were of shorter duration, but also showed declines, except for platelets where the decrease was not greater than placebo. The following table, extracted from p.79 of Dr. Boehm's review, shows that mean lymphocyte counts in Pool A MS trials began declining at week 4 (the time of the first lab data collection), and in the BID group, the mean decline from baseline at 48 weeks was approximately 30%. There was little additional decline thereafter. The mean lymphocyte count at baseline for the BG00012 bid subjects was $1.97X10^9$/L and was $1.34X10^9$/L at week 48. Dr. Boehm notes that lab data suggested that lymphocyte counts increased after stopping BG00012, but did not completely recover during the 4 week post-last dose observation period. According to Dr. Boehm, in the 299 MS Pool A subjects with baseline, post-baseline, and > 2weeks post-last dose lymphocyte counts, the mean percentage decrease at 4 weeks post last dose was 19.3%.

MS Pool A, Lymphocytes ($x10^9$/L), Mean change from Baseline

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
Week 4	-0.05 (729)	-0.10 (777)	-0.07 (1630)	0.04 (803)	-0.01 (332)
Week 8	-0.19 (693)	-0.19 (727)	-0.19 (1543)	0.04 (789)	0.04 (328)
Week 12	-0.30 (697)	-0.30 (718)	-0.30 (1536)	0.04 (787)	-0.04 (324)
Week 24	-0.49 (664)	-0.40 (700)	-0.45 (1475)	0.05 (756)	0.00 (315)
Week 48	-0.63 (609)	-0.54 (604)	-0.58 (1213)	0.02 (607)	-0.06 (298)
Week 60	-0.60 (594)	-0.53 (584)	-0.57 (1178)	0.08 (565)	0.02 (286)
Week 96	-0.66 (526)	-0.58 (503)	-0.62 (1029)	0.02 (479)	0.04 (251)

Outlier analyses demonstrated that BG00012 subjects in MS Pool A were at greater risk for low WBC and low lymphocyte counts compared to placebo, and I agree with Dr. Boehm that there did not appear to be to be differences for neutrophils, hemoglobin, hematocrit, or platelets. The same was true for Psoriasis Pool C. Low outlier results for WBC and lymphocytes in MS Pool A are shown in the table below, as extracted from Dr. Boehm's review.

MS Pool A, Select Hematology Lab Parameters, High/Low Outlier Risks

Parameter	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
WBC($x10^9$/L)	N=128	N=757	N=805	N=1690	N=830	N=347

<3.0	5% (6)	7% (54)	5% (42)	6% (102)	1% (10)	2% (7)
Lymphocytes($x10^9$/L)	N=128	N=757	N=805	N=1690	N=830	N=347
<0.8	13% (16)	28% (209)	21% (170)	23% (395)	3% (22)	4% (13)
<0.5	2% (2)	6% (43)	3% (24)	4% (69)	<1% (4)	<1% (1)

Shift analysis showed that in Pool A, compared to placebo, higher percentages of subjects in the BG00012 BID and TID groups experienced shifts to low WBC counts and lymphocytes counts, and the percentage of subjects with shifts to low in neutrophil counts was also slightly higher with BG00012 compared to placebo. Similar findings for WBC and lymphocytes were observed in Pool C Psoriasis trials that also showed greater shifts to high in monocytes percentage.

Dr. Boehm notes that the magnitude of the observed lymphocyte count decline with BG00012 is within the range of declines described for fingolimod and teriflunomide. For fingolimod the mean lymphocyte count decline from baseline at 6 months for the approved dose was $1.3X10^9$/L. For teriflunomide, a lymphocyte count of < $0.8x10^9$/L was observed in 7% and 10% of patients on teriflunomide approved doses of 7 mg and 14 mg, respectively, compared with 5% on placebo.

Eosinophilia: Dr. Boehm notes an early, transient increase in eosinophil count during the first 4 weeks of treatment in Pool A BG00012 compared to placebo, as shown below as extracted from Dr. Boehm's review on p. 79. Similar results were shown for Pool C. In outlier analysis, Dr. Boehm found that the majority of high outliers for eosinophil count ≥2X ULN in Pool A were reported during week 4. In shift analysis, a higher percentage of subjects in the BG00012 BID and TID and in the GA groups than in the placebo group had shifts to high in eosinophil counts (13%, 10%, 9%, and 3%, respectively). In Pool C, 22% of BG00012 TID subjects and 17% of placebo subjects had shifts to high in eosinophil percentage.

Study Week	Treatment			
	BG00012 Low doses (n)	BG00012 TID (n)	BG00012 Total(n)	Placebo (n)
Eosinophils ($x10^9$/L)				
Week 2	0.042 (71)	0.045 (130)	0.044 (201)	0.024 (101)
Week 4	0.074 (70)	0.101 (127)	0.091 (197)	0.040 (95)
Week 8	0.025 (66)	-0.016 (124)	-0.002 (190)	0.023 (97)
Week 12	0.020 (51)	-0.025 (114)	-0.011 (165)	0.051 (76)

Adverse events related to hematological test results: Dr. Boehm reports that no BG00012 subjects in MS Pools A/B experienced an SAE related to hematological test results. Four BG00012 subjects discontinued for AEs related to low WBC or lymphocyte counts, one of whom had an infection related AE of non-serious bronchitis around the time of lymphopenia. In Pools C/D, no BG00012 subjects experienced an SAE related to a hematologic test result. Reasons for discontinuation were not recorded in the Pool C/D trials. Dr. Boehm does not find robust evidence for differences reported by treatments for hematological common AEs in Pool A or in Pool C.

Chemistry: Transaminases, bilirubin, and ALP were reviewed under the discussion of hepatic disorders, and kidney related lab data were reported in the section on renal injury.

Dr. Boehm notes that BG00012 did not appear to affect sodium, potassium, magnesium, phosphorus, glucose, total cholesterol or uric acid.. He shows small decreases in chloride and triglycerides and small increases in bicarbonate thru 24 weeks and small decreases later, that I agree do not appear to be clinically important. I have shown the maximum changes for chloride, triglycerides, and bicarbonate from Pool A, as extracted from Dr. Boehm's review, p. 88, below.

MS Pool A, Select Chemistry Lab Parameters, Mean change from Baseline

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
Chloride					
Week 52	-0.46 (577)	-0.42 (576))	-0.44 (1153)	-0.01 (567)	0.29 (288)
Bicarbonate					
Week 24	0.55 (654)	0.63 (686)	0.48 (1453)	0.03 (738)	0.23 (315)
Week 52	-1.27 (574)	-1.08 (572)	-1.17 (1146)	-1.48 (557)	-1.89 (286)
Triglycerides					
Week 4	-0.16 (737)	-0.14 (734)	-0.15 (1471)	0.02 (756)	-0.02 (339)

In outlier analysis for Pool A trials, there was a slight increase in the percentage of patients with bicarbonate values > 32 mmol/L or > 32-34 mmol/L for BG00012 compared to GA or placebo but no differences above 34 mmol/L. According to Dr. Boehm, the sponsor reported no differences by treatment for AEs potentially associated with increased bicarbonate such as renal calculi, metabolic alkalosis, bone pain, or lethargy. In shift analysis for Pool A trials, BG 00012 subjects were more likely to shift high for bicarbonate than placebo subjects; there did not appear to be other meaningful differences. For Pool C data, mean change from baseline analyses were available only for sodium and potassium (p. 7991-7996 of the ISS) and I agree with Dr. Boehm that the mean changes for these were unremarkable.

Special Chemistry Tests: PTH and Vitamin D
Because of proliferative parathyroid changes in rats (attributed to end stage renal failure), BG00012 clinical trials MS 301 and 302 included parathyroid hormone (PTH) and vitamin D measurements. Dr. Boehm reviews the physiology of parathyroid hormone on p. 91 of his review as follows: Normally, low serum calcium levels stimulate relates of PTH and elevated calcium levels suppress PTH secretion. PTH directly inhibits calcium excretion and phosphate and bicarbonate reabsorption by the kidney, it stimulates production of Vitamin D by the kidney, and it activates osteoclasts to release calcium from bone. It also acts indirectly via Vitamin D to increase intestinal absorption of calcium. Vitamin D deficiency may be a cause of secondary or tertiary hyperparathyroidism.

BG00012 exposed subjects experienced greater mean increases in PTH and over 20% of BG00012 subjects had PTH > ULN compared to 17% of GA subjects and 9% of placebo subjects. These increases, as well as decreases in Vitamin D appeared to be dose related. At week 48 the percentage of subjects PTH > ULN was approximately 12% for BG00012 vs approximately 4% for placebo and 7% for GA and at week 96 was approximately 18% for BG00012, 7% for placebo and 13% for GA. For patients who did not have low vitamin D at baseline[8], at week 48 the percentage of subjects with Vit D < LLN was approximately 4% for BG00012 vs approximately 3% for placebo and 2% for GA and at week 96 was approximately 7% for BG00012, 4% for placebo and 3% for GA. Dr. Boehm finds that less than 15% of BG00012 subjects who had PTH > ULN at week 48 or 96 also had Vitamin D < LLN, as shown on p. 95 of his review. Dr. Boehm finds that the outlier risk for PTH above ULN increased and persisted over time (at 48 and 96 weeks). Dr. Boehm's analysis does not find marked differences in mean change from baseline by treatment for either calcium or phosphorous. Dr. Boehm also searched for AE terms associated with hyperparathyroidism, such as Vitamin D deficiency, Vitamin D decreased or increased, blood calcium increased or decreased, osteopenia, osteoporosis, spinal compression fracture, wrist fracture, femur fracture, and nephrolithiasis and does not find robust evidence for differences potentially related to hyperparathyroidism. There were few additional AEs potentially associated with hyperparathyroidism in MS pool B trials.

Dr. Boehm notes that given the lack of evidence of corresponding elevated calcium results, the elevated PTH appears consistent with secondary hyperparathyroidism. He notes that Vitamin D deficiency resulting in hypocalcemia is a recognized etiology of secondary hyperparathyroidism. However, the observation of Vitamin D < LLN in fewer patients than PTH >ULN and the observation that these two findings were not commonly seen at the same time in the same patient does not strongly support that etiology.

I agree that the clinical importance of the observed increase in PTH and decrease in Vitamin D is not known. Dr. Boehm reviews the literature regarding the evolving understanding of the relationship between MS and Vitamin D in which Vitamin D deficiency has been cited as a risk factor for MS, and the reports that vitamin D deficiency and elevated PTH have been observed in MS patients. I agree with Dr. Boehm that it is therefore difficult to know whether the observed changes in PTH and Vitamin D in this submission reflect effects of BG00012 or alterations in the underlying disease process. I agree that similarities with results for GA in these trials as well as lack of apparent increased risk of AEs that could be related to hyperparathyroidism is reassuring.

2.1.7 Vital Signs and ECG

Temperature – There did not appear to be notable differences in temperature across treatments.

[8] There were >1000 patients for BG00012, >540patients for placebo, and > 270 patients for GA that did not have low Vitamin D at baseline.

Pulse – BG00012 patients experienced slightly greater mean increases from baseline for pulse (2.5 bpm for BG00012 BID and 2.9 bpm for BG00012 TID) compared to 1.2 bpm for placebo and 0.1 bpm for GA. This was observed throughout the study. However, there did not appear to be meaningful differences by treatment in percentages of patients with potentially clinically significant (PCS) results for pulse (> 120 bpm or < 50 bpm) in Pool A trials.

Blood pressure – Dr. Boehm notes that BG00012 patients experienced slight mean declines from baseline in systolic and diastolic blood pressure that were more negative compared to the mean changes seen for placebo or GA, but there did not appear to be meaningful differences by treatment group for percentages of patients meeting criteria for PCS results.

Body weight – Dr. Boehm does not report meaningful changes in body weight at week 96 in MS trials 301 and 302.

2.1.8 ECGs

The FDA interdisciplinary review team (IRT) reviewed the results of a thorough QT study (Trial 109HV101) and found no significant effect on the QT interval.

ECG analyses were available for quantitative date from Pool A. For heart rate, PR interval, and QT intervals, I agree with Dr. Boehm that there do not appear to be meaningful differences by treatment for mean change from baseline, although as in the evaluation of vital signs, I note that heart rate increased slightly for BG0012 compared to placebo or GA. I agree with Dr. Boehm that there did not appear to be notable differences in QTc outliers by treatment.

2.1.9 Other findings and considerations

Drug Demographic Interactions: As previously noted, the MS Pool A clinical trials included patients between 18-55 years. The analyses of safety data by age was presented for < 40 years vs ≥ 40 years, but is limited by the age range. For the AEs that occurred in > 5% of BG00012 subjects and > 1.5x placebo, I agree with Dr. Boehm that there does not appear to be difference in risk by age. Dr. Boehm also does not find evidence of difference in risk by sex for these AEs (except for GI related AEs that were previously discussed). More than 80% of patients in the Pool A trials were White, and I agree that analysis based on race would not be useful.

Because DMF and MMF are metabolized through the TCA cycle, the Sponsor did not conduct formal drug-drug interaction studies. However, the Sponsor reports that PK was not altered in the presence of Avonex or GA and no new safety signals were identified in healthy volunteers when given with a single dose of Avonex or GA. The Sponsor reports no new safety concerns when give with or without ASA for 4 days.

2.2.0 Additional Safety Evaluations

Human Carcinogenicity: The Sponsor notes that BG00012 may be considered an immunomodulator and there is a potential for increased malignancy risk with such drugs. Renal tumors were reported in the nonclinical carcinogenicity study.

I agree with Dr. Boehm that the available data do not suggest that BG00012 is associated with an increased malignancy risk. In Pool A trials there did not appear to be a difference in malignancy risk between placebo or BG00012 BID or TID (<1% in each group). In Pool B there were 19 reported malignancies in 18 patients (4 from RCTs and 15 from extension trials). Dr. Boehm reports that the overall malignancy risk in the MS clinical trials was not elevated compared to SEER data. However, he notes that there were 2 renal cell malignancies and a single malignancy of the renal pelvis (transitional cell) from Pool B trials. The Sponsor stated that the patient with the renal pelvis malignancy (387-301) had a risk factor of a 40 pack year smoking history. One patient with renal cell cancer (147-404) had received BG00012 for 35 months and had risk factors of hypertension and borderline obesity. The second patient with renal cell cancer (463-307) had the malignancy diagnosed as an incidental finding during evaluation for concomitant endometrial cancer after 14.6 months of BG00012. The Sponsor felt that the renal cell malignancies diagnosed during the clinical trials were likely present in the BG00012 patients prior to initiating BG00012, although the sponsor did not have baseline imaging data to support this. The Sponsor felt that the incidence is compatible with the incidence in the general population and in the MS population in the US and concludes that there is no evidence of a causal relationship.

Dr. Boehm has reviewed evidence for consideration of fumarate as an oncometabolite. Please refer to p. 109-115 of his review for a detailed discussion. Dr. Boehm notes that fumarate is metabolized by fumarate hydratase (FH) via the TCA cycle. Mutations in the genes coding for FH can result in impaired FH function and increased intracellular fumarate that may result in a variety of potentially deleterious effects, including activation of oncogenic hypoxia-inducible factor (HIF) pathways and activation of Nrf2[9] resulting in tolerance to oxidants, which promotes tumor survival. Dr. Boehm notes that patients with FH mutations can develop hereditary leiomyomatosis and renal cell cancer syndrome, as well as other tumors. According to the Sponsor, with low or absent FH activity, there is significant accumulation of cellular fumarate, with levels achieving an approximate 500 fold increase over the normal concentration range.

As noted above, Biogen states that in preclinical and clinical studies using oral dimethyl fumarate, no elevations in fumarate levels were detected in circulation or in tissues. Dr. Boehm notes that the lower limit of quantification was 0.27 mg/L. It is not clear to me whether a sensitive assay has been sufficiently explored. Dr. Boehm also notes that we lack information to determine if ingesting BG00012 results in increased intracellular levels of fumarate.

The Sponsor believes that after oral dosing of dimethyl fumarate, tissue and cellular exposures do not achieve fumarate levels necessary for neoplastic conversion or for promotion of tumor growth and survival, and that pulsatile dosing would not result in an

[9] Nrf2 is considered by the Sponsor to be involved in the beneficial effect of the drug.

activation profile comparable to that seen after persistent activation of the Nrf2 pathway that would be expected in the case of FH deficiencies. The Sponsor also believes that the DMF-related preclinical renal cell cancer risk is attributed to rodent-specific nephropathy. The Sponsor does not believe there is an increased risk of renal tumors in clinical trials.

The incidence rate for these malignancies compared to SEER data and compared to an insurance database is shown below.

Incidence Rate/100,000PY (95% CI) for Malignancies of the Kidney (Excluding Pelvis), Renal Pelvis (Only), and Kidney and Renal Pelvis Combined

Site	BG00012 (Pool B)	US SEER 2008	(b) (4) Claims data	
			MS	Control
Kidney (excluding pelvis)	44.10 (5.34, 159.31)	14.5 (14.3, 14.8)	(b) (4)	
Renal Pelvis (only)	26.29 (0.67, 146.50)	1.0 (0.9, 1.03)		

From ISS table p.98 and SU table p.59

Dr. Boehm notes that although the risk is elevated compared to SEER and insurance database estimates, the point estimate for renal cell cancer risk in BG00012 treated patients is based on only 2 cases, and is comparable to the risk found for teriflunomide (3 cases in 6,000 patient years; 50/100,000 person years). In addition, Dr. Boehm notes that in the postmarketing data for Fumaderm, there were 4 reports of renal cell cancers, resulting in a rate of 2.4/100,000 person years for Fumaderm. In comparison to the reporting rates to Globocan[10] 2008 incidences for malignancies, this is below the Globocan reference data for renal cell cancers of 8.6/100,000 person years. Dr. Boehm does not find an increased risk for leiomyomata among DMF treated patients in the NDA database. I agree with Dr. Boehm, that there is little evidence to support an increased risk for leiomymata or renal cell cancer in BG00012 exposed patients resulting from BG00012 exposure. I agree with Dr. Boehm's recommendation that the Sponsor should monitor postmarketing reports for cases of leiomyomata and for renal cell cancers in patients treated with BG00012.

Human Reproduction and Pregnancy Data: There have been 35 pregnancies in women taking BG00012; one in a healthy volunteer following 2 doses and the remaining in women with MS. Fifteen resulted in live births, 3 were spontaneously aborted (1 in a woman who stopped BG00012 4 months prior to the event and was being treated with Avonex at the time of the event; the other 2 were exposed until 4 or 6 weeks gestation with the outcome at 9 or 10 weeks of gestation, respectively), 7 were terminated electively (no adverse prenatal testing was reported prior to the termination), and outcomes are not known for 10. No fetal abnormalities were reported for the 15 live births.

[10] Derived from malignancy incidences in developed countries/regions (North America, Europe, Japan, Australia, and New Zealand).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound: Dr. Boehm notes that no cases of overdose of BG00012 have been reported in the clinical studies performed to date. He notes that Biogen's search for MedDRA terms potentially related to drug abuse found that the majority of these AEs occurred in < 1% of BG00012 exposed patients. The Sponsor provided additional analyses in the response to the 74-day letter. Abuse potential will be reviewed by the Controlled Substances Staff (CSS).

2.1.10 Postmarket Experience

BG00012 is not yet approved by a regulatory authority. The Sponsor provided foreign postmarketing data for Fumaderm that has an estimated exposure of 159,000 person years thru 9/2011. Dr. Boehm notes that the Sponsor's summary of postmarketing reports and the medical literature demonstrates that the most commonly reported AEs with Fumaderm (lymphopenia, GI adverse events, and flushing) are the AEs commonly reported in BG00012 clinical trials. Infrequent but potentially concerning AEs included agranulocytosis, pancytopenia, acute pancreatitis, necrotizing pancreatitis, drug hypersensitivity, rhabdomyolysis, suicide attempt, and angioedema. Dr. Boehm notes that the most frequently reported SAEs by preferred term were breast cancer (n=7), lymphopenia (n=6), renal failure (n=6), ALT increased (n=5), and myocardial infarction (n=5).

There were 12 reports of serious liver event AEs including elevated liver transaminases (in which there were no other reported liver related symptoms or concomitant elevation of bilirubin), and hepatic cirrhosis (including 1 in a patient with previous hepatitis B), but no events coded to the terms of acute hepatic failure, hepatic failure, or liver failure.

There were 20 reports of serious renal event AEs including 8 reports of renal failure or acute renal failure (with few details, no baseline BUN or Cr data; 1 case had confounding factors of underlying vascular disease, hypertension; 1 case was in a patient who experienced dehydration in the setting of nausea and diarrhea and resolved with hydration and withholding medications), 4 reports of creatinine increased (few details and no baseline BUN or Cr; 1 case occurred in the setting of dehydration; 1 case was identified as post renal failure/obstruction), proteinuria, hematuria, tubulointerstitial nephritis/nephropathy toxic (in which the patients were treated with concomitant oral formulations of fumaric acid, fumaric acid ointment, and fumaric acid baths), osteomalacia, Fanconi Syndrome, and glycosuria.

The Sponsor reported that 15% of the postmarketing reports described lymphopenia or decreased lymphocyte count, but did not feel that there was evidence of increased risk of infection associated with those cases. There was 1 report of tuberculosis and one of Kaposi sarcoma. Of note, however are 3 cases of PML reported for Fumaderm. On case occurred after 1 month of exposure to Fumaderm in a patient treated with steroids and methotrexate. In a second case, confounding factors included prior treatment with efalizumab that is associated with an increased risk of PML. The third case occurred after 3 years of Fumaderm treatment in a patient who had decreased lymphocyte counts for over 2 years and who had been previously treated for psoriasis with acitretine (a

retinoid) and methotrexate. In that case, as Dr. Boehm notes, the Sponsor felt that this case "without clear risk factors" is "consistent with the expected background rate for this event consistent with the expected background rate for this event, based on the published incidence of PML in patients with autoimmune diseases". In fact, the Sponsor refers to a publication by Molloy and Calabrese (Arthritis and Rheumatism 2009; 60:3761-3765) that evaluates the rate of PML in hospitalized patients with rheumatic disease and this is not necessarily applicable to multiple sclerosis. Furthermore, methotrexate is an immunosuppressant that is considered to be a risk factor for natalizumab-associated PML. A 4th case, reported by the Sponsor on 12/10/12, was in a psoriasis patient treated with compounded dimethyl fumarate and copper monomethyl fumarate for 6-7 years with a lymphocyte count of 200 and no history of prior immunosuppressant therapies. The role of Fumaderm or dimethyl fumarate or other esters cannot be ruled out, particularly in the last 2 cases. I note, however, that no cases were observed in the NDA database for BG00012 and I agree with Dr. Boehm that the cases reported in the postmarketing setting for Fumaderm do not change the risk profile for BG00012.

The sponsor reviewed available postmarketing data regarding malignancy risk with Fumaderm. Although a variety of malignancies were reported, and acknowledging the limitations of the comparisons, likely underreporting of events, and lack of adjustment for age and gender, the Sponsor reports that the individual reporting rates with Fumaderm were all lower than the corresponding Globocan incidences.

2.1.11 Labeling and Post-Marketing Risk Management Plan

Dr. Boehm has recommended some changes to the Sponsor's proposed labeling; the Division has provided labeling changes to the Sponsor.

As previously mentioned, the Sponsor states that they intend to "conduct a large, global, observational study with the primary objective of determining the nature and incidence of serious infections, malignancies, and other SAEs (e.g., serious renal and hepatic events) or other medically significant events with marketed use of BG00012. Approximately 5000 MS patients treated with BG00012 would be enrolled and followed for up to 5 years, which would provide approximately 18,000 person-years of follow-up after accounting for treatment discontinuation and drop-out rates." I recommend that such an observational study be a postmarketing requirement. Consideration should be given to the duration of such a study given the lack of signals seen in the more than 2 years of follow- up already available in the NDA database, but with respect to the potential difficulty in maintaining enrollment in a long-term study.

Dr. Boehm recommends that Biogen should further evaluate the finding of elevated urinary ketone results observed in the MS trials, and as they proposed the elevated levels represent false positive results, they should evaluate this hypothesis by measuring serum ketones in BG00012 treated patients with positive urinary ketones. This could be included in the observational study. Perhaps an in vitro evaluation might also be helpful to determine whether this finding is due to a laboratory interaction.

Dr. Boehm also recommends that all postmarketing reviews (e.g. PSURs) should include specific discussion of events of potential renal toxicity, renal cell cancer, leiomyomata, and infections/opportunistic infections. I agree with this recommendation. In any further evaluation of renal toxicity, including follow up of cases to be reported in the postmarketing reviews, I recommend that evaluation of additional biomarkers for kidney injury, including kidney injury molecule-1 (KIM-1) and *N*-Acetyl-β-(D) glucosaminidase (NAG), be considered.

3 Conclusions

Dr. Boehm has not identified any issues in his review of the safety data that would prevent approval of BG00012. Recommendations for postmarketing evaluation of specific safety signals are outlined in section 2.1.11, above.

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/s/

SALLY U YASUDA
02/07/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204063
Priority or Standard	Standard
Submit Date(s)	02/24/12
Received Date(s)	02/27/12
PDUFA Goal Date	12/13/12
Division / Office	DNP/ODE1
Reviewer Name(s)	Gerard Boehm, MD, MPH
Review Completion Date	1/4/13
Established Name	BG00012
(Proposed) Trade Name	Tecfidera
Therapeutic Class	Fumarate ester
Applicant	Biogen Idec
Formulation(s)	Oral; 120mg, 240mg capsule
Dosing Regimen	120mg twice a day for 7 days then 240mg twice a day
Indication(s)	Relapsing Multiple Sclerosis
Intended Population(s)	MS patients at least 18 years old

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7 Review of Safety

Safety Summary

This review considers the safety data for BG00012 (dimethyl fumarate) as presented in Biogen's NDA 204063. BG00012 is an orally administered fumarate ester. Biogen asserts that BG00012 has anti-inflammatory, cytoprotective, and immunomodulating properties. BG00012 has not yet been approved by a regulatory agency, but Fumaderm, a combination product containing dimethyl fumarate and other fumarate esters, is approved in Germany for the treatment of Psoriasis. Dimethyl fumarate has also been used as a fungicide and a desiccant for furniture. Upon finding that dimethyl fumarate resulted in allergic skin reactions, several countries banned its use for this purpose.

Investigators conducted clinical trials using BG00012 in Multiple Sclerosis (MS), Psoriasis, and Rheumatoid arthritis (RA) patients. For NDA 204063, Biogen conducted trials in MS patients to support the indication of "treatment of patients with relapsing multiple sclerosis (b) (4) FDA approved treatments for relapsing forms of MS include interferons, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, and teriflunomide.

The BG00012 NDA submission summarizes safety data for 3,424 exposed subjects from clinical trials in healthy volunteers, and adults with MS, Psoriasis, and RA. Biogen also provided foreign post marketing safety data for Fumaderm. Biogen's clinical trials safety data presentations used data pools that were grouped by indication and trial design. Biogen primarily focused on safety data from MS clinical trials. Biogen's MS Pool A included the safety data from one phase II (C-1900 part A) and two phase III (MS 301, MS 302) randomized controlled trials (RCTs). MS Pool B includes data from the RCTs and their open label extension trials (C-1900 part B, MS 303). Biogen also presented pooled safety data analyses for Psoriasis Pool C trials (RCTs 201-WP-12/01 part 1, 201-KG-01/20) and Psoriasis Pool D trials (RCTs + open label extensions 201-WP-12/01 part 2 and 201-KG-03/03). Biogen did not pool data from the remaining clinical trials, but instead submitted those data in the form of individual clinical study reports.

The number of patients exposed to BG00012 in the NDA trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended dose (240mg twice a day). Acorda reported that 3,424 subjects were exposed to at least one dose of BG00012, including 2,665 MS subjects. Through the 120 Day Safety Update (SU) submission, 2,210 MS patients were exposed to BG00012 for at least 6 months, 1,787 were exposed for at least 1 year, 1,198 were exposed for at least 2 years

and 712 were exposed for at least 3 years. Biogen reported that 2,537 MS patients received BG00012 doses that were ≥ 240mg twice a day.

I identified no significant unresolved deficiencies in the NDA safety submission. Biogen submitted all necessary summaries and supporting data. There were no notable inconsistencies across the data sources (summaries, reports, data sets, etc.). The routine clinical safety testing in the MS clinical trials seemed appropriate and capable of identifying major safety signals with BG00012. The BG00012 NDA included instances of coding inadequacies, but Biogen addressed many of these in supplemental analyses.

Deaths occurred infrequently in the BG00012 clinical trials and there did not appear to be clusters of unusual causes of death. The reported causes of death for BG00012 clinical trial subjects were traumatic brain injury following bicycle accident; motor vehicle accident; complications of MS relapse; cardiopulmonary arrest/respiratory muscle weakness/MS relapse; sepsis/decubitis ulcers/respiratory arrest/aspiration pneumonia; mesothelioma; suicide/paracetamol overdose; sudden death; and acute MI.

17% of MS subjects exposed to BG00012 experienced one or more serious adverse events (SAEs). The only SAE that occurred in ≥1% of BG00012 exposed patients was MS relapse (9%, 227/2,513). Gastroenteritis (n=10), gastritis (n=8), UTI (n=8), fall (n=5), and road accident (n=5) were the only other SAEs reported by at least 5 patients. During the MS RCTs, SAEs were reported slightly more frequently by placebo patients compared to BG00012 patients. In these trials, no individual SAE was reported by at least 1% of BG00012 patients and more commonly compared to placebo. I identified few unexpected SAEs of potential concern in the BG00012 trials and in none of these cases did there appear to be clear evidence of a causal link to BG00012.

16% of MS subjects exposed to BG00012 experienced one or more AEs leading to discontinuation. The AEs leading to discontinuation of at least 1% of BG00012 treated patients were flushing (2%, n=57/2513), diarrhea (2%, n=39/2513), nausea (1%, n=33/2513), vomiting (1%, n=32/2513), MS relapse (1%, 35/2,513), abdominal pain upper (1%, n=31/2513), and abdominal pain (1%, n=28/2513). In the MS controlled trials, various GI AEs (diarrhea, nausea, vomiting, abdominal pain, abdominal pain upper) and flushing-related AEs led to discontinuation of a higher percentage of BG00012 patients than placebo patients.

Common AEs that occurred more frequently among BG00012 MS subjects included flushing, diarrhea, nausea, abdominal pain upper, abdominal pain, pruritis, vomiting, rash, hot flush, erythema, sinusitis, bronchitis, albumin urine, dyspepsia, and muscle spasms.

BG00012 causes flushing symptoms in almost half of treated patients. Preliminary evidence suggests that this phenomenon is similar to that seen with niacin and may share a similar mechanism (mediated by PGD_2). Though most patients who

experienced flushing seemed to tolerate the symptoms without need for decreasing/holding dose, symptomatic treatment, or discontinuation; there were a small number of patients who discontinued and/or had severe symptoms that required medical attention. Flushing AEs tended to begin soon after initiating BG00012 treatment. For many patients, the flushing AEs did not persist, but for almost 25% of patients, flushing or hot flush AEs apparently continued to occur during treatment. Aspirin appeared to mildly reduce flushing symptoms, although this evidence came from one small study (109HV106) and Biogen did not conduct formal statistical evaluations of the results. Although the clinical trials allowed for temporary dose reduction in patients experiencing flushing, Biogen did not evaluate if this therapeutic maneuver improves tolerability. Interestingly, data from the 109HV106 demonstrated that the BG00012 360mg BID dose group had lower flushing symptom scores than the 240mg BID and 240mg TID dose groups, raising questions about the dose response at the examined dose range and the usefulness of dose lowering to improve tolerability. During a food-effect trial, the flushing risk was slightly less in the fed state (68%) compared to the fasted state (94%). The relatively small difference in event occurrence suggests that food will have limited effectiveness in decreasing flushing symptoms.

Based on the criteria described in the FDA Guidance for Industry “Drug Induced Liver Injury: Premarket Clinical Evaluation”, BG00012 did not appear to demonstrate the potential for hepatic injury. Although a higher percentage of BG00012 patients compared to placebo experienced amino transferase results >ULN, the same was not true using cutoffs of 3xULN or above. BG00012 patients did not exhibit an increased risk of total bilirubin >ULN. Biogen reported that no BG00012 patients experienced amino transferase elevations>3xULN in association with total bilirubin increases >2xULN. There were cases of serious hepatic injury in BG00012 treated patients in the NDA safety database, but the clinical data did not clearly suggest a causal relationship with BG00012.

Despite preclinical evidence of BG00012 related renal toxicity in multiple animal species, the clinical trials in the NDA did not suggest that BG00012 exposed patients were at increased risk of renal toxicity. It is not clear if this is because humans are not similarly affected, or if development of renal toxicity requires longer exposures in humans than those provided in the NDA. Multiple species of animals exposed to BG00012 experienced renal tubular and interstitial toxicity. Because of these findings, in addition to the usually collected renal related lab data (BUN, creatinine, urinalysis), the MS RCTs incorporated enhanced renal monitoring that included urine microalbumin, and B2- microglobulin testing, requirements for renal consults for patients with specific test results, and special study medication stopping rules.

Analysis of renal-related AE results did not suggest an increased risk for BG00012 patients compared to placebo patients. Review of narratives for select renal SAEs and discontinuations for renal AEs did not identify convincing evidence of a causal relationship to BG00012 for these events. Lab data revealed negligible differences in

the percentages of BG00012 patients who developed B2-microglobulinuria or mircroalbuminuria compared to placebo or glatiramer acetate (GA). Evaluations of patients with renal related AEs by Biogen's consultant nephrologists did not identify clear evidence of BG00012 related renal toxicity. Biogen stated that they intend to monitor this potential risk in the post marketing setting with targeted follow up of cases suggestive of renal toxicity.

BG00012 patients were more likely to develop ketonuria. The etiology of ketonuria in BG00012 patients is not known. This finding did not appear to have meaningful clinical implications. Patients who developed ketonuria did not appear to be at increased risk for AEs or SAEs. BG00012 patients with pre existing diabetes mellitus were not at increased risk for developing ketonuria compared to those without pre existing diabetes mellitius.

BG00012 caused GI AEs that impacted tolerability. In the Pool A trials, 40% of BG00012 subjects experienced one or more GI AEs compared to 30% of placebo patients. Diarrhea, vomiting and abdominal pain were the individual GI AEs that most commonly occurred in BG0012 patients and that occurred more frequently compared to placebo. These events occurred most commonly around the time of initiating treatment with BG00012 and the greatest difference in risk compared to placebo occurred during the first month of treatment. Compared to placebo, BG00012 patients had slightly increased frequency of GI SAEs, GI AEs leading to discontinuation, and GI AEs rated by investigators as severe. The MS Pool A study protocols allowed for temporary dose reductions in patients with GI AEs but it is unclear to what extent this therapeutic maneuver improved tolerability. There was insufficient evidence to determine if taking BG0012 with food improved tolerability with respect to GI AEs.

The additional analyses of treatment emergent AEs that Biogen performed did not suggest that BG00012 was associated with infections (including opportunistic infections), cardiovascular disorders, or suicide and/or depression.

Lab data demonstrated BG00012 related lymphopenia and transient eosinophilia. Biogen noted that the mechanism of the reduction of lymphocyte counts is not known and that it was not observed in animal studies. After 1 year of BG00012 exposure, the mean lymphocyte count decline from baseline was 30% with limited additional decline thereafter. In the Pool A MS trials, among patients treated with the BID dose, the mean change from baseline for lymphocytes was -0.5 $x10^9$/L at 6 months, -0.6 $x10^9$/L at 1 year and -0.7 $x10^9$/L at 2 years, with minimal change observed in the placebo group. Furthermore, 6% of BID patients in the Pool A trials had a lymphocyte count <0.5 $x10^9$/L compared to <1% of placebo patients. Lab data suggested that patients' lymphocyte counts increased after stopping BG00012, but did not completely recover during the 4 week post-last dose observation period. The magnitude of the observed lymphocyte count decline with BG00012 is within the range of declines described for fingolimod and

teriflunomide, two recently approved MS treatments. In addition to effects on lymphocytes, BG00012 causes an early, transient increase in eosinophils.

After finding proliferative parathyroid changes in rats, Biogen included PTH and Vitamin D testing at weeks 48 and 96 of the MS RCTs. BG00012 exposed trial subjects experienced greater mean increases in PTH and were more likely to have PTH results that were >ULN. Over 20% of BG00012 subjects had PTH >ULN compared to 17% of GA subjects and 9% of placebo subjects. In addition, BG00012 subjects experienced Vitamin D<LLN. The majority of subjects with increases in PTH did not also experience Vitamin D<LLN. BG00012 subjects did not experience notable differences in calcium results compared to placebo or GA subjects. In addition, BG00012 treated subjects were more likely to have Vitamin D levels <LLN. Vitamin D deficiency resulting in hypocalcemia is a recognized etiology of secondary hyperparathyroidism, although the two abnormalities were not commonly seen occurring at the same time in the same subject in these MS trials.

The clinical importance of the observed increased PTH and decreased Vitamin D is not evident. There did not appear to be among BG00012 subjects an increased risk for AEs potentially associated with hyperparathyroidism. Although the difference in percentage of BG00012 patients with elevated PTH compared to placebo was notable, it was less pronounced compared to GA, which has not been previously recognized to be associated with increased PTH. Further complicating our understanding of these results is the evolving understanding of the role of Vitamin D in MS.

The remaining lab data, vital sign data and ECG data collected during the clinical trials did not find evidence of BG00012 related deleterious effects. A formal QT study did not find evidence of QT prolongation in subjects exposed to BG00012.

Late in the review cycle, we became aware of publications that identified fumarate, a metabolite of BG00012, as an “oncometabolite”. The medical literature explains that mutations resulting in significant declines or loss of fumarate hydratase (FH) function result in increased intracellular levels of fumarate. Increased intracellular levels of fumarate are presumed to be responsible for the sequelae of leiomyomata and renal cell cancers seen in the Heriditary Leiomyoma and Renal Cell Cancer (HLRCC) syndrome.

We lack information to determine if ingesting BG00012 results in increased intracellular levels of fumarate. Fumarate was not detected in plasma levels of patients administered DMF, but this does not necessarily preclude the possibility of increased intracellular fumarate levels.

We do not have affirmative evidence of increased risk for the outcomes seen in HLRCC. There was no evidence of increased risk for leiomyomata among BG00012 treated patients in the NDA database. Although elevated compared to SEER and insurance

database estimates, the point estimate for renal cell cancer risk in BG00012 treated MS patients was based on only 2 cases, and it was comparable to the renal cell cancer risk observed in the NDA database for a recently approved MS drug.

The available NDA data do not suggest that treatment with BG00012 results in the outcomes seen with reduced FH function. While this difference may be because treatment with BG00012 does not result in the increased intracellular fumarate levels seen with FH deficiency, as Biogen proposes, we do not currently have data to confirm this hypothesis. Biogen should monitor post marketing reports to identify cases of leiomyomata and or renal cell cancers in patients treated with BG00012.

Conclusions/Recommendations

There are no safety issues that preclude approval of this NDA.

Specific safety labeling recommendations will be presented and discussed with the review team.

Biogen should further evaluate the finding of elevated urinary ketone results observed in the MS trials. Because Biogen proposed that the observed elevated urinary ketones possibly represent false positive results, they should evaluate this hypothesis by measuring serum ketones in BG00012 treated patients with positive urinary ketones.

All post marketing reviews (ex. PSURs) should include specific discussions of events of potential renal toxicity, renal cell cancer, leiomyomata, and infections/opportunistic infections.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Biogen included safety data from 23 clinical trials in the BG00012 (dimethyl fumarate) NDA (SCS p.15). In the following table, I identify the trials that Biogen included in the BG00012 NDA safety presentations.

Clinical Trials in NDA 204063

Phase II/III Trials, MS	C-1900 parts 1 and 2, 109MS301, and 109MS 302, 109MS303
Phase II/III Trials, Psoriasis	201-WP-12/01 parts 1 and 2, 201-KG-01/02, 201-KG-03/03
Phase I Trial MS	109MS101
Phase I Trials, Healthy volunteers	201-FG-PK-02/02, C-1903, 201-FG-PK-03/04, IKP/ID32, IKP/ID33, 109HV101,

	109HV102, 109HV103, 109HV104, 109HV105, 109HV106, and 109HV107
Phase II Trial, Rheumatoid Arthritis	109RA201
Phase IIa Trial, Psoriasis	210-BG-PK-01/02
Ongoing Phase II Trial, MS	109MS201

Biogen's safety data presentations focused on MS trials C-1900 parts 1 and 2, 109MS301, and 109MS 302, 109MS303. In the following paragraphs I will provide safety-related information about the design of these trials.

C-1900 was a Phase 2 dose-ranging, randomized, placebo-controlled trial with a 24 week randomized controlled treatment phase (part 1) followed by a 24 week dose-blinded extension phase (part 2). Forty-three investigators in 10 European countries enrolled a total of 257 patients. C-1900 included placebo and the following BG00012 dose groups: 120mg qd, 120mg TID, and 240mg TID. The study enrolled MS patients aged 18-55 years.

109MS301 and 109MS302 were both Phase 3, randomized, placebo-controlled trials of 2 years duration. Both trials were multi-national, multi-site MS trials. 109MS301 enrolled 1237 subjects at 198 investigational sites in 28 countries. The countries that enrolled at least 100 patients were United States (n=203), Germany (n=172), Poland (n=132), and India (n=114) (109MS301 Study report, p.97). 109MS302 enrolled 1430 subjects at 200 investigational sites in 28 countries. The countries that enrolled at least 100 patients were Poland (n=282), United States (n=267), India (n=107), and Ukraine (n=104) (109MS302 Study report, p.97). Both trials included placebo and the following BG00012 dose groups: 240mg BID and 240mg TID. 109MS302 also had an active comparator arm (glatiramer acetate, GA). These trials enrolled MS patients aged 18-55 years.

C-1900, 109MS 301, and 109MS 302 had similar exclusion criteria. I list safety-related exclusion criteria from these trials below.

Safety Related Exclusion Criteria C-1900, 109MS301, 109MS302

Safety related exclusion criteria	**C-1900**	**109MS301**	**109MS302**
At any time			
History of malignancy	X	X	X
History of hypersensitivity/severe allergic reactions	X	X	X
HIV	x	X	X
Significant underlying disease	X	X	X
Total lymphoid irradiation treatment	X	X	X
Prior treatment with Fumaderm, BG00012	X	X	X
Prior treatment with cladribine	X	X	X
T-cell or T-cell receptor vaccination	X	X	X

Prior treatment with a therapeutic monoclonal antibody except natalizumab	X	X	X
Within past 2 years			
Drug or alcohol abuse	X	X	X
Within past 1 year			
Treatment with cyclophosphamide	X	X	X
Treatment with mitoxantrone	X	X	X
Within past 6 months			
Treatment with cyclosporine	X	X	X
Treatment with azathioprine	X	X	X
Treatment with methotrexate	X	X	X
Treatment with natalizumab	X	X	X
Treatment with mycophenolate mofetil		X	
Treatment with IVIg	X	X	X
Plasmapharesis or cytapharesis	X	X	X
Treatment with another study drug or approved therapy for investigational use	X	X	X
Within past 3 months			
Glatiramer acetate	X	X	
Interferon alpha	X	X	X
interferon-beta (patients who were positive for neutralizing antibodies to interferon-beta may have received interferon-beta treatment up to 2 weeks prior, C-1900 only)	X	X	X
Within past 50 days			
MS relapse/unstable disease	X	X	X
IV/oral corticosteroids		X	X
4-aminopyridine		X	X
Within past 30 days			
IV/oral corticosteroids	X		
4-aminopyridine	X		
At screening			
Weight >100kg	X		
HepCAb+, HepBsAg+	X	X	X
AST,ALT,GGT>2xULN	X	X	X
WBC<3500/mm^3	X	X	X
Eosinophils >0.7x10^3/uL	X	X	X
Creatinine >ULN	X		
Lab results indicating significant underlying disease		X	X
Urine protein >=1+ (confirmed by second Test in 109MS301)		X	X
Hematuria, unexplained		X	X

Glycosuria, unexplained		X	X
Females considering pregnancy	X	X	X
Pregnant or breastfeeding females	X	X	X

From Study reports C-1900, 109MS301, and 109MS302

These trials also shared many of the same safety-related criteria for mandatory early discontinuation. I list those criteria below.

Safety related Discontinuation Criteria C-1900, 109MS301, 109MS302

Safety related discontinuation criteria	**C-1900**	**109MS301**	**109MS302**
Pregnancy	X	X	X
AST, ALT, GGT>4xULN at any time	X		
AST, ALT, GGT>3xULN, sustained for 4 consecutive weeks	X	X*	X*
BUN>4xULN at any time	X		
BUN>2.5xULN, sustained for 4 consecutive weeks	X		
Creatinine >2xULN at any time	X		
Creatinine>1.2xULN, sustained for 4 consecutive weeks	X	X*	X*
WBC<1,500 at any time	X		
WBC<2,000, sustained for 4 consecutive weeks	X	X*	X*
Experienced elevation of >2 laboratory parameters that met the threshold limits		X	X
More than 1 elevation of the same laboratory parameter that met the threshold limits	X	X	X
Unable to tolerate study drug	X	X	X
Medical emergency	X	X	X
Positive urine cytology following unexplained hematuria		X	X
Renal dysfunction diagnosed by nephrologist		X	X

From Study reports C-1900, 109MS301, and 109MS302
* sustained 4 weeks after study drug withheld

Other Safety Data
In addition to the development program clinical trials safety data, Biogen provided post marketing safety data for Fumaderm, a combination product that includes dimethyl fumarate and 3 different salts of monoethyl fumarate. Germany licensed Fumaderm in 1994 for the treatment of Psoriasis (SCS, p.147).

7.1.2 Categorization of Adverse Events

Biogen defined AEs as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment.” (Trial 301 Study protocol, p.59). Investigators elicited AEs by general questioning of subjects, and did not use checklists for specific AE identification. Investigators for MS trials recorded the date(s) (onset/resolution) of the event, treatment given, and whether the event led to withdrawal from the study. Study protocols required investigators to follow up reported AEs until they resolved/returned to baseline. Investigators provided opinions about relationship of AE to treatment and classified the AE as mild, moderate, or severe (CRF review).

Biogen explained that they used the Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 to code investigator verbatim terms to preferred terms for use in AE analyses (ISS, p.38). In their AE data sets, Biogen provided the investigator verbatim terms and the preferred terms for all AEs. I reviewed the AE data set to assess the AE term coding process. In general, the coding process seemed appropriate and allowed for reliable estimates of AE risks.

There were few instances where the coding process could have led to splitting of likely related events into separate preferred terms but Biogen adequately addressed these in subsequent analyses. For example, the coding process resulted in verbatim terms describing flushing reactions to be mapped to a number of different preferred terms including flushing, hot flush, erythema, generalized erythema, burning sensation, etc. To address this result of the coding process, Biogen submitted additional analyses that grouped the preferred terms listed above as flushing-related events. Biogen undertook similar analyses for gastrointestinal related events. In addition, for other analyses, Biogen used SMQs for events such as suicide and depression and opportunistic infections, to examine the AE data for evidence of drug related risk.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Integrated analyses

Biogen performed integrated safety analyses using data pools defined by indication and trial design, and the approach seemed appropriate given the similarities in the population, design, and duration of the included trials. I present the different data pools that Biogen used for their presentations, and provide the exposure (number of patients and person time) for these pools in the following sections.

MS indication
Biogen presents integrated MS safety data analyses using 2 data groupings, pools A and B. Pool A includes data from placebo-controlled trials in MS (C-1900 part 1, 109MS301, and 109MS 302) and pool B includes data from placebo-controlled and uncontrolled trials in MS (C-1900 parts 1 and 2, 109MS301, and 109MS 302, 109MS303). In the following table, I summarize information about the trials included in pools A and B and I identify the source of the denominators used in the safety analyses.

MS Pool A		
Trial (duration)	Treatment groups (n)	Denominators used in safety analyses
C-1900 part 1 (6 months)	Placebo (65) BG00012 120mg QD (64) BG00012 120mg TID (64) BG00012 240mg TID (63)	Placebo n=836 (65+408+363); 1,161.5PY GA n=351; PY=548.8 PY BG00012 low dose (BG00012 120 QD and BG00012 120 TID) n=128 (64+ 64); 54.8PY BG00012 240mg BID n=769 (410+359); 1,128.7PY BG00012 240 TID 823 n=(63+416+344); 1,140.0PY Total BG00012 n=1,720; 2,323.5PY
109MS301 (2 years)	Placebo (408) BG00012 240mg BID (410) BG00012 240mg TID (416)	
109MS302 (2 years)	Placebo (363) BG00012 240mg BID (359) BG00012 240mg TID (344) GA (351)	
MS Pool B		
C-1900 Parts 1 and 2 (6 months)	Continued BG00012 in extension DMF 120mg QD (58) DMF 120mg TID (56) DMF 240mg TID (52) Took placebo in RCT and 1st exposure to BG00012 in extension BG00012 240mg TID (59)	BG00012 Low dose (from Pool A) n=128; 105.6PY BG00012 240mg BID n=1,136 (Pool A=769, New exposure in extension=367); 2079.3 PY BG00012 240 TID n=1,249 (Pool A=823, New exposure in extension=59+367); 2121.7 PY Total BG00012 n=2,513; 4,306.7 PY
109MS301 109MS302 109MS303 (up to 5 years)	Continued BG00012 in extension DMF 240mg BID (501) DMF 240mg TID (501) Took placebo or GA in RCT and 1st exposure to BG00012 in extension BG00012 240mg BID (249 PBO, 118 GA) BG00012 240mg TID (248 PBO, 119 GA)	

Study and subject number (n) data from Table 6, SCS p.26., 120 Day SU, p.18, p.78
Person year (PY) data from Table 8, ISS p.35 and Appendix 1 Table 6 ISS p.237, 120 Day SU, p.1

Psoriasis indication
Biogen provides integrated safety data from Psoriasis clinical trials to supplement the data from MS trials. As with the MS safety data presentations, Biogen presents the Psoriasis safety data analyses using 2 groupings, pools C and D. Pool C includes the data from placebo-controlled trials for Psoriasis (201-WP-12/01 part 1, 201-KG-01/02) and pool D includes data from placebo-controlled and uncontrolled trials for Psoriasis (201-WP-12/01 parts 1 and 2, 201-KG-01/02, 201-KG-03/03). In the following table, I summarize information about the trials included in pools C and D.

Psoriasis Pool C		
Trial (duration)	Treatment groups (n)	Denominators used in safety analyses
201-WP-12/01 part 1 (3 months)	Placebo (36) BG00012 120mg QD (36) BG00012 120mg TID (36) BG00012 240mg TID (36)	Placebo n=106 (36+70); 26.4 PY BG00012 low dose (BG00012 120 QD and BG00012 120 TID) n=72 (36+36); 15.1 PY BG00012 240 TID n=141 (36+105); 37.4 PY Total BG00012 n=213; 52.5 PY
201-KG-01/02 (4 months)	Placebo (70) BG00012 240mg TID (105)	
Psoriasis Pool D		
201-WP-12/01 parts 1 and 2 (6 months)	Continued BG00012 in extension BG00012 120mg QD or 240mg TID (80) Took placebo in RCT and 1st exposure to DMF in extension DMF 120mg QD or 240mg TID (28)	Total BG00012 n=296 (Pool C=213, New exposure in extension=28+55); 317.7 PY
201KG01/02 201-KG-03/03 (2 years)	Continued BG00012 in extension BG00012 120mg QD or 240mg TID (88) Took placebo in RCT and 1st exposure to BG00012 in extension BG00012 120mg QD or 240mg TID (55)	

Study and subject number (n) data from Table 7, SCS p.28.
Person year (PY) data from Table 22, ISS p.134 and Appendix 1 Table 206 ISS p.7654

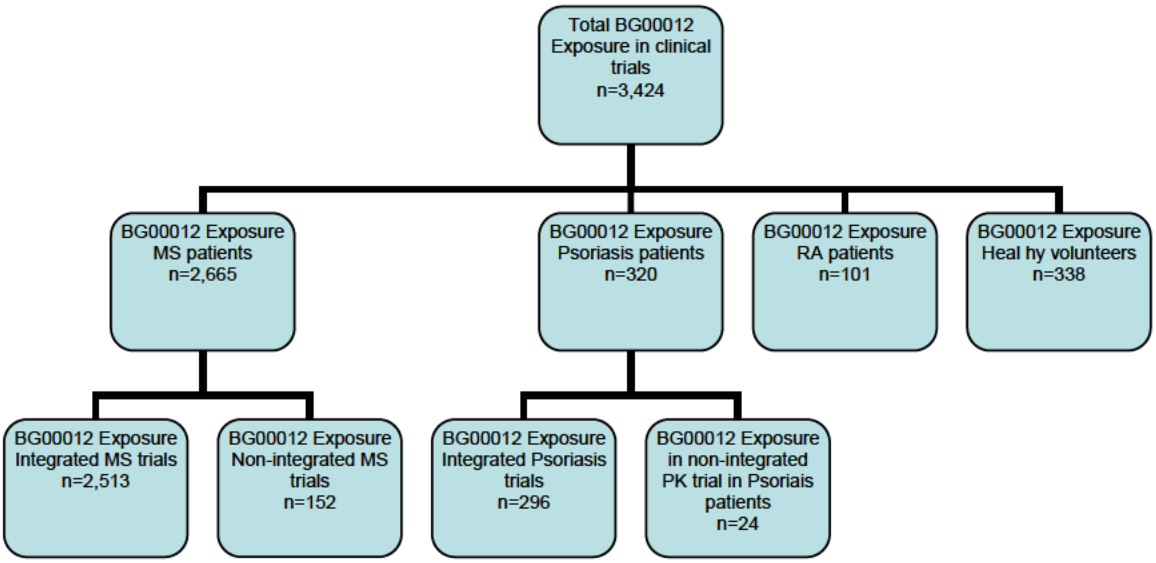
Non-integrated safety data
Biogen also provided safety data that were not integrated. Biogen presented non-integrated safety data in the format of individual study reports. Non-integrated data came from trials 109MS101 (phase I trial in MS patients), 109MS201 (phase 2 trial in MS patients), 210-BG-PK-01/02 (phase 2a trial in Psoriasis patients), and 109RA201 (phase 2 trial in RA). In addition, Biogen provided safety data for 12 phase I trials in

healthy volunteers (201-FG-PK-02/02, C-1903, 201-FG-PK-03/04, IKP/ID32, IKP/ID33, 109HV101, 109HV102, 109HV103, 109HV104, 109HV105, 109HV106, and 109HV107).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Biogen's clinical trials safety database includes human subject exposure to BG00012 that exceeds ICH guidelines. Biogen presented safety data for 3,424 BG00012 exposed clinical trial subjects (Table 2, SCS, p.11, 120 Day SU, p.15). The following diagram summarizes the exposure across the different indications and data groupings that Biogen presented in the NDA and 120 Day SU.



Exposure by duration, MS patients
Biogen reports the following exposure by duration for the 2,665 MS patients:

Exposure to BG00012 ≥ 6 months:	n= 2,210
Exposure to BG00012 ≥ 1 year:	n= 1,787
Exposure to BG00012 ≥ 2 years:	n= 1,198
Exposure to BG00012 ≥ 3 years:	n= 712

(120 Day SU, p.14)

Demographics of the target population
MS Pool B (integrated controlled and uncontrolled trials in MS), included a majority of females and the average age of participants was 38.4 years. I summarize demographic data from MS Pool B in the table below.

MS Pool B, Summary of the Demographic Profile of the Target Population

	BG00012 lower doses	BG00012 240mg BID	BG00012 240mg TID	BG00012 total
N	128	1,136	1,249	2,513
Age				
<40 yrs	61% (78)	54% (619)	52% (649)	54% (1346)
>=40 yrs	39% (50)	46% (517)	48% (600)	46% (1167)
Mean age (yrs)	35.5	38.4	38.7	38.4
Median age (yrs)	35.0	39.0	39.0	39.0
Min, Max	18,54	18,57	18,57	18,57
Sex				
Male	33% (42)	29% (331)	30% (376)	30% (749)
Female	67% (86)	71% (805)	70% (873)	70% (1764)
Race				
White	98% (126)	81% (925)	83% (1,041)	83% (2,092)
Other	2% (2)	14% (161)	13% (165)	13% (328)
Unknown	0	4% (50)	3% (43)	4% (93)

From SU Appendix Table 13

7.2.2 Explorations for Dose Response

In proposed labeling, Biogen recommends that BG00012 be initiated at 120mg twice a day for 7 days and then increased to 240 mg twice a day. The 240 mg twice a day dose is the only recommended regimen. (b) (4)

The majority of the MS exposure safety data comes from patients who received the intended recommended dose. Biogen reported that 2,537 MS patients received BG00012 doses that were ≥ 240mg twice a day (120 Day SU, p.14).

The Pool A MS trials included “lower dose groups” (120 mg QD and 120 mg TID), the intended to be marketed dose of 240 mg twice a day, and 240 mg three times a day. Biogen presented their safety data results tables stratified by dose groups to allow for assessment of dose response.

7.2.3 Special Animal and/or In Vitro Testing

Biogen submitted animal/in vitro testing results for cardiovascular safety testing for BG00012. Biogen reported that in canine testing there were no adverse effects on ECG tracings, blood pressure, heart rate, respiratory rate, or peak value of the respiration waveform (thoracic pressure) throughout 24 hours after dosing. In addition, Biogen noted that there were no effects on the QTc, and no ECG abnormalities, at doses up to 1000 mg/kg. Biogen reported that DMF and MMF also showed no inhibition of hERG channel activity in vitro or have effects on action potential duration in isolated dog Purkinje fibers. Biogen noted that in the CV study in the dog, they observed increases in heart rate and decreases in arterial blood pressure, but they attributed the findings to the physiological stress of vomiting and blood sampling (Nonclinical Overview, pp. 17-18).

7.2.4 Routine Clinical Testing

Pool A Trials
The clinical testing in the Pool A trial protocols appeared adequate to allow assessment of the safety of BG00012.

During Pool A trials, investigators captured AEs and vital signs from the first visit through 4 weeks following the last dose.

During trial C-1900 part 1 (6 months duration), investigators collected hematology, chemistry, and urine samples at screening, baseline, weeks 4, 8, 12, 16, 20, 24, and at the final/follow up visit. In trials 301 and 302 (2 years duration each), investigators collected chemistry and urine samples at each visit and hematology samples at screening, baseline, weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, and at the end of study visit.

In trial C-1900 part 1, investigators recorded ECGs at screening, week 12, week 24, and at the final/follow up visit. In trials 301 and 302, investigators recorded ECGs at baseline, weeks 24, 48, 72, 96, and at the end of study visit.

All 3 trials included baseline Hepatitis C antibody and Hepatitis B surface antigen testing. Trials 301 and 302 also included lipid profiles, parathyroid hormone, and Vitamin D levels.

In the following table, I summarize lab and vital sign data captured during the Pool A trials.

Clinical Safety Data Captured During Pool A MS Trials

Hematology	hematocrit, hemoglobin, MCHC, MCV, RBCs, WBCs/differential, platelets,
Chemistry	ALT, AST, Albumin, ALP, Bicarbonate, Bilirubin, BUN, Calcium, Chloride, Creatinine, GGT, Glucose, LDH, Magnesium, Potassium, Phosphorus, Sodium, Uric acid
Urine	Blood, color, pH, ketones, protein, glucose, urine microscopy, microalbumin, Beta-2 microglobulin
Other	Lipid profile, PTH, Vitamin D, Hep C antibody, HBsAg
Vital signs	Systolic blood pressure, diastolic blood pressure, pulse, temperature, weight
ECG	12-lead

Pool B
In addition to the safety data collected in the RCTs, Pool B includes safety data collected during trial C-1900 part 2 (6 months duration) and trial 303 (open label extension for 301 and 302, up to 5 years duration).

In trial 1900 part 2 and trial 303, investigators recorded AEs and vital signs at each visit.

During trial C-1900 part 2, investigators collected hematology, chemistry, and urine samples at weeks 28, 32, 36, 40, 44, 48, and at the final/follow up visit. In trial 303 investigators collected chemistry and urine samples at each visit and hematology samples every 12 weeks and at the end of study visit.

In trial C-1900 part 2, investigators recorded ECGs at weeks 36, 48, and at the final/follow up visit. In trial 303 investigators did not record ECGs.

Pool C
During Pool C Psoriasis RCTs (WP-12/01 part 1, 12 weeks; KG01/02, 16 weeks), investigators captured AEs, vital signs, hematology, chemistry and urinalysis at each study visit. In trial WP-12/01, investigators recorded ECGs at baseline and week 12. Investigators did not record ECGs during trial KG/01/02.

Pool D
In addition to the safety data collected in the Psoriasis RCTs, Pool D includes safety data collected during trials WP-12/01 part 2 and trial KG-03/03 (open label extension for trial KG01/02). During WP-12/01 part 2, (24 weeks) investigators captured AEs, vital signs, hematology, chemistry and urinalysis at each study visit and ECGs at week 24. During KG-03/03 (60 weeks), investigators captured AEs, vital signs, hematology, chemistry and urinalysis at each study visit (every 2 weeks until week 8, and then every 4 weeks until week 60). Investigators did not record ECGs in KG-03/03.

7.2.5 Metabolic, Clearance, and Interaction Workup

Biogen notes that dimethyl fumarate is rapidly metabolized to monomethyl fumarate by esterases, before reaching the systemic circulation. Dimethyl fumarate is not quantifiable in plasma following oral administration. Further metabolism occurs by the tricarboxylic acid (TCA) cycle with no involvement of the cytochrome P450 system. After metabolism through the TCA cycle, exhalation of CO_2 is the primary route of elimination (60% of dose). Renal and fecal routes account for 15.5% and 0.9% of elimination, respectively.

Biogen reports that the terminal half life of monomethyl fumarate is about 1 hour and accumulation does not occur with the therapeutic regimen. T_{max} is 2-2.5 hours and the C_{max} is 1.72mg/L. The volume of distribution varies between 60 and 90L. Human plasma protein binding of monomethyl fumarate ranges between 27-40%.

Biogen did not identify drug interaction risks from in vitro CYP inhibition and induction studies, a p-glycoprotein study, or studies of the protein binding of dimethyl fumarate and monomethyl fumarate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Dimethyl fumarate is a new molecular entity and does not belong to an approved class of drugs.

7.3 Major Safety Results

7.3.1 Deaths

Reviewer Summary
Biogen identified relatively few deaths in the BG00012 clinical trials. There was no meaningful difference in mortality risk by treatment in the BG00012 MS controlled trials, based on a small number of deaths. The reported causes of deaths in BG00012 treated patients reflected the expected causes in the underlying population (MS progression, accidents, etc.) and there did not appear to be clusters of deaths due to unusual causes.

Overall Clinical Trials
In the 120 day SU Biogen reported a total of 11 deaths in their BG00012 clinical trials (10 deaths occurred by the cutoff date of the SU and 1 death occurred after the cutoff date). Nine deaths occurred in BG00012 exposed subjects in the integrated trials (7 MS, 2 Psoriasis). One death occurred in a subject exposed to GA, and one death occurred

in a placebo subject (both from the integrated MS trials). There were no deaths in the non-integrated trials.

Integrated MS Trials
Seven BG00012 patients from the integrated MS trials died (0.3%, 7/2,513; 1.6/1,000PY). The reported causes of death for the BG00012 subjects were traumatic brain injury following bicycle accident; motor vehicle accident; complications of MS relapse; cardiopulmonary arrest/respiratory muscle weakness/MS relapse; sepsis/decubitis ulcers/respiratory arrest/aspiration pneumonia; mesothelioma; and suicide/paracetamol overdose. The placebo patient's death was due to ischemic stroke and the GA patient's death was due to suicide (self-inflicted gunshot wound).

In the integrated, controlled MS trials (Pool A), mortality appeared to be similar among the treatment groups, based on the small number of events. In these controlled MS trials, 3 BG00012 subjects died compared to 1 placebo subject and 1 GA subject. The table below summarizes the mortality percentage and rate for the integrated MS controlled trials.

Summary of Mortality, Pool A MS Controlled Clinical Trials

	BG00012 Low dose	BG00012 240mg BID	BG00012 240mg TID	BG00012 Total	PBO	GA
Deaths	N=128 PY=54.8	N=769 PY=1128.7	N=823 PY=1140.0	N=1720 PY=2323.5	N=836 PY=1161.5	N=351 PY=548.75
(n)	0	1*	2	3	1	1
%	0	0.1%	0.2%	0.2%	0.1%	0.3%
Rate (/1000PY)	0	0.9	1.8	1.3	0.9	1.8

*The sponsor classified this death by assigned dose and not dose at the time of the event. This death occurred on study day 5, when patient was taking 120mg BID (titration phase days 1-7). This patient would not have reached the target dose of 240mg BID until study day 8 (SR 109MS301, Table 9-2, p.54).

MS Trials Death Summaries

Bicycle Accident, Traumatic Brain Injury; Study 301
Subject 453-316
This 54-year-old female received BG00012* for 5 days when she experienced a traumatic brain injury resulting from a bicycle accident (BG00012 discontinued at that time). The accident occurred as the subject attempted to avoid a collision with a driver who was under the influence of alcohol. Upon admission, a head CT showed a subdural hematoma and cerebral contusion. Neurosurgical intervention (not specified) was performed on admission and the following day; a follow-up head CT revealed brain edema. The subject remained in a coma after the accident. Her hospital course was complicated by nosocomial pneumonia (K. pneumoniae), UTI (P. aeruginosa), and

recurrent fevers. She underwent tracheostomy and feeding tube placement. Due to her poor prognosis, the family withdrew care and the patient died 94 days after the accident.

*This subject was assigned to the 240mg BID group but was taking 120mg BID at the time of the event. In this study, during week 1, patients assigned to the 240mg BID took 120mg BID and then at week 2 increased to the target dose of 240mg BID.

Road Traffic Accident; Trial 301
Subject 008-304: This 38-year-old female, assigned BG00012 240 mg TID, received study treatment for 61 days. On Study Day 62, the subject was in a motor vehicle accident and was pronounced dead upon arrival at the hospital. The subject showed no changes in behavior in the days before the accident, and had reported no other AEs during the study.

Complications of MS Relapse; Trial 302
Subject 954-405, a 55-year-old woman, died and her death was attributed to complications of an MS relapse (tumefactive type). She had received 196 days of BG00012 treatment and died 23 days after her last dose. She had a medical history of transient ischemic attack and patent foramen ovale (status post septal occluder). Significant concomitant medications at event onset included dipyramidole/ASA. Approximately 1 week after her last dose of BG00012, she developed vomiting and refused to take anything by mouth. She was subsequently hospitalized with bulbar speech, right hemiparesis, and right facial weakness. A magnetic resonance imaging scan of the head showed an acute disseminated encephalomyelitis/tumefactive MS picture involving bifrontal areas and temporal regions bilaterally with an area of pathological enhancement. Evidence of associated edema with a 4 mm midline shift to the left was also reported. Lumbar puncture was not performed due to cerebral edema. A follow-up head MRI showed extension of the lesion in the rostral part of the corpus callosum and bifrontally with perifocal edema involving the basal ganglia bilaterally, greater on the left than right, where it extended into the area of the pons and brain stem. She was treated with IV steroids, mannitol, and dalteparin. Her hospital course was complicated by a UTI (E. coli). She developed a markedly increased WBC count (75,000 cells/uL) and an increased CRP level (not reported). On hospital day 15, the subject's neurologic condition acutely deteriorated, and a head CT scan showed diffuse brain edema and hemorrhage into the fourth ventricle. She died the same day, with her death attributed to MS and intraventricular cerebral hemorrhage. The family refused a postmortem exam.
Note: The MS relapse was initially assessed by the investigator as "possibly related." As more information became available, the Investigator re-assessed the relationship to treatment as "unrelated."

Complications of MS Relapse; Trial 303
Subject 287-309, a 31-year-old female, received BG00012 240mg BID during Study 301 and continued on the same regimen in Study 303. She had a baseline EDSS (in Study 303) of 8.5 and paraplegia. During Study 301, she had multiple hospitalizations for MS

relapse and UTIs. On Day 176 of Study 303, she was admitted with fever, UTI, difficulty breathing and swallowing, increasing upper extremity paresis, and severe pain. She was treated with piperacillin/tazobactam and paracetamol. On the second hospital day, she was found unresponsive and in cardiorespiratory arrest. Resuscitative measures were unsuccessful and she died. The Investigator attributed her death to MS relapse and cardiopulmonary arrest, which he suggested was related to paraplegia and respiratory muscle weakness.

Completed Suicide, Drug Toxicity, Hepatic Failure; Trial 303
Subject 903-302, a 40-year-old female, received BG00012 240mg TID in Trial 301 and continued on the same regimen in Study 303. She had a history of depression, previously well controlled with citalopram. Her depression was aggravated by “personal problems” and her psychiatrist added bupropion (study day 46). On Day 88 she intentionally ingested an overdose of paracetamol (40 tablets, dose not specified). Her paracetamol level was 574umol/L (ref. range 66-199) and her benzodiazepine level was 37.8ng/mL (ref. range <3.0). Admission labs included ALT 235U/L, AST 191U/L, and conjugated bilirubin 6umol/L. Over the next 3 days, ALT increased to 15,642U/L, and AST to 8,633 U/L. She subsequently developed hepatic failure and became comatose. She died 4 days after the overdose.

Decubitus ulcers, Sepsis, Aspiration
Subject 032-406, a 32 year old female received BG00012 240mg BID for 200 days in trial 302, switched to IFNB-1a, and then enrolled in trial 303 and received BG00012 240mg BID for 146 days. She was bed bound at the start of trial 303 and on day 64 had AEs of decubitus ulcers of the left heel and left gluteal region. These ulcers were treated with dressings and antibiotics. She was hospitalized on day 94 for decubitus ulcers and the event was described as resolved (no details provided). She subsequently developed fever and was hospitalized on day 141. Her skin ulcers were treated with wound care and antibiotics. Skin grafts for the ulcers were planned, but on study day 150, she developed dyspnea, and sudden chest pain and died. Death was attributed to sepsis from the skin ulcers, aspiration, and cardiopulmonary arrest. An autopsy was not performed.

Mesothelioma
Subject 287-308, a 49 year old female, received placebo during trial 301 and BG00012 240mg BID for 406 days in trial 303. The subject did not have a documented history of asbestos exposure or tobacco use. On study day 340 she was diagnosed with a respiratory tract infection and was treated with doxycycline. On study day 355 she experienced cough, fever, shortness of breath and on study day 361 she was hospitalized. Her admission chest x-ray documented a right sided pleural effusion with adjacent air space opacities, and mild cardiomegaly. A chest ultrasound showed a right pleural effusion with collapse of the basal segment of the right lower lobe and trace pleural fluid on the left side. She was treated with ampicillin/cloxacillin, trihexyphenadil, and codeine. In addition, she was treated presumptively for tuberculosis (INH,

pyrazinamide, ethambutol, rifampicin). She improved and was discharged on day 368. She was re-admitted 10 days later and on study day 380 underwent video pleuroscopy. Histopathology from that test was consistent with mesothelioma. She was discharged from the hospital on study day 388 and withdrew from the study on day 406. She died approximately 3 months later. Biogen noted that "asbestos consumption has increased dramatically in India over the past 2 decades and is a major public health concern."

Integrated Psoriasis Trials
Investigators reported 2 deaths in BG00012 exposed patients from the integrated Psoriasis clinical trials (0.7%, 2/296; 6.3/1,000PY). One death occurred during a controlled trial and the other during an open label extension trial. I summarize the clinical details for these deaths in the following paragraphs.

Psoriasis Trials Death Summaries
Sudden Death; Trial 12/01
Subject 03-104, a 44-year-old man with a history of untreated borderline hypertension, alcohol use (10 drinks of vodka per day), and cigarette smoking (20 cigarettes per day), received BG00012 240 mg TID and died suddenly on Day 75 of the double-blind portion of the Phase 2 clinical trial. The subject had a BMI of 28 kg/m^2. Although the cause of death was unknown, MI was suspected by the subject's personal physician. An autopsy was not performed. The Investigator considered the event unlikely related to the study treatment.

Acute MI; Trial 03/03
Subject 04-159, a 48-year-old man, received BG00012 240 mg TID and died on approximately Day 249 of the Phase 3 uncontrolled extension trial from acute left heart failure, presumed to be due to acute MI as a consequence of coronary heart disease (documented by post-mortem examination). Relevant medical history included hyperlipidemia and borderline hypertension, history of myocardial ischemia, and cigarette smoking (10 to 15 cigarettes per day for >20 years). The Investigator considered the event to be not related to the study treatment.

7.3.2 Serious Adverse Events

Reviewer Summary
17% of MS patients experienced one or more SAEs during the BG00012 MS trials. During the MS controlled trials, SAEs were reported slightly more frequently by placebo patients compared to BG00012 patients. In these trials, no individual SAE was reported by at least 1% of BG00012 patients and more commonly compared to placebo. I identified few unexpected SAEs of potential concern in the BG00012 trials and in none of these cases did there appear to clear evidence of a causal link to BG00012.

Methods
In my review of SAEs, I first summarize the most commonly occurring SAEs in BG00012 MS clinical trials using the largest pool of integrated trials MS safety data (pool B). I then provide comparative data for SAEs using the integrated pool of MS safety data that included only controlled trial data (Pool A), and provide a similar analysis using the integrated Psoriasis clinical trials data. I then summarize the SAEs in the non-integrated trials. Lastly, I identify infrequently occurring, but potentially important SAEs from all clinical trials.

Results
Integrated Controlled and Uncontrolled MS Trials (Pool B)
In the integrated controlled and uncontrolled MS trials (Pool B), 17% (438/2,513) of BG00012 exposed patients experienced one or more SAEs (SU Appendix Table 22). The only SAE that occurred in ≥1% of BG00012 exposed patients was MS relapse (9%, 227/2,513). Gastroenteritis (n=10), gastritis (n=8), UTI (n=8), fall (n=5), and road accident (n=5) were the only other SAEs reported by at least 5 patients in Pool B.

Integrated Controlled MS Trials (Pool A)
SAEs were infrequently reported in these MS clinical trials and there did not appear to be notable differences in risk when comparing the different treatment groups.
The percentages of patients who experienced one or more SAEs in the integrated controlled MS clinical trials were similar when comparing placebo (21%, 173/836), BG00012 240mg BID (18%, 135/769), BG00012 240mg TID (15%, 126/823) and GA (17%, 60/351) treatment groups. Using a cutoff of at least 1%, I identify body systems and event preferred terms for the more commonly occurring SAEs in BG00012 treated patients.

MS Pool A SAEs Occurring in at least 1% of Patients

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Any SAEs	9% (11)	18% (135)	15% (126)	16% (272)	21% (173)	17% (60)
Infections and Infestations	<1% (1)	2% (17)	2% (15)	2% (33)	1% (12)	1% (4)
Nervous System Disorders	8% (10)	11% (81)	9% (74)	10% (165)	15% (123)	11% (40)
MS Relapse	7% (9)	10% (78)	8% (67)	9% (154)	14% (116)	10% (36)
Gastrointestinal Disorders	0	1% (8)	1% (11)	1% (19)	<1% (5)	0
Injury, Poisoning, Procedural Complications	0	1% (10)	1% (9)	1% (19)	1% (10)	<1% (3)

From ISS Appendix Table 51

Integrated Controlled and Uncontrolled Psoriasis Trials (Pool D)
In the Pool D Psoriasis trials, 9% (27/296) of subjects experienced one or more SAE. Myocardial infarction (1%, 3/296) was the only SAE that occurred in at least 1% of patients in the controlled and uncontrolled Psoriasis trials.

Integrated Controlled Psoriasis Trials
The percentages of patients who experienced one or more SAEs in the integrated controlled Psoriasis clinical trials were similar when comparing placebo (2%, 2/106), BG00012 low doses (0/72), and BG00012 240mg TID (3%, 4/141) treatment groups. No individual SAE preferred term occurred in at least 1% of BG00012 patients. Using a cutoff of at least 1%, I identify body systems for the more commonly occurring SAEs in BG00012 treated patients.

Psoriasis Pool C SAEs Body Systems Occurring in at least 1% of Patients

	BG00012			PBO
	Low dose	240mg TID	Total	
	N=72	N=141	N=213	N=106
Any SAEs	0	3% (4)	2% (4)	2% (2)
Respiratory, Thoracic, Mediastinal Disorders	0	1% (2)	<1% (2)	0

From ISS Appendix Table 224

Non-Integrated Clinical Trials
There were no SAEs reported for BG00012 exposed subjects in the Phase I trials of healthy volunteers (ISS, p.30), the Phase I trial in patients with MS (Study report 109MS 101, p.7), the Phase I trial in Psoriasis patients (Study Report BG-PK-01/02, p.82), or the RA trial, 109RA201 (ISS p. 186). In trial 109MS201, the ongoing open label trial in patients with MS, 3 patients experienced SAEs at the time of the SU. One subject experienced SAEs epigastric abdominal pain with gastrointestinal chest pain, one subject experienced SAEs of muscular weakness and diabetes mellitus, and the third subject experienced an SAE of C. difficile infection (SU Appendix Table 86).

Infrequent SAEs of potential concern
Infrequently occurring SAEs of potential concern included hypersensitivity (n=2, both from trial 301, MSP3-354-301, MSP3-852-305), anaphylactic reaction (n=1, trial 303, MSP3-368-303), anaphylactoid reaction (n=1, trial 301, MSP3-198-310), Stevens Johnson syndrome (n=1, trial 301, MSP3-683-303), dermatitis allergic (n=1, trial 301, MSP3-578-301), chronic hepatitis (n=1, trial 303, MSP3-237-301), hepatic failure (n=1, trial 303, MSP3-903-302), hepatitis cholestatic (n=1, trial 301, MSP3-505-303), rhabdomyolysis (n=1, trial 303, MSP3-364-302), Beta-2 microglobulin increased (n=1, trial 302, MSP3-017-405), proteinuria (n=1, trial 301, MSP3-278-301) and myopericarditis (n=1, Psoriasis trial KG-03/03, 04-158). I discuss these events in the following paragraphs.

Allergic reaction SAEs
Biogen identified several BG00012 exposed patients with SAEs that suggest allergic reactions including hypersensitivity (n=2), anaphylactic reaction (n=1), and anaphylactoid reaction (n=1). I discuss one SAE of hypersensitivity (354-301) and one SAE of anaphylactoid reaction (198-310) below, in the section of the review that examines flushing related AEs.

The narrative for the anaphylactic reaction event documented a plausible alternative (non-BG00012) etiology for this event. The patient with the anaphylactic reaction event (MSP3-368-303) had a documented allergy to nuts and the event occurred on study day 236, following ingestion of a Brazil nut. This patient continued in the study without recurrence of anaphylaxis.

The narrative for one of the hypersensitivity SAEs did not identify a clear diagnosis, but did not appear to describe a severe or life-threatening event. According to the narrative, subject MSP3-852-305 experienced only asymptomatic hypereosinophilia and discontinued from the trial.

Skin Reaction SAEs
The narratives for the dermatitis allergic and the SJS SAEs documented plausible alternative (non-BG00012) causes for these events. The patient with the dermatitis allergic event (MSP3-578-301) developed a rash 9 days after experiencing pharyngitis and initiating amoxicillin and clavulanate potassium. The patient with the SJS event (biopsy diagnosed) was taking carbamazepine at the time of the event. She was hospitalized, carbamazepine was stopped, and she was treated with corticosteroids, acyclovir, and flucloxacillin, and recovered. She remained on BG00012 throughout the event and for 1 month after the event without recurrence of SJS.

Hepatic SAEs
Biogen identified 3 hepatic SAEs from BG00012 clinical trials. The patient with hepatic failure (MSP3-903-302) committed suicide by intentional acetaminophen overdose and was discussed above, with the deaths. The remaining hepatic SAEs were chronic hepatitis and cholestatic hepatitis. I summarize those events in the AEs of special interest section of this review that discusses all relevant hepatic injury data.

Proteinuria/ Increased Beta-2 microglobin SAEs
Biogen identified one proteinuria and one Beta-2 microglobulin SAE. I summarize those events in the AEs of special interest section of this review that discusses all relevant renal injury data.

Rhabdomyolysis
Subject 364-302, a 26-year-old female with RRMS, was hospitalized for treatment of rhabdomyolysis on (b) (6). She was enrolled in Study 109MS303 and received BG00012 240 mg BID. The subject received her first dose of study treatment (b) (6)

[redacted] (b) (6) and remained in the study at the data cutoff date for this report. Prior to enrollment in Study 109MS303, the subject completed Study 109MS301 and had received BG00012 240 mg BID. The subject's medical history included Sjogren's syndrome, asthma, and elevated anti-SSA-A antibodies. Concomitant medications at the time of the event included cyproterone/ethinylestradiol. The subject used marijuana once monthly. Relevant events reported during Study 109MS301 included Sjogren's syndrome from Study Day 527 to 535 and elevated anti-SS-A antibodies beginning on Study Day 511, which was not resolved at the end of the study. On [redacted] (b) (6), Study Day 146, the subject's AST was 247 U/L (ref. range: 9 to 34) and ALT was 73 U/L (ref. range: 6 to 34) and study treatment was interrupted. Two days later, on [redacted] (b) (6), the subject was hospitalized for treatment of rhabdomyolysis. On the day of admission, creatine kinase was 16,874 U/L (ref. range: 26 to 140), myoglobin was 356 mcg/l (ref. range: <72), creatine kinase MB was 370 U/L (ref. range: <25), creatine kinase MB% was 2% (ref. range not provided), AST was 506 U/L (ref. range: <35), ALT was 135 U/L (ref. range: <35), LDH was 454 U/L (ref. range: 120 to 247), and serum creatinine was 0.95 mg/dL (ref. range: 0.6 to 1.1). Later on the same day, creatine kinase was 10,945 U/L, myoglobin was 197 mcg/L, AST was 428 U/L, ALT was 135 U/L, serum creatinine was 0.86 mg/dL, and urine leucocytes were 75 cells/µL (ref. range: 0 to 20). On [redacted] (b) (6), creatine kinase was 4,837 U/L, myoglobin was 200 mcg/L, AST was 261 U/L, ALT was 139 U/L, and serum creatinine was 0.84 mg/dL. On [redacted] (b) (6), creatine kinase was 2,492 U/L, AST was 144 U/L, ALT was 114 U/L, and urine leucocytes were 500 cell/uL. Treatment included hydration. The subject was discharged from the hospital on [redacted] (b) (6), Study Day 150. The Investigator reported that all laboratory values normalized after discharge, and the event was reported as resolved on 19 April 2010. According to the Investigator, the event was probably caused by excessive muscular activity. In a 6/12/12 response to a Division request for additional information about this event, Biogen reported that the patient had initiated a weight training regimen involving leg presses, and that the patient had not exercised or been involved in sports related activities in the 2 years prior to the event. A gastroenterology consult was obtained to rule out hepatic disease. Study treatment was resumed [redacted] (b) (6) [redacted] (b) (6). The Investigator assessed the rhabdomyolysis as mild and considered the event to be unrelated to study treatment. Study treatment was interrupted (exact dates not available) as a result of the event but the patient continued in the study.

Myopericarditis
Subject 04-58, a 64 year old male with Psoriasis experienced an SAE of myopericarditis. On Day 174, the subject experienced pain in the upper thorax with radiation to the neck, especially on inspiration. He was admitted to a hospital with an ECG that showed high ST elevation in leads II, III, aVF, and also V1-V6 and the posterior leads. Cardiac enzymes were unremarkable. Coronary angiography revealed 2-vessel disease with 60% stenosis of the posterior lateral branch and right coronary artery. ST alterations seen were possibly indicative of myopericarditis. The treatment of his underlying coronary risk factors included an increment in the pravastatin dose for hyperlipidemia, metoprolol for coronary artery disease, ramipril for hypertension, and

recommendations to optimize glycemic control and to stop smoking. He was discharged (b) (6) (Day 175). The Investigator graded both events of myopericarditis and coronary heart disease as moderate in severity and having an unlikely relationship to study drug. The study drug was discontinued on (b) (6) (Day 178) due to adverse event and the subject was withdrawn from the study on the same day.

7.3.3 Dropouts and/or Discontinuations

Reviewer Summary
AEs and "consent withdrawn" were the most commonly reported reasons for prematurely discontinuing study medication in the MS Pool A trials. BG00012 subjects more frequently withdrew for AEs compared to placebo. Placebo patients more commonly discontinued than BG00012 subjects for MS relapse and MS progression. There did not seem to be notable differences by treatment in the percentages of patients who prematurely discontinued for the remaining reasons.

Results
The following table lists the reasons for premature discontinuation from the MS Pool A trials. Although there appeared to be notable percentages of patients who discontinued for "consent withdrawn" and "other", there did not appear to be important differences by treatment.

MS Pool A Trials, Reasons for prematurely discontinuing study drug

C-1900	PBO	Low doses	240mg TID
Total	9.2% (6/65)	7.0%(9/128)	9.4% (6/64)
AE	0	2.3% (3/128)	6.3% (4/64)
Voluntary W/D	4.6% (3/65)	2.3% (3/128)	1.6% (1/64)
Lack tolerance for study drug	1.5% (1/65)	1.6% (2/128)	1.6% (1/64)
Noncompliance	1.5% (1/65)	0.8% (1/128)	0
Loss to follow up	1.5% (1/65)	0	0
109MS301	PBO	240mg BID	240mg TID
Total	34.9% (143/410)	30.7% (126/411)	30.5% (127/416)
AE	5.4% (22/410)	14.8% (61/411)	13.5% (56/416)
Consent W/D	8.3% (34/410)	4.4% (18/411)	4.3% (18/416)
Other	6.8% (28/410)	4.9% (20/411)	3.1% (13/416)
MS relapse	7.6% (31/410)	1.0% (4/411)	2.4% (10/416)
MS progression	3.4% (14/410)	1.7% (7/411)	1.7% (7/416)
Loss to follow up	1.7% (7/410)	2.2% (9/411)	2.6% (11/416)
Noncompliance	0.7% (3/410)	0.7% (3/411)	2.2% (9/416)
Investigator decision	1.0% (4/410)	1.0% (4/411)	0.5% (2/416)
Death	0	0	0.2% (1/416)

109MS302	PBO	240mg BID	240mg TID	GA
Total	35.5% (129/363)	29.3% (106/362)	27.8% (96/345)	23.9% (86/360)

AE	5.8% (21/363)	10.0% (36/362)	11.0% (38/345)	7.5% (27/360)
Consent W/D	3.9% (14/363)	2.5% (9/362)	4.3% (15/345)	2.8% (10/360)
Other	13.5% (49/363)	9.4% (34/362)	7.8% (27/345)	5.8% (21/360)
MS relapse	5.0% (18/363)	1.7% (6/362)	0.9% (3/345)	1.7% (6/360)
MS progression	2.2% (8/363)	1.9% (7/362)	1.4% (5/345)	2.2% (8/360)
Loss to follow up	1.9% (7/363)	2.2% (8/362)	1.2% (4/345)	2.2% (8/360)
Noncompliance	2.5% (9/363)	1.1% (4/362)	0.9% (3/345)	0.8% (3/360)
Investigator decision	0.8% (3/363)	0.6% (2/362)	0.3% (1/345)	0.6% (2/360)
Death	0	0	0	0.3% (1/360)

From C-1900 Study Report, Part 1 Table 10.1-1, p.74; 109MS301 Study Report, Table 10-1, p.99; 109MS302 Study Report Table 18, p.100.

Discontinuations for AEs

Reviewer Summary
Investigators reported that AEs were the reason for discontinuation of treatment of 16% of BG00012 MS patients in the Pool B trials. In the MS controlled trials, various GI AEs and flushing-related AEs led to discontinuation of a higher percentage of BG00012 patients than placebo patients.

Background
In the integrated MS clinical trials, patients who discontinued from their assigned study drug for AEs had the option of continuing in the trial on another approved MS therapy. Therefore, it is possible to discontinue study treatment, and remain in the trial. In the following sections, I consider as discontinuations for AEs, those patients who discontinued the assigned study medications for AEs, regardless of whether or not they continued in the trial.

Methods
I first summarize the most commonly occurring AEs leading to discontinuation in BG00012 MS clinical trials, using the largest pool of integrated trials MS safety data (Pool B). I then provide comparative data for AEs leading to discontinuation, using the integrated pool of MS safety data that included only controlled trial data (Pool A).

Because of the unusual protocol requirements in the Psoriasis clinical trials, analysis of discontinuation due to AEs is not possible. Biogen explained that in these Psoriasis trials, investigators were required to record the reason for discontinuation (ex. withdrew consent, AE, etc.), but they were not required to identify the specific AEs that led to treatment discontinuation (ISS, p.148). Therefore, Biogen did not present AEs leading to discontinuation from the Psoriasis clinical trials.

In addition to the analyses of the MS integrated data, I provide a summary of AEs leading to discontinuation from the non-integrated clinical trials. Lastly, I identify

infrequently occurring, but potentially important AEs leading to discontinuation from all clinical trials.

Results
Integrated Controlled and Uncontrolled MS Trials (Pool B)
In the integrated controlled and uncontrolled MS trials (Pool B), 16% (394/2,513) of BG00012 exposed patients with MS discontinued for 1 or more AEs. The AEs leading to discontinuation of at least 1% of BG00012 treated patients were flushing (2%, n=57/2513), diarrhea (2%, n=39/2513), nausea (1%, n=33/2513), vomiting (1%, n=32/2513), MS relapse (1%, 35/2,513), abdominal pain upper (1%, n=31/2513), and abdominal pain (1%, n=28/2513) (SU Appendix Table 24).

Integrated Controlled MS Trials (Pool A)
AEs leading to discontinuation were infrequently reported in these MS clinical trials and with the exception of flushing and certain GI AEs, there did not appear to be notable differences in risk when comparing the different treatment groups. The percentages of patients who discontinued for one or more AEs in the integrated controlled MS clinical trials were similar when comparing placebo (11%, 94/836), BG00012 low doses (9%, 12/128), BG00012 240mg BID (14%, 109/769), BG00012 240mg TID (14%, 117/823) and GA (10%, 35/351) treatment groups. Using a cutoff of at least 1%, I identify body systems and event preferred terms for the more commonly occurring AEs leading to discontinuation in BG00012 treated patients.

MS Pool A AEs leading to discontinuation of ≥1% BG00012 treated patients (any dose group)

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Any AEs leading to D/C	9% (12)	14% (109)	14% (117)	14% (238)	11% (94)	10% (35)
Nervous System Disorders	<1% (1)	3% (23)	3% (24)	3% (48)	7% (55)	3% (11)
MS Relapse	<1% (1)	1% (11)	2% (13)	1% (25)	6% (48)	2% (6)
Vascular disorders	<1% (1)	3% (26)	2% (14)	2% (41)	<1% (2)	0
Flushing	<1% (1)	3% (24)	2% (13)	2% (38)	<1% (1)	0
Gastrointestinal Disorders	3% (4)	4% (30)	6% (46)	5% (80)	<1% (8)	<1% (3)
Diarrhea	2% (2)	<1% (7)	2% (15)	1% (24)	<1% (2)	0
Nausea	0	<1% (6)	2% (14)	1% (20)	0	<1% (2)
Vomiting	0	1% (8)	1% (12)	1% (20)	0	<1% (1)
Abd pain upper	0	<1% (6)	1% (10)	<1% (16)	<1% (2)	<1% (1)
Abd pain	0	<1% (5)	1% (9)	<1% (14)	0	0
Skin, subcut tissue disorders	<1% (1)	2% (19)	2% (15)	2% (35)	<1% (3)	<1% (3)
Investigations	3% (4)	1% (10)	<1% (8)	1% (22)	2% (14)	1% (4)

ALT increased	2% (2)	<1% (3)	<1% (2)	<1% (7)	<1% (5)	<1% (2)

From ISS Appendix Table 57

Dose reductions
MS Pool A trial protocols allowed for temporary dose reductions for patients experiencing AEs. The sponsor's presentation underestimates the total number of patients who had their BG00012 dose reduced because any AEs leading to dose reductions that subsequently led to permanent discontinuation were captured only as leading to discontinuation on the CRF (ISS, p.71).

In the Pool A trials, 167 BG00012 patients had their dose reduced for AEs (10%, 167/1720) and the percentage did not vary by dose (BID 10%, 74/769; TID 10%, 83/823). In these same studies, 2% of placebo subjects (19/863) and <1% of GA subjects (1/351) had their dose reduced.

The majority of dose reductions in the Pool A MS trials were due to GI events and flushing. Seven percent (113/1720) of BG00012 patients had their dose reduced for GI events and 2.6% (45/1720) for flushing or hot flush. Although the protocols specifically allowed for flushing and GI AEs as reasons for dose reductions, Biogen noted that investigators listed additional AEs as the reason for reducing the dose of study drug. None of these other AEs led to dose reduction of at least 1% of BG00012 patients. One BG00012 patient had their dose reduced for lymphocyte count decreased and one for WBC count decreased (ISS Appendix table 60).

Dose interruption
The MS Pool A trial protocols allowed for temporary dose interruption for patients experiencing lab abnormalities or other AEs. Thirteen percent (100/769) of BG00012 BID patients had their dose interrupted compared to 15% (120/823) of BG00012 TID patients, 9% (79/836) of placebo patients and 7% (26/351) of GA patients. The AEs leading to dose interruption of at least 1% of BG00012 patients were diarrhea (2%, n=31), nausea (1%, n=25), vomiting (1%, n=22), abdominal pain (1%, n=19), and abdominal pain upper (1%, n=18). In addition, 14 BG00012 patients had dose interrupted for flush or hot flush, 13 for ALT increased, and 10 for AST increased. One patient had their dose held for leucopenia (ISS Appendix table 61).

Non-Integrated Clinical Trials

Healthy Volunteers
Biogen reported that 7 BG00012 exposed subjects discontinued from Phase I trials in healthy volunteers. The AEs leading to discontinuation were elevated transaminases (n=2), corneal edema, influenza-like illness, nausea, flushing/pruritis, and Herpes simplex.

MS
Biogen reported that no subjects discontinued for AEs in trial 109MS101 (ISS p.31) and that 14% (n=6) of subjects discontinued for AEs in MS trial 109MS201 (ISS, p.186). The AEs leading to discontinuation of more than one patient were flushing/hot flush (n=4), abdominal pain (n=2), abdominal pain upper (n=2), and vomiting (n=2) (SU Appendix Table 86).

Psoriasis
Investigators did not identify any subjects who discontinued for AEs in trial BG-PK-01/02, the Phase I trial in Psoriasis patients (Study Report BG-PK-01/02, p.82).

RA
In RA trial 109RA201 18% (18/101) of subjects discontinued for AEs. This percentage was similar to the percentage of placebo subjects who withdrew for AEs (16%, 8/51). The AEs that led to discontinuation of more than 1 subject were ALT increased (n=3), dermatitis allergic (n=3), nausea (n=3), vomiting (n=3), abdominal pain (n=2), and pruritis (n=2) (Study report 109RA201, pp.128-132).

Infrequent AEs leading to discontinuation
In addition to the common AEs leading to discontinuation, I reviewed the submitted tables and data sets to identify infrequently reported, but potentially important, AEs leading to discontinuation. In Pool B trials no BG00012 MS patients discontinued for Stevens Johnson syndrome, toxic epidermal necrolysis, angioedema, rhabdomyolysis, aplastic anemia, or pancytopenia. In the following paragraphs I summarize data for select AEs leading to discontinuation.

Allergic reaction AEs
Eleven BG00012 subjects experienced AEs of hypersensitivity and one experienced anaphylactoid reaction that were identified as the reason for discontinuing study drug. Three of these events were described above with the allergic reaction SAEs (hypersensitivity n=2, anaphylactoid reaction n=1). These allergic reaction AEs leading to discontinuation were generally not well described, but some of the narratives included the following signs/symptoms: itching, edema of the lips/face, flushing, pruritis, shortness of breath, and burning face. No narrative noted tongue or throat swelling. Some narratives reported that patients were treated for these events and the treatments included antihistamines and steroids. Four events occurred on the first day of treatment, with the remaining events occurring on days 2, 6, 13, 29, 30, 82, 121, and 392.

Swelling face
Subject 806-003, a 38 year old female with RA, discontinued from trial 109RA201 for facial swelling. The narrative reported that this patient developed swelling, redness and pruritis of the face on the second day of treatment with BG00012. Study drug was stopped but no other intervention was required. The patient recovered from the event.

7.3.4 Significant Adverse Events

All significant AEs are included in other sections of this review.

7.3.5 Submission Specific Primary Safety Concerns

Background
Biogen identified a subset of AEs of special interest from the BG00012 development program and presented individual reviews for these AEs. Biogen chose these AEs based on frequency of occurrence (flushing and related symptoms, GI events), signals from animal studies (renal AEs), and potential importance (ex. hepatic events, infections, cardiovascular events, suicide and depression). I review these AEs in the following sections.

Flushing and related symptoms

Reviewer Summary
BG00012 causes flushing symptoms in almost half of patients. Preliminary evidence suggests that this phenomenon is similar to that seen with niacin and may share a similar mechanism (mediated by PGD_2). Though most patients who experienced flushing seemed to tolerate the symptoms without need for decreasing/holding dose, symptomatic treatment, or discontinuation; there were a small number of patients who discontinued and/or had severe symptoms that required medical attention. Flushing AEs tended to occur soon after starting BG00012 treatment and for many patients also resolved quickly, but for almost 25% of patients, flushing or hot flush AEs apparently did not resolve with ongoing BG00012 treatment. Aspirin appeared to mildly reduce flushing symptoms, although this evidence came from one small study (109HV106) and Biogen did not conduct formal statistical evaluations of the results. Although the clinical trials allowed for temporary dose reduction in patients experiencing flushing, Biogen did not evaluate if this therapeutic maneuver improves tolerability. In addition, data from 109HV106 demonstrated that the BG00012 360mg BID dose group had lower flushing symptom scores than the 240mg BID and 240mg TID dose groups, raising questions about dose response for flushing in the examined dose range and the usefulness of dose lowering to improve tolerability. Biogen reported that during a food-effect trial, the flushing risk was slightly less in the fed state (68%) compared to the fasted state (94%). The relatively small difference in event occurrence suggests that food will have limited effectiveness in decreasing flushing symptoms.

Methods
Biogen examined the frequency of flushing related symptoms by using a case definition that included the preferred terms *flushing, hot flush, erythema, generalized erythema, burning sensation, skin burning, feeling hot, and hyperemia* (ISS, p. 73). Biogen examined flushing incidence and described serious/severe cases. In addition, Biogen

conducted a special study (109HV106) that examined flushing events, the relationship to BG00012 dose, and use of aspirin to prevent flushing.

Results
During MS clinical trials, BG00012 treated subjects frequently experienced AEs coded to the preferred terms of “flushing” and “hot flush”. The verbatim terms that were mapped to these preferred terms commonly identified flushing of the face and neck, but also included upper extremity, chest, and generalized flushing. During PK/PD trial 109HV106, which specifically examined BG00012 related flushing, investigators used validated questionnaires (Global Flushing Severity Scale, GFSS; Flushing Severity Scale, FSS) to captured information about flushing-related symptoms and their severity. Specifically, subjects rated the severity of redness, warmth, tingling, or itching of the skin. Based on my review of the data listings in the trial report, the subjects with a flushing response generally experienced more than one of the four symptoms included in the questionnaire.

Frequency
Biogen reported that in Pool A MS controlled trials, the frequency of flushing-related symptoms among BG00012 treated subjects was 45% for the BID group and 42% for the TID group compared to 9% for placebo group and 5% for the GA group. This frequency comparison was based on events that met Biogen’s case definition for flushing-related symptoms, described above. Flush and hot flush were the most commonly identified preferred terms in the group of flushing-related events.

Severity
I describe the severity of flushing AEs by reviewing SAEs, discontinuations, dose interruptions, and severity ratings from the BG00012 clinical trials.

Biogen identified 4 SAEs potentially related to flushing reactions in the BG00012 development program (all from trial 109 MS 301), including 2 “flushing” 1 “hypersensitivity” and 1 “anaphylactoid reaction” events. I describe those events below. None of the events appeared to be life threatening, and none of the narratives identified potential alternative (non BG00012) etiologies.

680-302 Flushing
Thirty minutes following her first dose of BG00012, this 23-year old female, experienced a whole body, erythemic, pruritic, rash. She also experienced nausea, shivering, and mid-abdominal pain, but no wheezing, dyspnea, or pharyngeal swelling sensation. She was noted to have BPs ranging from 90-95/55-60 mm Hg with HRs ranging from 100-110 bpm. She was hospitalized and treated with methylprednisolone, ranitidine, promethazine, and alizapride. She discontinued BG00012 and recovered.

197-303 Flushing
This 40 year old female experienced pruritis and flushing 1 hour after a dose of BG00012, on day 152 of the trial. The narrative did not mention hospitalization, emergency department visit, or treatment for these events. She discontinued BG00012 and recovered.

354-301 Hypersensitivity
This 49 year old female, experienced fever, flushing and skin redness, but no angioedema, urticaria, dyspnea, wheezing, or cardiovascular instability, 2 hours after her first dose of BG00012. She was treated with methylprednisolone and recovered.

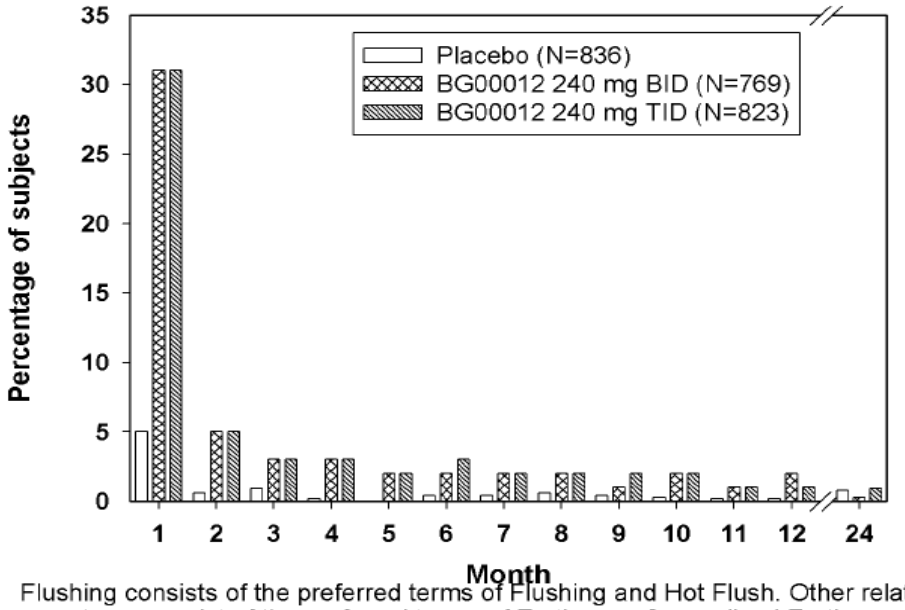
198-310 Anaphylactoid reaction
This 36 year old female experienced increased flushing and pruritus after initiation of BG00012 240 mg TID and dose titration. Subsequently, on Study Day 13, she developed flushing and shortness of breath approximately 2 to 3 hours after her dose of BG00012. She went to an emergency department for evaluation, and had no evidence of cardiovascular or respiratory instability. She was treated with diphenyhydramine, famotidine, dexamethasone, and prednisone and recovered.

In Pool B, the largest pool of integrated data for MS clinical trials in the NDA, Biogen reported that among the BG00012 subjects, 2% (56/2,468) discontinued treatment for “flushing” AEs and <1% (8/2,468) discontinued for “hot flush” AEs (ISS Appendix Table 58).

Investigators rated the majority of “flushing” and “hot flush” AEs in the Pool A MS trials as mild or moderate. For example, in Pool A patients treated with BG00012 240mg BID, for the 265 flushing AEs, 67% (174/265) were mild, 30% were moderate (80/265) and 4% (11/265) were severe. Similarly, for the 52 “hot flush” events, 73% (38/52) were mild, 23% (12/52) were moderate and 4% (2/52) were severe (ISS Table 27).

Onset/Course/ Resolution
In the MS clinical trials, the incidence of flushing-related events was highest in the first month of treatment but continued to be elevated compared to placebo during the first 12 months of treatment. Those data are summarized below.

Incidence of flushing and other related symptoms by 1-month intervals: Placebo, BG00012 240 mg BID and TID in controlled MS studies (Pool A)



Flushing consists of the preferred terms of Flushing and Hot Flush. Other related symptoms consist of the preferred terms of Erythema, Generalised Erythema, Burning Sensation, Skin Burning Sensation, Feeling Hot, and Hyperaemia.

I used the AE dataset to characterize the onset/resolution/duration of flushing events in the MS Pool A trials. I identified 658 BG00012 patients with one or more flushing or hot flush AEs. I selected the first reported event for each patient and then examined the recorded onset day, the recorded resolution day, and the recorded duration of these events.

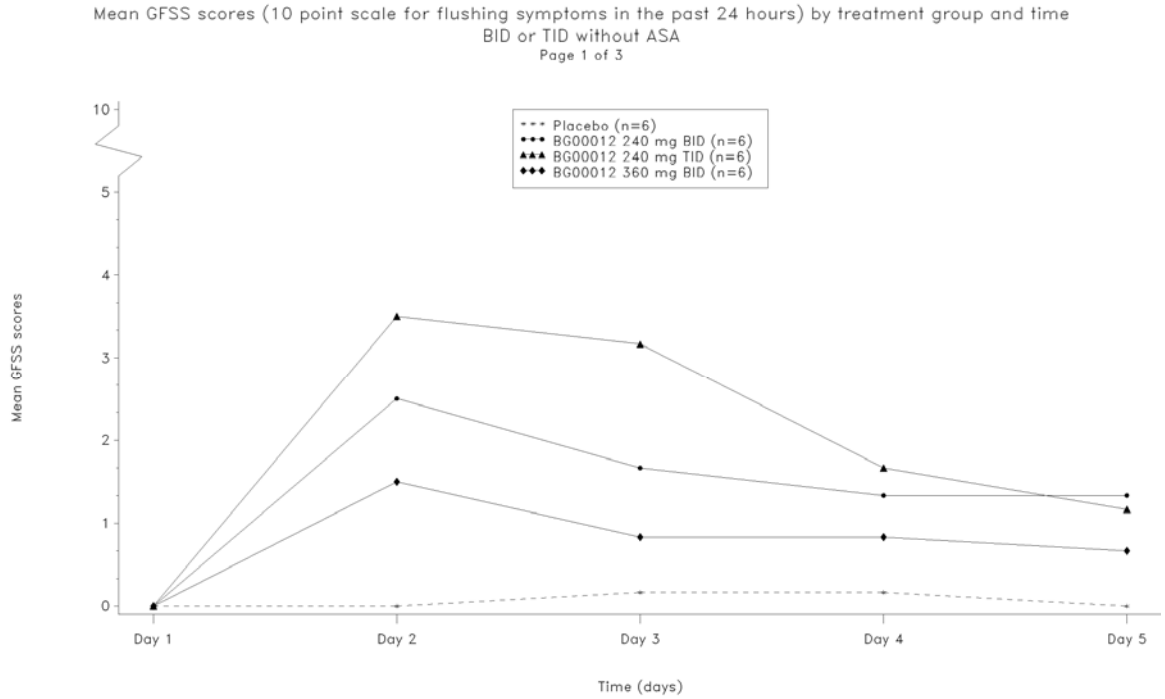
Of the 658 BG00012 patients, 50 did not have a recorded onset day and one patient had a recorded start date of -658. After removing these 51 patients, the median onset day was study day 2 (range day 1 to day 642). The reported onset day was study day 1 for 45% (274/607) and was within the first week for 62% (379/607).

I found that 192 patients did not have a recorded end day. Apparently not all of these patients had persistent AEs because the recorded outcome was “not resolved” for only 155 patients (24%, 155/658). After excluding those with a missing end date, the median end day was study day 42.5 (range day 1 to day 692). For the 466 patients with a recorded end date, 13% (64/488) resolved on study day 1 and 25% (121/488) resolved in the first week.

450 patients had both a start date and end date that allowed for calculation of AE duration. The median duration for these patients was 17 days (range 1 day to 689 days). For these 450 patients, the calculated duration was 1 day for 27% (123/450) and 1 week for 40% (182/450).

Data from a flushing symptom questionnaire (FSS) used in trial 109HV106 suggest that flushing symptoms can begin as soon as 30 minutes following ingestion of BG00012. Biogen reported that the median onset from the most recent dose of the first flushing event (BG00012 alone) was 80 minutes (109HV106 Study Report).

During trial 109HV106, the severity of flushing symptoms was highest on the first treatment day (day 2), declined, and then plateaued on subsequent days. That information is summarized in the following plot of mean scores from a flushing symptom questionnaire (GFSS) by day (109HV106 Study Report). This plot also raises questions about dose relationship, and the usefulness of lowering doses for flushing, since the 360mg BID dose group had lower flushing symptom scores than the 240mg BID and 240mg TID dose groups.



NOTE: GFSS is a 10 point scale from 0 to 10 and represents flushing symptoms in the past 24 hours.

Flushing risk by sex, age

I used the sponsor's submitted tables that stratified AEs by sex and age to look for differences in risk by these factors for "flush" and "hot flush". The data suggest that the relative risks for these events did not appear to vary markedly by sex or age, although it is important to consider that the age range of subjects in these trials was 18-55 years.

MS Pool A, Percentage of Patients with Flushing, Hot Flush Stratified by Sex, Age

AE		PBO	BG00012	RR
Flush	Male Female	3% (12/243) 5% (31/593)	28% (139/495) 35% (431/1225)	9.3 7.0
Hot Flush	Male Female	(0/243) 3% (16/593)	7% (35/495) 6% (78/1225)	- 2.0
Flush	<40 yrs ≥40 yrs	4% (18/461) 6% (21/375)	33% (313/949) 33% (257/771)	8.25 5.5
Hot Flush	<40 yrs ≥40 yrs	(0/461) 3% (12/375)	<1% (1/949) 9% (67/771)	- 3.0

From ISS Appendix Tables 183 and 185

Effects of dosing schedule, aspirin pretreatment, on flushing
As noted above, in clinical trial 109HV106, Biogen explored whether a specific alternative dosing regimen or pretreatment with aspirin might mitigate flushing reactions and looked at possible mediators of flushing. Biogen compared the flushing reactions for a treatment group administered BG00012 using an alternative dosing schedule (120mg every hour x 3, twice a day) to a group given placebo. In addition, Biogen studied treatment groups that employed various permutations of BG00012 dosing regimens (240 mg BID, 240 mg TID, 360mg BID) and pretreatment with aspirin or placebo. Pretreatment consisted of a non-enteric coated 325 mg aspirin tablet (or placebo) administered 30 minutes prior to study drug dosing. This study used small treatment groups (6 subjects in each of 8 treatment groups and 8 subjects in the ninth treatment group), and Biogen did not conduct formal statistical analyses of the flushing response results across the studied interventions.

109HV106 used 2 validated flushing symptom questionnaires, GFSS and FSS. Both questionnaires employ a 10 point scale where 0 represents no symptoms, with increasing severity to 10, which represents extreme symptoms. The GFSS records the subject's rating of flushing symptoms in the previous 24 hours. The FSS records the subjects rating following dosing (every 30 minutes for the first 3 hours and hourly thereafter) for each of the following domains: overall symptoms, redness, warmth, tingling, and itching. Biogen compared responses for groups administered BG00012 and pretreated with aspirin to groups administered BG00012 and pretreated with placebo.

Biogen acknowleged that the alternative dosing regimen examined in 109 HV 106 did not result in decreased flushing reactions.

For aspirin pre-treatment, Biogen reported that "Results of this analysis showed that pre-treatment with ASA reduced the incidence and intensity of flushing in subjects who received BG00012." Biogen's conclusion was based on several observations. Biogen noted that 94% (17/18) subjects who received BG00012 alone experienced flushing symptoms compared to 61% (11/18) of patients in the BG00012 with ASA pre-treatment

group. Considering only the 240mg BID group (the dose intended for marketing), 50% (3/6) pre-treated with ASA experienced flushing compared to 83% (5/6) without pre-treatment. When BG00012 was administered with placebo, mean GFSS scores ranged from 1.5 to 3.5 (mild), from 0.8 to 3.2, from 0.8 to 1.7, and from 0.7 to 1.3, on Days 2 through 5, respectively. When BG00012 was administered with aspirin pretreatment, mean GFSS scores ranged from 0.3 to 1.0 from 0.2 to 0.3, from 0 to 0.3, and from 0 to 0.2 on days 2 though 5, respectively. (Study report 109HV106)

In addition, Biogen summarized FSS score data for flushing symptoms. Biogen reported that for subjects administered BG00012 with placebo, the mean overall FSS scores were highest on Day 1 with a peak mean value of 2.7 at Hour 5 in the BG00012 240 mg TID group. Mean overall FSS scores decreased through Day 4. In all cases, the mean overall FSS scores reflected mild (FSS graded as 1 through 3) flushing. In addition, Biogen commented that mean elevated excursions of overall FSS scores tended to cluster on Day 1 and usually were worst around the time of the first dose of the day. Most subjects reported mild to moderate overall FSS scores on Day 1, although one subject in the BG00012 240 mg BID treatment group reported severe overall FSS score. Overall FSS scores for all subjects decreased over time. Subjects who had higher overall FSS scores on Day 1 tended to subsequently have higher scores, although these often decreased, through Day 4. Among subjects treated with BG00012 and aspirin, the mean overall FSS scores were also highest on Day 1 with a peak mean value of 1.2 at 3 hours in the BG00012 360 mg BID group. Mean overall FSS scores decreased every day through Day 4, and all mean scores were in the mild category (FSS graded as 1 through 3). No subject reported severe flushing (FSS grade 7 through 9) (Study Report 109HV106).

Aspirin was not routinely used for flushing symptoms in the MS Pool A trials. Using the concomitant medication data set, I determined that 5.5% (7/128) of BG00012 low dose patients, 8.1% (62/769) of 240 BID patients, 8.1% (67/823) of TID patients, and 6.5% (54/836) of placebo patients had recorded concomitant use of aspirin. The most commonly reported indications for aspirin use were cardiac disease prevention, pain, and fever. Flushing was listed as the indication for aspirin use in 4 BG00012 patients.

Effect of food on flushing
Biogen reported that during C-1903, the randomized, 2-period crossover food-effect trial (6-10 day washout period), the flushing risk was 94% (34/36) in the fasting state compared to 68% (23/34) during the fed state (Study Report C-1903).

Dose Interruption/Reduction
In the Pool A MS trials, Biogen allowed investigators to hold, or temporarily reduce the dose (for up to 1 month) of study drug in patients with flushing, but it is unclear if this improved tolerability. As noted above, investigators temporarily reduced the study drug dose for flushing or hot flush for 2.6% (45/1720) of BG00012 patients in Pool A trials. Investigators temporarily held study drug for flushing or hot flush in 0.8% (14/1720) of

BG00012 patients. (Note: patients who had their dose reduced or held and subsequently discontinued are not included in these percentages). Since every patient in these trials had the option to have their dose reduced/held, it is unclear if these interventions improved tolerability.

Potential flushing mediators
During clinical trial 109HV106, Biogen looked for potential mediators of the flushing reaction by measuring prostaglandin metabolites ($PGF_{2\alpha}$, 8-iso-$PGF_{2\alpha}$, 9α 11β-PGF_2, PGD-M), serotonin and histamine. Biogen measured prostaglandin metabolites based on previous research with BG00012, and also because of the similarity between the BG00012 flushing and the flushing caused by niacin. Biogen noted that 9α 11β-PGF_2 increased as much as 800-fold in patients treated with lipid lowering doses of niacin. Biogen reported the following results from 109HV106:

Prostaglandin metabolites $PGF_{2\alpha}$, 8-iso-$PGF_{2\alpha}$

> The data did not show clear trends in $PGF_{2\alpha}$ and 8-iso-$PGF_{2\alpha}$ concentrations over the 12-hour collection time period on Days 1 and 4 for any treatment group.

Prostaglandin metabolite 9α 11β-PGF_2

> Some subjects who received BG00012 alone had increased plasma levels of 9α 11β-PGF_2 (the main metabolite of PGD2) on Day 1, but the levels returned to near baseline on Day 4.
>
> Subjects who received BG00012 with ASA, and subjects who received placebo did not have increased concentrations of 9α 11β-PGF_2.
>
> Subjects with normal or mildly elevated 9α 11β-PGF_2 levels generally had milder flushing scores.

Serotonin, Histamine

Elevated serotonin levels were seen in BG00012-treated subjects as well as placebo subjects. Histamine levels were not elevated in BG00012-treated patients.

Biogen noted that these preliminary results support that PGD_2 may be a mediator of BG00012 induced flushing (Study report 109HV 106, p.72).

Flushing and Eosinophilia
As described below in the laboratory results section of this review, BG00012 patients are at increased risk of experiencing transient eosinophilia. In the Pool A trials, 13% of BG00012 BID patients and 10% of BG00012 TID patients had one or more eosinophil count that was above ULN. To look for an association between eosinophil counts and

flushing, I used Biogen's data sets to identify the percentage of patients with flushing AEs that also had elevated eosinophil counts. For the 570 BG00012 Pool A patients with a flushing AE, 11% (n=64) also had one or more elevated eosinophil count. Flushing and eosinophilia did not appear to be related given that the percentage of BG00012 patients with flushing that had elevated eosinophil counts was similar to the overall percentage of BG00012 patients with elevated eosinophil counts.

Biogen Conclusions
Biogen recognizes that BG00012 causes flushing but does not view flushing related symptoms as a serious risk. Biogen stresses that in the safety database trials the majority of such events were mild or moderate, there were few flushing SAEs or events leading to discontinuation, and that the incidence decreased after the first month (ISS, p.189).

Hepatic disorders

Reviewer summary
Based on the criteria described in the FDA Guidance for Industry "Drug Induced Liver Injury: Premarket Clinical Evaluation", BG00012 did not appear to demonstrate the potential for hepatic injury. Although there was an excess of amino transferase results >ULN for BG00012 compared to placebo, the same was not true using cutoffs of 3xULN or above. There was no increased risk of total bilirubin >ULN with BG00012 and no cases of amino transferase elevations>3xULN in association with total bilirubin increases >2xULN. There were cases of serious hepatic injury in BG00012 treated patients in the NDA safety database, but the cases did not seem to clearly suggest a causal relationship with BG00012. One case was due to an intentional overdose with paracetamol. In a second case, the patient had fluctuating amino transferase results during treatment with BG00012, and these abnormalities did not resolve during a 6 month non-treatment interval between trials. In another case, the patient had normal amino transferase test results for over 1 year during BG00012 treatment prior to developing amino transferase elevations.

Methods
Biogen assessed the liver injury potential of dimethyl fumarate by examining the amino transferase and bilirubin lab data results and by assessing liver related AEs that occurred in dimethyl fumarate treated trial subjects.

To evaluate the Biogen presentation, I focus on indicators of the potential for severe drug induced liver injury as described in the FDA Guidance for Industry "Drug Induced Liver Injury: Premarket Clinical Evaluation". Specifically, I present amino transferase elevations to 3 X ULN compared to a control group, evaluation of marked elevations of amino transferases to 5x, 10x, or 20x ULN, and identification of any cases of newly elevated total serum bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct

disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic factors, with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs).

Results
Amino Transferase and Total Bilirubin
The following data demonstrate that in the Pool A MS trials, dimethyl fumarate treated trial subjects were more likely than placebo patients to experience transaminases above ULN, but not results >=3X, >5X, >10X, or >20X ULN. When comparing the treatment groups there appeared to be no difference in risk for elevated total bilirubin.

Pool A MS Trials, Comparison of ALT, AST, and Total Bilirubin Elevations

Parameters	BG00012 low dose	BG00012 240mg BID	BG00012 240mg TID	BG00012 Total	PBO	GA
	n=128	n=769	n=823	n=1720	n=836	n=351
ALT						
% Total n	100% (128)	100% (756)	100% (804)	100% (1688)	100% (831)	100% (346)
≤1 X ULN	72% (92)	52% (391)	47% (376)	51% (859)	65% (536)	63% (217)
>1 X ULN	28% (36)	48% (365)	53% (428)	49% (829)	35% (293)	37% (129)
≥ 3 X ULN	2% (3)	6% (46)	6% (49)	6% (98)	5% (38)	7% (24)
>5 X ULN	2% (3)	2% (13)	2% (14)	2% (30)	2% (20)	3% (10)
>10 X ULN	<1% (1)	<1% (3)	<1% (3)	<1% (7)	1% (9)	1% (4)
>20 X ULN	0	<1% (1)	0	<1% (1)	<1% (2)	<1% (1)
AST						
% Total n	100% (128)	100% (765)	100% (804)	100% (1688)	100% (831)	100% (346)
≤1 X ULN	85% (109)	73% (556)	69% (553)	72% (1218)	79% (656)	75% (260)
>1 X ULN	15% (19)	26% (200)	31% (251)	28% (470)	21% (171)	25 (86)
≥ 3 X ULN	2% (2)	2% (15)	2% (15)	2% (32)	2% (15)	4% (14)
>5 X ULN	<1% (1)	<1% (4)	<1% (2)	<1% (7)	1% (10)	2% (6)
>10 X ULN	0	<1% (2)	<1% (1)	<1% (3)	<1% (5)	<1% (1)
>20 X ULN	0	<1% (1)	0	<1% (1)	<1% (1)	0
T bilirubin						
% Total n	100% (128)	100% (757)	100% (804)	100% (1689)	100% (831)	100% (347)
≤1 X ULN	90% (115)	93% (705)	91% (732)	92% (1552)	91% (759)	92% (319)
>1 X ULN	10% (13)	7% (52)	9% (72)	8% (137)	9% (72)	8% (28)
> 1.5 X ULN	2% (3)	2% (13)	3% (23)	2% (39)	2% (20)	3% (9)
>2 X ULN	0	<1% (4)	<1% (4)	<1% (8)	1% (10)	1% (4)

From ISS table 28, pp. 120-121

No patients in these trials had transaminases >=3X ULN concurrently with total bilirubin >2 X ULN. Furthermore, Biogen confirmed that no subjects in any of the clinical trials submitted as part of the BG00012 NDA experienced elevated transaminases >=3X ULN concurrently with total bilirubin >2 X ULN (Biogen 5/15/12 response to Reviewer request).

The amino transferase and total bilirubin outlier data from the controlled Psoriasis trials were similar to the results from the controlled MS trials. No BG00012 treated subjects had AST or ALT >5 X ULN or a bilirubin >2x ULN.

Pool C Psoriasis Trials, Comparison of ALT, AST, and Total Bilirubin Elevations

Parameters	BG00012 low dose	BG00012 240mg TID	BG00012 Total	PBO
	n=72	n=141	n=213	n=106
ALT				
% Total n	100% (72)	100% (140)	100% (212)	100% (104)
≤1 X ULN	63% (45)	38% (53)	46% (98)	62% (64)
>1 X ULN	38% (27)	62% (87)	54% (114)	38% (40)
≥ 3 X ULN	0	1% (2)	<1% (2)	3% (3)
AST				
% Total n	100% (72)	100% (140)	100% (212)	100% (104)
≤1 X ULN	82% (59)	47% (66)	59% (125)	74% (77)
>1 X ULN	18% (13)	53% (74)	41% (87)	26% (27)
≥ 3 X ULN	0	1% (2)	<1% (2)	2% (2)
T bilirubin				
% Total n	100% (72)	100% (140)	100% (212)	100% (104)
≤1 X ULN	94% (68)	91% (127)	92% (195)	96% (100)
>1 X ULN	6% (4)	9% (13)	8% (17)	4% (4)
> 1.5 X ULN	1% (1)	3% (4)	2% (5)	<1% (1)

From ISS table 257, pp. 8461-2.

Hepatic SAEs

As noted above, Biogen identified 3 hepatic SAEs from BG00012 clinical trials. The patient with hepatic failure (MSP3-903-302) committed suicide by intentional acetaminophen overdose and was discussed above, with the deaths. The remaining hepatic SAEs were chronic hepatitis and cholestatic hepatitis. I summarize those events in the following paragraphs.

Chronic Hepatitis

Subject 237-301, a 29-year-old female with RRMS, had an SAE of chronic hepatitis on 15 March 2011. She had a medical history that included cholecystitis in 2002, cholecystectomy in 2003, and urinary tract infection in 2008. At the time of the event, she was enrolled in Study 109MS303 and received BG00012 240 mg BID. The subject received her first dose of BG00012 in this trial on 23 February 2011 and her final dose on 14 March 2011 (total 20 days). Prior to enrollment in Study 109MS303, she completed Study 109MS301, where she received BG00012 240 mg BID. There was an interval of 6 months between completion of study 301 and starting study 303. Concomitant medications at the time of the event included drospirenone and ethinylestradiol.

Beginning on Study Day 29 of Study 109MS301, ALT, AST and GGT fluctuated from normal to elevated to near normal on a few occasions, with ALT up to 182 U/L (ref.

range: 6 to 34), AST up to 140 U/L (ref. range: 9 to 34), and GGT up to 103 U/L (ref. range: 4 to 49). Study treatment was continued throughout the study. On the final visit day of Study 109MS301, ALT and GGT were slightly increased at 47 U/L and 58 U/L, respectively; AST, ALP, and total bilirubin were within normal range.

On 23 February 2011, Baseline Day 1 of Study 109MS303, approximately 6 months after her last dose of study treatment in Study 109MS301, the subject's ALT, AST, and GGT were elevated at 110 U/L, 72 U/L, 68 U/L, respectively; ALP and total bilirubin were within normal range. Study treatment was discontinued on 14 March 2011, Study Day 20. Her LFTs reached a peak on 15 March 2011, Study Day 21, with ALT 314 U/L, AST 264 U/L, and GGT 57 U/L. On 12 April 2011, 28 days after discontinuation of study treatment, the subject was asymptomatic, and her LFT results were elevated with ALT 99 U/L, AST 59 U/L, and GGT 85 U/L. Testing for viral hepatitis was negative (narrative did not identify the specific viral hepatitis tests performed). On 28 Jul2011, approximately 4.5 months after her last dose of study treatment in Study 109MS303, her ALT and AST remained elevated at 127 U/L and 73 U/L, respectively. The subject denied the consumption of alcohol, acetaminophen, or any other substances that may have caused the elevated LFTs. The Investigator diagnosed the subject with chronic hepatitis due to the chronic elevation of liver enzymes.

Study Subject 237-301, Select Liver-Related Lab Test Results

Date, Study day	ALP (U/L) ref. range:31–106	ALT (U/L) ref. range: 6 – 34	AST (U/L) ref. range: 9 – 34	T Bili (µmol/L) ref. range: 3.42 – 20.52	GGT (U/L) ref. range: 4 – 49
109MS301					
03SEP2008 Baseline Day 1	60	26	20	9	16
02OCT2008 Day 29	52	37	33	5	32
08JUNE2010 Day 643	59	106	91	5	42
16JUN2010 Day 651	59	54	32	12	46
06JUL2010 Day 671	56	182	140	12	49
11AUG2010 Day 707 final study visit	66	47	30	9	58
109MS303					
23FEB2011 Day 1 after 6 months off study treatment	77	110	72	10	68
14MAR2011 Day 20	68	314	264	10	57
15MAR2011 Day 21 Study	-	-	-	-	-

drug discontinued					
12APR2011 Day 49	76	99	59	12	85
15MAY2011 Day 83	76	121	75	10	41
08JUN2011 Day 106	98	129	72	9	77
28JUL2011 Day 156 final Evaluation	96	127	73	10	35

From patient narrative

The Investigator assessed the chronic hepatitis as severe and considered the event to be related to study treatment. Study treatment was discontinued on 14 March 2011 and the subject was withdrawn from the study on 28 July 2011 as a result of the event.

Reviewer comment
Given that the patient experienced fluctuating amino transferase results during treatment with BG00012, and these abnormalities did not resolve during a 6 month non-treatment interval between trials, relationship to BG00012 seems unlikely.

Cholestatic Hepatitis
Subject 505-303, a 45 year old female with RRMS, had a medical history of hyperbilirubinemia, vertebral degenerative joint disease, depression, and surgery for crural varices. Se received her first dose of dimethyl fumarate on (b) (6). Concomitant medications at the time of this event included tizanidine. At the onset of the event the subject had received study treatment for 446 days. The subject's pre-treatment LFTs were notable for elevated total bilirubin (29 µmol/L) at Screening and elevated ALP (111 U/L) on Baseline Day 1. Other LFTs were normal at those visits (see table below).

After beginning treatment, her blood chemistries over the first 393 days of the study revealed stable, normal ALT ranging from 11 to 22 U/L, AST ranging from 12 to 25 U/L, ALP of 51 to 67 U/L, gamma-glutamyl transferase (GGT) of 7 to 9 U/L, and lactate dehydrogenase (LDH) of 105 to 122U/L. During that same interval, the subject had total bilirubin that was intermittently elevated, ranging from 18 to 37 µmol//L (ref. range: 3.42 to 20.52), consistent with the subject's history of hyperbilirubinemia, possibly Gilbert's Disease. On (b) (6), approximately 3 weeks after being hospitalized for an MS relapse, the subject's ALT, AST, and total bilirubin were elevated (see table below). At the next study visit on (b) (6), LFT abnormalities (which now also included ALP, GGT, and LDH) reached their peak. Based on the elevated ALT and AST, the study treatment was discontinued and the subject was hospitalized for evaluation of possible viral hepatitis on (b) (6), Study Day 446. The Investigator stated that there were no symptoms except for general weakness at the time of the event. Testing for hepatitis

A, B and C was negative and an autoimmune etiology was ruled out with normal antinuclear (ANA) and antimitochondrial antibody serologies. Additional laboratory testing showed no other signs of liver dysfunction (i.e., normal prothrombin index, international normalized ratio, total protein, and albumin). An abdominal ultrasound was normal. Treatment with phospholipids and vitamins was initiated (b) (6). The transaminitis improved and the total bilirubin remained at stable levels. The event was reported as resolved and the subject was discharged from the hospital on (b) (6) with a diagnosis of cholestatic hepatitis and with instructions for hepatology follow-up. In response to a reviewer request for additional information, in a 6/22/12 email Biogen provided a summary from progress notes (translated from Polish documentation) from outpatient follow up visits with the Infectious Diseases, Monitoring and Hepatic Diseases Department. These follow up visits describe normalization of hepatic transaminase levels by (b) (6) with levels remaining normal through the end of documented follow up on (b) (6). A repeat hepatitis C antibody serology was reported as negative as was an abdominal ultrasound on (b) (6). It is also noted that at the time of initial hospitalization that the subject was previously immunized for hepatitis B (anti-hepatitis B core negative, anti-hepatitis B surface antigen positive). No additional sequela was noted in the progress notes.

The event was reported as resolved on (b) (6), the results for ALT, AST, GGT, and bilirubin were reported as normal by the Investigator (specific values were not available). Selected LFT results over the course of the study were as follows:

Study Subject 505-303, Select Liver-Related Lab Test Results

Date, Study day	ALP (U/L) ref. range: 31– 106	ALT (U/L) ref. range: 6 – 34	AST (U/L) ref. range: 9 – 34	T Bili (µmol/L) ref. range: 3.42 –20.52	GGT (U/L) ref. range: 4 – 49
(b) (6) (Day –32: Screening)	73	14	19	29	9
(Day1Baseline)	111	26	28	5	40
(b) (6) (Day 393)	54	12	14	17	7
(b) (6) (Day 421)	63	122	72	28	12
(b) (6) (Day 444)	151	1276	827	38	173
(b) (6) (Day 505)	72	38	31	29	39

LDH 2710 on Day 444 (ref. range 53-234), remaining days was WNL
From patient narrative

The Investigator assessed the cholestatic hepatitis as severe and considered the event to be possibly related to study treatment. Study treatment was discontinued on (b) (6) as a result of the event. The subject elected to continue in the study and received

alternate MS therapy with interferon beta-1A until she withdrew consent on (b) (6) .

Reviewer comment
Given that the patient had normal amino transferase test results for over 1 year during BG00012 treatment prior to developing amino transferase elevations, relationship to BG00012 seems unlikely.

Biogen Conclusions
Biogen felt that the hepatic safety data characterizes “transient increases in liver transaminases relative to placebo that does not appear to be associated with any increase in clinically significant liver pathology.” (ISS, p.190) This appears to be a reasonable conclusion.

Renal Toxicity

Reviewer Summary
Despite preclinical evidence of BG00012 related renal toxicity in multiple animal species, the clinical trials in the NDA did not suggest that BG00012 exposed patients were at increased risk of renal toxicity. Animals exposed to BG00012 experienced renal tubular and interstitial toxicity. Because of these findings, in addition to the usually collected renal related lab data (BUN, creatinine, urinalysis), the MS RCTs incorporated enhanced renal monitoring that included urine microalbumin, and B2- microglobulin testing, requirements for renal consultations for patients with pre-specified abnormal test results, and special study medication stopping rules.

Analysis of renal related AE results did not suggest an increased risk for BG00012 patients compared to placebo patients. Review of narratives for select renal SAEs and discontinuations for renal AEs did not identify convincing evidence of a causal relationship to BG00012 for these events. Lab data revealed negligible differences in the percentages of BG00012 patients who developed B2-microglobulinuria or mircroalbuminuria compared to placebo or GA. Evaluations of patients with renal related AEs by consultant nephrologists did not identify clear evidence of BG00012 related renal toxicity.

BG00012 patients were more likely to develop ketonuria. The etiology of ketonuria in BG00012 patients is not known. This finding did not appear to have meaningful clinical implications. Patients who developed ketonuria did not appear to be at increased risk for AEs or SAEs. BG00012 patients with pre existing diabetes mellitus were not at increased risk for developing ketonuria compared to those without pre existing diabetes mellitius.

Background
Preclinical trials identified BG00012-related renal toxicity in multiple species. Findings included nephropathy (rat 6 months), cortical tubular changes, regeneration of tubule epithelium (rat 6 months; dog 11 months), atrophy of cortical parenchyma, inflammatory cells in renal papilla, hyperplasia of papillary urothelial cells (dog 11 months), regeneration and single cell necrosis of the tubular epithelium, interstitial renal fibrosis (monkey 12 months), adenoma, and carcinoma (mouse carcinogenicity 2 years; rat carcinogenicity, 2 years).

Biogen reported that preclinical studies demonstrated a correlation between urinary albumin and early BG00012 renal related changes (Non Clinical Overview, p.30). As a result, Biogen required tests for urinary β2-microglobulin and microalbuminuria in the human MS Phase 3 trials. In addition, any subjects in Phase 3 trials who developed casts [other than hyaline casts], proteinuria, β2-microglobulinuria, urinary microalbuminuria, or glycosuria in the setting of normal serum glucose, confirmed on repeat testing, were referred for evaluation by a nephrologist. If the nephrologist determined that there was evidence of renal dysfunction, the subject was to discontinue study treatment (ISS, p.94). Data for all subjects referred to a nephrologist were collected for a secondary evaluation by a blinded, independent, external nephrologist (ISS, p.95). Assessment of the potential for BG00012 to cause renal injury is based on AE data, laboratory data and evaluation of select study subjects by nephrologists.

Renal Adverse Events

In Pool A, there did not appear to be notable differences in risk for AEs included under the Renal and Urinary Disorders SOC. Below, I summarize the Renal and Urinary Disorders, and Investigations AEs that occurred in at least 3 BG00012 subjects and more frequently among BG00012 subjects (any dose group) compared to placebo.

Pool A MS Controlled Trials, Renal Adverse Events

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Renal and Urinary Disorders	3% (4)	19% (146)	22% (178)	19% (328)	18% (152)	17% (58)
Proteinuria	0	9% (67)	10% (85)	9% (152)	7% (59)	9% (30)
Hematuria	0	4% (33)	5% (42)	4% (75)	4% (34)	3% (10)
Microalbuminuria	0	5% (35)	4% (36)	4% (71)	3% (24)	4% (15)
Ketonuria	<1% (1)	<1% (7)	2% (15)	1% (23)	<1% (6)	<1% (1)
Dysuria	0	<1% (7)	2% (13)	1% (20)	1% (12)	<1% (1)
Urinary incontinence	0	1% (8)	<1% (5)	<1% (9)	<1% (7)	<1% (3)
Urge incontinence	0	<1% (2)	<1% (4)	<1% (6)	0	<1% (1)
Albuminuria	0	<1% (2)	<1% (2)	<1% (4)	0	<1% (2)

Investigations	7% (9)	28% (212)	28% (228)	26% (449)	25% (205)	30% (106)
Albumin urine present	0	6% (45)	4% (36)	5% (82)	3% (27)	5% (18)
Protein urine present	0	4% (28)	2% (20)	3% (48)	3% (22)	4% (15)
Blood urine present	0	2% (16)	2% (18)	2% (34)	<1% (7)	1% (4)
Urine ketone body present	0	<1% (7)	1% (10)	<1% (17)	<1% (2)	<1% (2)
RBC urine positive	0	1% (8)	<1% (5)	<1% (13)	<1% (6)	<1% (2)

From ISS Appendix Table 24

In addition to the AEs above, one BG00012 and no placebo or GA subjects in Pool A trials had an AE of renal failure chronic. One BG00012 and no placebo or GA subjects had an AE of renal tubular acidosis. Neither of these events were SAEs. No BG00012 subjects had AEs of acute renal failure, tubulointerstitial nephropathy, acute interstitial nephritis, chronic tubulointerstitial nephropathy, acute tubular necrosis, nephrotic syndrome, or glomerulonephritis.

I examined the AEs in other BG00012 NDA data pools to look for events suggestive of renal injury. In MS Pool B, 3 subjects had an AE of renal failure chronic. Investigators reported the following events one time each: renal tubular acidosis, tubulointerstitial nephritis nephritic syndrome, and nephritis (SU Appendix Table 16). None of these events were SAEs. No BG00012 subjects in Pool B had AEs of acute renal failure, acute interstitial nephritis, chronic tubulointerstitial nephropathy, acute tubular necrosis, nephrotic syndrome, or glomerulonephritis (SU Appendix Table 16). In Psoriasis Trials Pool D, no BG00012 subjects had AEs of acute or chronic renal failure, renal tubular acidosis, tubulointerstitial nephropathy, acute interstitial nephritis, chronic tubulointerstitial nephropathy, acute tubular necrosis, nephrotic syndrome, or glomerulonephritis (ISS Appendix Table 215). In the RA trial (109 RA 201), hematuria (one BG00012 and one placebo subject each) and microalbuminuria (one BG00012 and one placebo subject each) were the only renal AEs reported. In the ongoing Phase II MS trial (109 MS 201) the only reported renal AEs were glycosuria (one subject receiving BG00012+GA) and neurogenic bladder (one subject receiving BG00012+INF B). The only renal AEs reported in Phase I studies (healthy volunteers, MS, or Psoriasis patients) were dysuria (n=1) and hematuria (n=1).

Renal SAEs in BG00012 subjects
In Pool B MS trials, Biogen identified one nephrotic syndrome, one proteinuria and one Beta-2 microglobulin SAE from their clinical trials (SU Appendix Table 22). The proteinuria SAE (278-301) occurred in a study patient prior to initiation of study treatment. The patient also experienced hematuria at the same time. These events were reported as resolved prior to initiation of study treatment. The same patient experienced elevated Beta-2 microglobulin later in the trial and that event was not

considered an SAE. In the following paragraphs I summarize the Nephrotic syndrome and increased Beta-2 microglobulin SAEs.

Nephrotic Syndrome
Subject 512-308, a 51 year old female with RRMS had no history of renal disease, hypertension or diabetes. At the onset of the AE of nephrotic syndrome, the subject had received study treatment for 369 days. On Baseline Day 1 of Study 109MS301, urine protein, urine microalbumin, and urine beta-2 microglobulin were within normal ranges. During Study 109MS301, the subject experienced transient episodes of proteinuria after approximately 8 months on BG00012 (which was discontinued due to an MS relapse) and another episode of proteinuria after approximately 8 months on interferon beta-1a. During Study 109MS301, urine protein values ranged from 0 to +1, urine microalbumin ranged from 0.0 to 12.9 mg/dL (ref. range 0.0 to 1.8), and urine beta-2 microglobulin ranged from 0 to 0.34 mg/L (ref. range 0.0 to 0.3). On 17 November 2010, Baseline Day 1 of Study 109MS303, urine protein, urine microalbumin, and urine beta-2 microglobulin were within normal ranges. On [redacted] (b) (6), Study Day 351, the subject had an MRI of the brain and received IV gadobutrol. On that same day, the subject was examined because she was complaining of edema of the feet. No other abnormalities were observed on physical exam. Laboratory tests showed urine protein of +2 and urine microalbumin of 168 mg/dL. On [redacted] (b) (6), urine protein was +3 and urine microalbumin was 448 mg/dL. The subject was seen by a nephrologist on [redacted] (b) (6), Study Day 369, who suspected nephrotic syndrome and initiated treatment with enalapril, spironolactone, and furosemide. Study treatment was discontinued on [redacted] (b) (6) 1. At the Premature Withdrawal Visit on [redacted] (b) (6), urine protein was +3 and urine microalbumin was 652 mg/dL. BUN and creatinine were within normal limits on all evaluations during the study. The subject was subsequently hospitalized for evaluation and treatment of nephrotic syndrome on [redacted] (b) (6), Study Day 378. A physical examination was significant for superficial edema of the calves, dorsal feet, and toes. Laboratory analysis revealed mildly decreased serum protein and albumin. BUN and creatinine were normal. Serum protein electrophoresis, autoantibody testing (ANA, c-ANCA, and p-ANCA) and cancer marker testing (AFP, CA-125, CA 15-3, CA 19-9, and CEA) were normal or negative (specific laboratory values during hospitalization were not provided). An echocardiogram showed normal systolic function and diastolic dysfunction. A renal biopsy was not performed. She was treated with enalapril, spironolactone, and furosemide. The nephrotic syndrome was reported as resolved on [redacted] (b) (6). The Investigator assessed the AE of nephrotic syndrome that began on [redacted] (b) (6) as moderate and unrelated to study treatment and assessed the SAE of nephrotic syndrome that led to hospitalization [redacted] (b) (6) as moderate and possibly related to study treatment. Study treatment was discontinued on 23 November 2011 and the subject was withdrawn from the study on 06 December 2011 as a result of the events. Concomitant medications at the time of the event included venlafaxine and tizanidine.

Beta-2 microglobulin
Subject 017-405, a 42 year old female with RRMS, had no history of renal disease, hypertension, or diabetes mellitus. At baseline, clinical laboratory data showed a normal beta-2 microglobulin and a slightly increased urine microalbumin of 2.5 mg/dL (reference range 0-1.8 mg/dL); a urinalysis was trace high for urine protein with a few RBCs and WBCs noted on microscopy. She experienced an increased urine beta-2 microglobulin on [redacted] (b) (6) and was evaluated by a nephrologist, as required by the protocol. On [redacted] (b) (6), urine beta- 2 microglobulin was increased at 1.08 mg/L (reference range: 0-0.3 mg/L) and urine microalbumin remained slightly elevated. On [redacted] (b) (6), urine beta-2 microglobulin had decreased, but was still slightly elevated at 0.534 mg/L; microalbumin had increased to 5 mg/dL. During the study, all kidney function studies (BUN, creatinine, and all serum electrolytes) were within normal range at all time points. Urine pH was also within reference range (5.5 to 7) throughout the study. Urinalyses were occasionally trace to 1+ for protein and ketones. Most urine samples were hazy or cloudy with mucus and showed a few RBCs and WBCs, although occasional samples revealed numerous RBCs. On [redacted] (b) (6) (day 270), the investigator reported a non serious AE of mild renal tubular acidosis. According to the investigator, an arterial blood gas (date not specified) showed mild acidosis, but no other basis for the diagnosis was provided.

The nephrology consultant requested an ammonium chloride loading test to rule out proximal renal tubular acidosis. On [redacted] (b) (6) (day 274), the subject was hospitalized for administration of the ammonium chloride and further testing. During hospitalization, laboratory testing showed a normal serum creatinine (0.5 mg/dL) and estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m2. Urine spot testing for uric acid (36.9 mg/dL), creatinine (118.6 mg/dL), and phosphorous (12.2 mg/dL) were also within normal range. Anti-HIV 1and 2 were negative. ANA was negative. Serum protein electrophoresis was normal. The ammonium chloride test was negative for renal tubular acidosis.

After 11 May 2010, all subsequent measurements of urine beta-2 microglobulin and micoalbumin were within reference range. No action was taken with study treatment as a result of this event. Concomitant medications at the time of the event included sertraline, levetiracetam, and cyproheptadine hydrochloride. The subject continued to participate in the study until study completion on 02 July 2011.

Discontinuations of BG00012 Subjects for Renal AEs
In Pool B MS trials, the renal-related AEs that led to discontinuation of BG00012 included proteinuria (n=3), hematuria (n=2), nephrolithiasis (n=2), nephrotic syndrome (n=1), renal failure chronic (n=1), renal impairment (n=1), renal pain (n=1), tubulointerstitial nephritis (n=1), B-2 microglobulin increased (n=1), Protein urine present (n=2), and albumin urine present (n=1) (SU, Appendix Table 24). The narratives suggested that some of the abnormalities were either present at baseline, recurred off BG00012, and, in one case, was present in the preceding RCT when the patient

received placebo. I summarize potentially important renal AEs leading to discontinuation below.

Nephrotic syndrome
Subject 512-308, presented above as SAE

Proteinuria
010-306 This 40 year old male had trace proteinuria at baseline followed by negative results until study day 203 when he had trace proteinuria again and 1+ proteinuria approximately 1 and 2 months later. He was discontinued from the study and UA was negative for protein at the follow up visit. BUN and creatinine were normal throughout.

361-310 This 43 year old male had a beta 2 microglobulin of 0.25 mg/L (0.29 mg/L ULN) and a microalbumin of 1.1 mg/dL (1.8 mg/dL ULN) at baseline. On study day 86, his beta 2 microglobulin was 0.4 mg/L and a microalbumin was 1.9 mg/dL and U/A demonstrated 6 RBCs per HPF. On study day 101, his beta 2 microglobulin was 0.95 mg/L and a microalbumin was 2.7 mg/dL. On study day 101, his beta 2 microglobulin declined to <0.22 mg/L and a microalbumin to 1.0 mg/dL. He was discontinued on study day 225 and no beta 2 microglobulin or microalbumin were reported for that day. On follow up days 248 and 317, his microalbumin results were 2.2 mg/dL and 2.0 mg/dL, respectively (beta 2 microglobulin not reported). His BUN and creatinine were normal throughout the study.

Proteinuria and Renal failure chronic
107-401 This 39 year old female had a baseline U/A that was negative for protein and ketones. On Study day 29, her UA showed +2 ketones and +1 protein. On Study day 55, her UA was negative for ketones and had +1 protein. Her only elevated beta-2 microglobulin occurred on day 85 (result 0.39 mg/L, ULN 0.29 mg/L). Urine microalbumin was normal throughout the trial. Study treatment was stopped on day 209 and she continued on alternative MS treatment (interferon beta-1-b). Her BUN and creatinine were normal throughout the trial.

Protein urine present
149-402 This 40 year old female with RRMS participated in trial 302 and received GA. Her baseline UA for trial 302 showed +1 occult blood (ref. range = none), urine microalbumin of 3.7 mg/dL (ref. range: 0 to 1.8), and other values within normal limits (see table below). Urinalysis abnormalities continued intermittently throughout her participation in trial 302, with mild urine protein present (trace or +1) on most evaluations from Study Day 113 to the end of the study. Other relevant adverse events included RBCs and WBCs in the urine from Study Day 123 to 228, urine protein and albumin present from Study Day 165 to Day 228, and urine albumin present from Study Day 421 to 510. Serum creatinine and BUN were within normal limits on all evaluations during trial 302. On the last day day of trial 302 (Day 673) and the first day of trial 303, the subject's urinalysis showed protein "trace", occult blood 2+, WBCs 95/HPF (ref.

range: 0 to 12), and microalbumin 6.5 mg/dL. On Day 41 of trial 303, the subject was diagnosed with cysitis (assessed as moderate and unlikely related to study treatment) and was treated with sulfamethoxazole/trimethoprim. The event was reported as resolved on Day 51. Urinalysis abnormalities continued, with urine protein reaching a peak of +4 on Study Day 111. Abnormal urinalysis results reported as AEs during the study included elevated urine WBCs from Study Day 111 to 136 (mild, unrelated), elevated urine protein from Study Day 111 to 174 (mild, unlikely related), elevated urine ketones from Study Day 133 to 140 (mild, unrelated), elevated urine WBCs from Study Day 140 to 171 (mild, unrelated), and elevated urine creatinine and microalbumin beginning on Day 521 (mild, possibly related, unresolved at data cutoff date). On 01 December 2011, Day 580, the subject was found to have an elevated 24-hour urine protein test result and study treatment was discontinued (specific value was not reported). The event was not resolved at the data cutoff date for this report. Serum creatinine and BUN were within normal limits on all evaluations during the study. Urinalysis results from Study 109MS302 and 109MS303 included:

Date (**Study**, Study Day)	Urine Protein Ref. Range: None	Occult Blood Ref. Range: None	Urine RBCs (HPF) Ref. Range: 0 – 8	Urine WBC (HPF) Ref. Range: 0 – 12	Urine Microalbumin (mg/dL) Ref. Range: 0 – 1.8
27JUN2008(**109MS302** Baseline Day 1)	NEG	+1	8	2	3.7
30APR2010 (**109MS302** Day 673 [last day] and **109MS303** Baseline Day 1)	Trace	+2	4	95	6.5
19AUG2010 (**109MS303** Day 111)	+4	NEG	10	134	NEG
10SEP2010 (**109MS303** Day 133)	+1	Trace	7	121	NEG
16SEP2011 (**109MS303** Day 504)	Trace	+1	14	43	8.2
12DEC2011(**109MS303** Day 591–Premature Withdrawal Visit)	Trace	+2	26	25	6.9

From patient narrative summary

The Investigator assessed the presence of urine protein on 01 December 2011 as mild and considered the event to be possibly related to study treatment. Study treatment was discontinued on 12 December 2011 and the subject was withdrawn from the study on 05 March 2012 as a result of the event.

304-305 This 26 year old female had a baseline UA that was negative for protein. On study day 21, a UA showed +2 protein. On study day 35, UA showed +1 protein with occult blood and microalbumin was elevated (2.5 mg/dL). On study day 56, BG00012

was stopped for AEs of flushing, diarrhea, abdominal discomfort and proteinuria. On study day 70, UA was negative for protein but positive for occult blood and microalbumin was 3.2mg/dL. On study day 99, UA was negative for proteinuria and occult blood, and microalbumin was within the reference range. She continued in the study on alternative MS treatment and on study day 350 she had proteinuria (+1) and elevated microalbumin (11.5mg/dL). Her microalbumin had been normal for over 4 months prior to this event. Urine microalbumin levels showed improvement on subsequent tests during the following week (7.2mg/dL and 2.2mg/dL, respectively), with only trace levels of urine protein detected. Urine microalbumin returned to reference range two months after the 11.5mg/dL result. After returning to normal, she again experienced elevated levels of albumin again six months and ten months later (6.0 and 2.0, respectively) and she was withdrawn from the study as a result of this event.

Albumin urine present
148-309 This 54 year old male had a pretreatment elevated microalbumin of 17.9mg/dL and +1proteinuria. Microalbumin decreased to 2.6mg/dL and proteinuria “resolved” on treatment (day 29). Treatment was stopped 6 days later. This subject continued on alternative MS treatment and had intermittently elevated microalbumin. His BUN and creatinine were normal throughout the study.

B2 microglobulin urine present
212-404 This 42-year-old male had a baseline urinalysis that showed trace protein and all other values within normal limits. During the preceding RCT, 109MS302, he received placebo and he had increased urine beta-2 microglobulin twice, once on Study Day 420, resolving in 33 days; and again on Study Day 588, resolving in 83 days. After completing trial 109MS302, he enrolled in trial 109MS303. On Day 168 of 109MS303, the increased urine beta-2 microglobulin reoccurred and study treatment was discontinued the same day. Urinalysis on that day showed protein of +1, WBCs 23/HPF, (ref. range: 0 to 5), microalbumin 5.1 mg/dL (ref. range: 0 to 1.8), and all other values within normal limits. There were no concomitant medications reported at the time of the event.

Hematuria
152-302 This 54-year-old female enrolled in Study 109MS301 and randomized to receive BG00012 240 mg BID. Medical history included urinary tract infection, hypertension, edema, obesity, arthritis, dysphagia, and acid reflux disease. Baseline urinalysis results showed no occult blood in the urine, RBC count was not available, and WBC count was 36/HPF (ref. range = 0 to 12). She was treated with sulfamethoxazole/trimethoprim for a urinary tract infection for these results. On Study Day 28, urinalysis results were significant for trace occult blood; 2 RBCs/HPF (ref. range = 0 to 8); and 9 WBCs/HPF. On Study Day 41, urine occult blood was +1, RBCs peaked at 33/HPF, and WBCs were 43/HPF. BG00012 was discontinued on Study Day 54. Two days later the subject’s urinalysis showed normal RBCs and WBCs (1/HPF and 9/HPF, respectively), and trace occult blood. The subject continued on alternative MS

treatment and intermittently had elevated occult blood, reaching a post-event peak of +1 on Study Days 252 and 625. Creatinine and BUN were normal on all assessments during the study. Urine RBCs remained normal until Study Day 625, at which time her RBCs were 12/HPF, urine occult blood was +1, and WBCs were 58/HPF. No further laboratory results were available.

630-401 This 47-year-old female was enrolled in RCT 109MS302 and received BG00012 240 mg TID. The subject's relevant medical history included the use of an intra-uterine contraceptive device since April 2008. On Baseline Day 1 of Study 109MS302, prior to receiving the first dose of study treatment, abnormal findings for her urinalysis included occult blood of +3, RBCs >150/HPF (ref. range: 0 to 8), protein of +1, and microalbumin of 7.2 mg/dL (ref. range: 0 to 1.8). Elevated urine protein, occult blood, RBCs, WBCs, and microalbumin continued intermittently during the study. She experienced an AE of hematuria during this trial and the event was ongoing when she enrolled in Study 109MS303. On the last day of Study 109MS302 she also had a positive urine bacteria test (assessed as mild and unrelated to study treatment) that was reported as an AE. No medical treatment was administered and no action was taken with study treatment as a result of either event during Study 109MS302. At the start of Study 109MS303, abnormal findings for the subject's urinalysis included occult blood of +2, bacteria positive, and squamous epithelial cells of 25/HPF (ref. range: 0 to 3). Study treatment was discontinued Day 29 of trial 109MS303. On that same day, the subject's occult blood was negative, urine bacteria test was positive, and other values were within normal limits. The urine bacteria were treated with cefixime from Study Day 43 to 50. The hematuria was reported as resolved on Day 43 of trial 109MS303, without further intervention. The event of positive urine bacteria was not resolved at the data cutoff date for this report. Laboratory test results for serum creatinine and BUN were within normal limits on all assessments during Study 109MS302 and Study 109MS303.

Renal impairment
289-303 This 45 year old female had a history of hypertension on atenolol, folic acid, phenytoin, methycobalamin, domperidone and panprotazole. At baseline, her urine microalbumin was normal (1.4 mg/dL) with no protein, blood, and 3 WBCs on UA. On Day 61, microalbumin was not reported but she had 1+ protein, occult blood, and 16 WBCs on UA. She was treated with ofloxacin for 5 days. On Day 84, her microalbumin was 34.2 mg/dL with 1+ protein and 2+ occult blood. On study day 222, the investigator reported an AE of renal dysfunction and she was discontinued from the trial. Microalbumin was not reported and UA on that day showed protein and occult blood +1. BUN and creatinine were normal throughout the trial.

Chronic tubulointerstitial nephritis
989-409 This 30-year-old female was enrolled in 109MS303 and received BG00012 240 mg BID. Prior to enrollment in 109MS303, the subject completed RCT 109MS302 and had received BG00012 240 mg BID. At the Screening Visit for 109MS302 on a UA showed protein of 2+, squamous cells of 36/HPF (ref. range: 0 to 3), and other values

within normal limits. Urinalysis abnormalities continued intermittently throughout her participation in 109MS302, with urine protein again reaching 2+ on Study Day 635. The event of proteinuria was unresolved at the end of 109MS302. Additionally, the subject was treated for a urinary tract infection with ciprofloxacin from Day 645 to 651. On the last day (Day 674) of 109MS302/the first day of 109MS303, her UA showed protein 1+, ketones 1+, squamous cells 94/HPF, WBCs 39/HPF (ref. range: 0 to 12), and microalbumin 3.3mg/dL (ref. range: 0 to 1.8mg/dL). On Day 5 of 109MS303, she was diagnosed with tubulointerstitial nephritis. UA abnormalities present on Day 29 of Study 109MS303 included protein 1+, squamous cells 31/HPF, and WBCs 25/HPF. Study treatment was discontinued on Day 36, at which time urine ketones and protein had decreased to trace, and other urinalysis values were within normal limits. Creatinine and BUN were within normal limits on all evaluations during Studies 109MS302 and 109MS303. The tubulointerstitial nephritis was not resolved at the data cutoff date for this report.

Renal related lab results

BUN/Creatinine
In MS Pool A, the mean change from baseline for BUN for BG00012 subjects was similar to the mean changes in the placebo and GA subjects. BG00012 subjects experienced mean declines in creatinine while placebo subjects experienced mean increases. I summarize those data below.

MS Pool A, BUN/Creatinine, Mean change from Baseline, select study visits

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
BUN (mmol/L)					
Week 4	-0.07 (734)	-0.14 (793)	-0.12 (1653)	0.15 (817)	-0.07 (340)
Week 24	0.03 (658)	-0.04 (693)	-0.02 (1465)	0.07 (741)	-0.03 (317)
Week 48	0.05 (604)	0.02 (608)	0.03 (1212)	0.10 (605)	0.09 (296)
Week 96	0.08 (534)	0.06 (523)	0.07 (1057)	0.23 (490)	0.17 (263)
Creatinine (umol/L)					
Week 4	-4.50 (734)	-6.58 (793)	-5.48 (1653)	0.23 (817)	-0.75 (340)
Week 24	-5.34 (658)	-6.83 (693)	-5.88 (1465)	0.19 (756)	-0.40 (317)
Week 48	-5.18 (604)	-6.52 (608)	-5.85 (1212)	0.63 (607)	-0.53 (296)
Week 96	-3.89 (534)	-5.68 (523)	-4.77 (1057)	1.96 (490)	1.79 (263)

From ISS Appendix Table 125

In their analysis of shifts from a normal or low (< LLN) result at baseline to at least one high (>ULN) result during treatment; and from normal or high (>ULN) result at baseline to at least one low (<LLN) result during treatment, there was no notable difference for BUN and creatinine when comparing across treatment groups (ISS Appendix table 133, data not shown).

Urinalysis, B2-microglobulin, microalbumin
Biogen reported that in the Pool A trials, when comparing treatment groups there was no remarkable difference in the percentage of patients who experienced 2 consecutively positive UAs for protein (placebo 47%, BG00012 BID 51%, BG00012 TID 53%, GA 56%). Shift table analyses revealed similar findings with 73% of placebo subjects shifting to positive for urine protein compared to 79% of BG00012 BID subjects and 75% of BG00012 TID subjects (ISS Appendix table 150).

There was a notable difference in the percentage of patients with 2 consecutive positive urine ketone results. In Pool A, 5% (40/831) of placebo subjects 4% (15/347) of GA subjects had 2 consecutive positive results for urinary ketones compared to 21% (162/769) of BG00012 BID patients and 30% (244/823) of BG00012 TID patients (ISS Appendix table 144). Similar findings were reported for the shift analyses. For urine ketones, the incidence of shifts to high/positive in the BG00012 BID and TID groups was 63% and 68%, respectively, compared to 26% with placebo and 32% in the GA group (ISS Appendix Table 150). Biogen did not provide an explanation for these findings in the NDA safety presentation.

The elevated urinary ketone results were not associated with increased serum glucose and were not generally associated with an increased anion gap (AG). Using data from trials 301 and 302, I identified BG00012 subjects with post baseline urinary ketone results ≥3+. I found 69 urinary ketone results ≥3+ (in 54 BG00012 patients). On the day of the elevated urinary ketone result, none of the patients had a serum glucose >126mg/dL. I calculated the anion gap (Na-(Cl+bicarb)) on the day when the elevated urinary ketone result occurred. Of the 69 instances of elevated urinary ketones, the anion gap was <=13 for 28, <=15 for 48 and was <19 for 65.

The Division asked Biogen to explain why a higher percentage of BG00012 patients had positive tests for urinary ketones. Biogen replied the “The reason for this effect is unknown.” Biogen hypothesized that a possible pharmacodynamic effect may occur, resulting in upregulation of glutathione synthesis by DMF and MMF. Glutathione has a free sulfhydryl group which, theoretically, could react with sodium nitroprusside, the reagent used to test urine for ketone bodies. Biogen also suggested that urinary metabolites of BG00012 may directly interfere with the nitroprusside assay for urinary ketones (7/30/12 Response to Division questions, pp.218-219).

Biogen also proposed, but rejected, that increased urinary ketones may be due to the GI AEs of BG00012, which could result in decreased oral intake, diarrhea, and vomiting, and ultimately, starvation ketosis. To evaluate the possibility of an association between ketonuria and GI tolerability events, Biogen analyzed actual values over time, worst-post-baseline ketone values, and the incidence of ≥2 consecutive, positive tests for urinary ketones for the subgroups of subjects with and without a GI tolerability event (defined using the AE of special interest definition). Biogen did not find an increased

incidence of ketonuria in BG00012-treated subjects with GI tolerability events. In the table below, I summarize the results from the analysis of patients with 2 consecutive positive results for urine ketones, stratified by presence/absence of GI intolerability AEs(7/30/12 Response to Division questions, p.219).

MS Pool A, Percent of Patients with 2 Consecutive Positive Results for Urine Ketones, Stratified by Patients with and without GI Intolerability AEs

Treatment					
BG00012 Low doses	BG00012 BID	BG00012 TID	BG00012 Total	Placebo (n)	GA
Patients with one or more GI intolerability AE					
5% (2/39)	13% (39/309)	18% (61/351)	15% (102/699)	<1% (2/256)	2% (1/53)
Patients without a GI intolerability AE					
3% (3/89)	11% (48/460)	18% (84/472)	14% (135/1021)	2% (12/580)	1% (3/298)

From Tables 5 and 6, Response to FDA Questions, received 7/30/12

The Division also asked Biogen to address the potential safety related implications of elevated urinary ketones, particularly among patients with diabetes mellitus.

To investigate if patients who developed ketonuria had increased risk for developing AEs or SAEs, Biogen performed stratified analyses. Biogen first separated study patients into those who experienced ketonuria (1+ or greater) and those who did not. Biogen then calculated the AE and SAE risks for these groupings of patients. There did not appear to be meaningful differences in the percentages of patients with AEs or SAEs when comparing those with urinary ketones to those without. In the following table, I compare the percentages for select Endocrine, Metabolism, and Investigation SOC and AE preferred terms, stratified by urinary ketone results (1+ or greater v. trace/negative).

MS Pool A, Percentages of Select Endocrine, Metabolism, and Investigation SOC and AE preferred terms, Stratified by patients with/without Urinary Ketones

		BG00012				PBO	GA
		Low dose	240mg BID	240mg TID	Total		
	Ketones						
Endocrine disorders	**+**	0	1% (4)	1% (5)	1% (9)	1% (1)	0
	-	0	<1% (3)	1% (5)	<1% (8)	<1% (7)	<1% (3)
Metabolism/ nutrition disorders	+	1% (4)	7% (25)	7% (30)	7% (56)	6% (5)	4% (2)
	-	<1% (1)	6% (25)	6% (22)	5% (48)	7% (54)	6% (18)
Dec appetite	+	4% (1)	2% (6)	2% (9)	2% (16)	0	2% (1)
	-	<1% (1)	3% (11)	2% (6)	2% (18)	2% (13)	<1% (1)
Diabetes mellitus	+	0	<1% (1)	<1% (1)	<1% (2)	0	2% (1)

	-	0	0	<1% (1)	<1% (1)	<1% (2)	<1% (1)
DKA	+	0	0	<1% (1)	<1% (1)	2% (2)	0
	-	0	0	0	0	0	0
Hyperglycemia	+	0	<1% (2)	<1% (4)	<1% (6)	0	0
	-	0	<1% (1)	<1% (1)	<1% (2)	<1% (7)	<1% (1)
Ketosis	+	0	0	<1% (1)	<1% (1)	0	0
		0	0	0	0	0	0
Type 1 DM	+	0	<1% (1)	0	<1% (1)	0	0
	-	0	0	0	0	0	0
Type 2 DM	+	0	<1% (1)	0	<1% (1)	1% (1)	0
	-	0	<1% (1)	0	<1% (1)	0	0
Investigations	+	12% (3)	25% (86)	29% (128)	27% (217)	26% (21)	37% (17)
	-	6% (6)	30% (126)	27% (100)	26% (232)	24% (183)	30% (89)
Glucose inc	+	0	<1% (2)	2% (10)	2% (12)	2% (2)	0
	-	0	2% (8)	2% (8)	2% (16)	<1% (5)	2% (7)
Blood ketone inc	+	0	<1% (1)	<1% (1)	<1% (2)	0	0
	-	0	0	0	0	0	<1% (1)

From Tables 9 and 10, Response to FDA Questions, received 7/30/12

Lastly, Biogen compared safety parameters in patients with underlying diabetes or other metabolic conditions to those without those conditions. Specifically, Biogen compared ketonuria in patients with a history of diabetes to those without. Biogen also compared AE and SAE risk in patients with a history of diabetes to those without.

BG00012 treated patients with a history of diabetes were not markedly more likely to develop ketonuria compared to placebo. Among subjects with diabetes or other metabolic conditions, the incidence of ≥2 consecutive positive test results for ketonuria was 9%, 6%, and 13% in the placebo, BG00012 BID, and BG00012 TID groups, respectively. Among subjects without those conditions, the incidence of ≥2 consecutive positive test results for ketonuria 1%, 12%, and 18% in the placebo, BG00012 BID, and BG00012 TID patients, respectively.

Patients with diabetes did not appear to be at greater risk for AEs or SAEs. When comparing patients with underlying diabetes or other metabolic conditions to those without, there did not appear to be robust differences in risk for AEs or SAEs (Data not shown, 7/30/12 Response to Division questions, pp.220-221).

Biogen concluded that the etiology of the increased incidence of ketonuria observed with BG00012 treatment relative to placebo is unknown and that this finding does not have clinically meaningful implications (7/30/12 Response to Division questions, p.221).

As part of the increased renal monitoring in the MS RCTs 301 and 302, Biogen required B2-microglobulin and microalbumin measurements. Evaluation of mean change from

baseline did not suggest notable increases in either parameter among the BG00012 subjects. I provide those data below.

MS RCTs 301 and 302, B2-microglobulin and microalbumin, Mean change from Baseline, select study visits

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
B2-microglobulin (mg/L)					
Week 12	-0.01 (611)	-0.07 (596)	-0.04 (1207)	0.00 (597)	0.00 (294)
Week 24	0.05 (566)	-0.11 (543)	-0.03 (1109)	0.00 (567)	-0.01 (286)
Week 48	-0.02 (537)	-0.13 (511)	-0.07 (1048)	-0.04 (517)	-0.02 (266)
Week 96	-0.01 (467)	-0.16 (441)	-0.08 (908)	-0.05 (423)	-0.03 (234)
Microalbumin (mg/dL)					
Week 12	-0.11 (682)	0.01 (675)	-0.05 (1357)	-0.10 (687)	-0.30 (322)
Week 24	-0.04 (633)	0.18 (608)	0.07 (1241)	-0.22 (650)	-0.34 (307)
Week 48	0.16 (587)	0.22 (572)	0.19 (1159)	-0.11 (579)	0.57 (291)
Week 96	0.41 (502)	-0.04 (487)	0.19 (989)	-0.33 (460)	-0.48 (251)

From ISS Appendix Table 153

A slightly higher percentage of BG00012 treated patients shifted to high for microalbumin, but there did not appear to be differences by treatment in the percentage of patients who shifter to high for B2-microglobulin. I present those results below.

MS RCTs 301 and 302, B2-microglobulin and microalbumin, Shift to High

Parameter	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
B2-microglobulin	10% (69/710)	9% (66/707)	10% (135/1417)	9% (62/728)	9% (29/336)
Microalbumin	36% (232/651)	37% (239/652)	36% (471/1303)	29% (198/686)	33%(102/311)

From ISS Appendix Table 158

Nephrologist Consults/Review

As noted above, subjects participating in the Phase 3 MS studies who developed casts (other than hyaline casts), proteinuria, β2-microglobulinuria, urinary microalbuminuria, or glycosuria in the setting of normal serum glucose, confirmed on repeat testing, were referred for evaluation by a nephrologist. In addition, data from subjects who qualified for and/or had a nephrology consult were evaluated by a blinded, independent, external nephrologist. The subject records reviewed included demographic information, medical history, concomitant medications, AE data, physical examination findings, laboratory results, and nephrology consult reports (if available). Biogen reported that the percentage of subjects whose data underwent blinded review by the independent nephrologist was similar across treatment groups (16% placebo versus 20% BG00012 BID, 20% BG00012 TID, 21% GA). The independent nephrologist felt that the majority

of subjects included in the review (93% to 96% across groups) did not have renal dysfunction prior to dosing. Furthermore, the independent nephrologist felt that there was no evidence of drug-induced nephrotoxicity in any BG00012-treated subject (ISS, p.95).

Biogen Conclusions
Biogen concluded that BG00012 was not associated with an increased risk of renal or urinary events. Biogen noted that most renal related AEs were mild in severity and did not result in treatment discontinuation and that there have been no serious cases of renal failure.

The Division asked Biogen why they omitted mention of [redacted] (b) (4)

Gastrointestinal Adverse Events

Reviewer Summary
BG00012 use is associated with select GI AEs. In the Pool A trials, 40% of BG00012 subjects experienced one or more GI AEs compared to 30% of placebo patients. Diarrhea, vomiting and abdominal pain were the individual GI AEs that most commonly occurred in BG0012 patients and that occurred more frequently compared to placebo. These events occurred most commonly around the time of initiating treatment with BG00012 and the greatest difference in risk compared to placebo occurred during the first month of treatment. Compared to placebo, BG00012 patients had slightly increased frequency of GI SAEs, GI AEs leading to discontinuation, and GI AEs rated by investigators as severe. The MS Pool A study protocols allowed for temporary dose reductions in patients with GI AEs but it is unclear to what extent this therapeutic maneuver improved tolerability. There was insufficient evidence to determine if taking BG0012 with food improved tolerability with respect to GI AEs.

Background
Based on prior experimental evidence, Biogen was aware of the BG00012's ability to cause gastrointestinal AEs and therefore incorporated into the Phase III trial designs allowances to temporarily reduce the study drug dose (to one 120mg capsule BID or TID for up to 1 month) in patients reporting GI AEs.

Methods
Biogen provided additional analyses to better describe the occurrence of GI AEs. Specifically, Biogen performed supplemental analyses for AEs based on an SMQ containing preferred terms associated with GI tolerability. These pooled analyses considered GI nonspecific inflammations (under Level 1 SMQ Gastrointestinal nonspecific inflammation and dysfunctional conditions) as well as GI nonspecific symptoms and therapeutic procedures (under Level 1 SMQ Gastrointestinal nonspecific inflammation and dysfunctional conditions) (ISS, p.8612).

Results
Frequency
Biogen reported that in the Pool A MS RCTs, BG00012 subjects more frequently reported one or more AEs included in the GI tolerability group compared to placebo or GA. GI tolerability AEs were reported by 40% of BG00012 subjects, 43% of BG00012 TID subjects, 31% of placebo subjects and 15% of GA subjects (ISS, p.78). These results based on the GI tolerability SMQ did not differ meaningfully when compared to the risks for all AEs subsumed under the GI disorder SOC. I present the GI tolerability AEs for the Pool A trials in the following table. I include only the AEs that occurred in at least 1% of BG00012 subjects (any dose group) and that were reported at a higher frequency compared to placebo.

Pool A MS Controlled Trials, GI Tolerability AEs that occurred in ≥1% of BG00012 subjects (any dose) and more frequently compared to placebo

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Any GI Tolerability AE	30% (39)	40% (309)	43% (351)	41% (699)	31% (256)	15% (53)
GI Disorders	30% (39)	40% (305)	42% (342)	40% (686)	30% (248)	14% (48)
Diarrhea	9% (11)	14% (107)	17% (136)	15% (254)	10% (86)	4% (14)
Nausea	8% (10)	12% (93)	14% (115)	13% (218)	9% (72)	5% (16)
Abd pain upper	7% (9)	10% (76)	11% (94)	10% (179)	6% (47)	1% (4)
Abd pain	3% (4)	9% (73)	8% (69)	8% (146)	4% (37)	1% (5)
Vomiting	2% (3)	8% (65)	7% (58)	7% (126)	5% (38)	3% (9)
Constipation	<1% (1)	3% (23)	4% (31)	3% (55)	4% (35)	3% (9)
Gastritis	0	3% (22)	3% (21)	3% (43)	2% (14)	1% (4)
Abd discomfort	5% (6)	2% (19)	2% (15)	2% (40)	2% (13)	<1% (1)
Abd distension	0	<1% (4)	2% (14)	1% (18)	1% (11)	0
Dysphagia	2% (2)	<1% (5)	<1% (5)	<1% (12)	<1% (7)	<1% (2)
Gen disorders and admin site conditions	0	2% (12)	2% (20)	2% (32)	1% (12)	2% (6)
Chest pain	0	1% (9)	2% (14)	1% (23)	1% (10)	<1% (3)

From ISS Appendix Table 68

Severity
I examine the severity of GI AEs by reviewing SAEs, discontinuations, dose interruptions, and severity ratings from the BG00012 clinical trials.

The serious GI SAEs occurring in more than 1 BG00012 subject in the Pool A trials were vomiting (n=4), abdominal pain (n=3), and gastritis (n=3) (from ISS Appendix Table 51) One placebo patient had a SAE of vomiting and no placebo patients had SAEs of abdominal pain or gastritis.

In the Pool A trials, BG00012 subjects discontinued more frequently for GI AEs. GI AEs led to discontinuation of 4% of BG00012 BID subjects, 6% of BG00012 TID subjects, <1% of placebo subjects and <1% of GA subjects (ISS, p.78). Diarrhea, nausea, vomiting, abdominal pain upper and abdominal pain were the GI AEs leading to discontinuation of at least 1% of BG00012 subjects (any dose group) and more frequently compared to placebo (from ISS Appendix Table 57).

As noted above, the trial protocols for the Pool A MS trials allowed investigators to temporarily reduce the BG00012 dose for subjects experiencing GI adverse events. In these trials, 7% (113/1,720) of BG00012 subjects had their doses reduced for AEs in the GI SOC compared to 2% (14/836) placebo patients and 0 GA patients (ISS Appendix Table 60). Note- this total does not include subjects who had their dose reduced and subsequently discontinued for these events (they were counted only among the discontinuations) (ISS, p.71). In the following table, I identify the GI AEs that led to dose reduction for at least 10 BG00012 patients.

Pool A MS Trials, GI AEs that led to temporary dose reductions of ≥10 BG00012 subjects (any group)

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
GI Disorders	6% (8)	6% (49)	6% (49)	7% (56)	7% (113)	0
Nausea	2% (3)	2% (12)	2% (18)	2% (33)	<1% (1)	0
Abd pain upper	<1% (1)	2% (14)	2% (14)	2% (29)	<1% (1)	0
Diarrhea	<1% (1)	1% (11)	2% (17)	2% (29)	<1% (3)	0
GI disorder	0	<1% (7)	2% (16)	1% (23)	<1% (2)	0
Abd pain	0	2% (13)	<1% (8)	1% (21)	<1% (5)	0
Vomiting	0	<1% (6)	1% (12)	1% (18)	0	0

From ISS Appendix Table 60

BG00012 patients were more likely to have investigators rate their GI AE as severe. To calculate the percentage of events rated as severe, I divided the number of specific GI events rated as severe (from ISS Appedix Table 42) by the total number of specific GI events reported, x 100. For BG00012 patients, investigators rated 9.3% (64/686) of the AEs included under the GI Disorders SOC in Pool A trials as severe, compared to 6% (15/248) of the GI disorder AEs for placebo patients. No GA patient had a GI AE rated

as severe. Below, I present for the GI AEs reported by >=5% of all BG00012 patients, the percentage of GI AEs rated as severe.

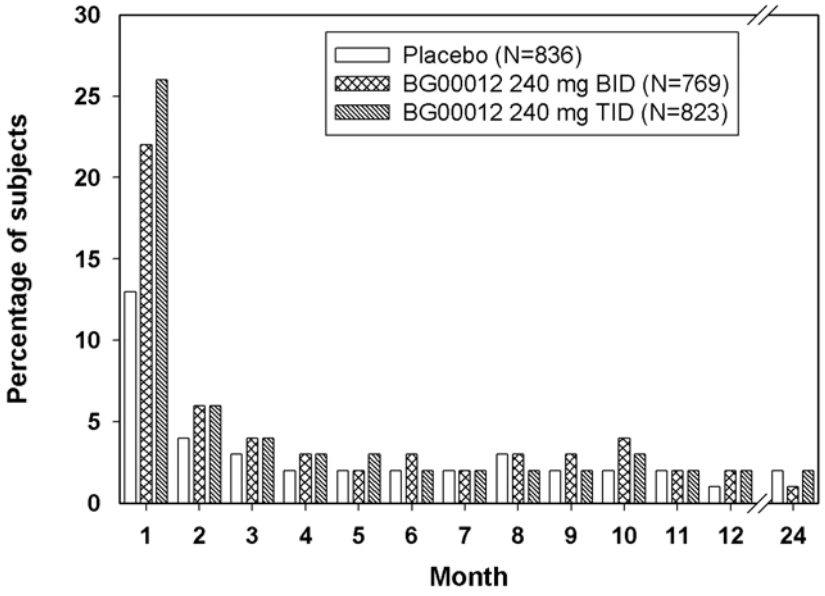
Pool A MS Trials, Common GI AEs (>=5% of all BG00012 Patients), Percentage Rated as Severe

	BG00012				PBO
	Low dose	240mg BID	240mg TID	Total	
GI Disorders	5.1% (2/39)	9.2% (28/305)	9.9% (34/342)	9.3% (64/686)	6.0% (15/248)
Diarrhea	9.1% (1/11)	2.8% (3/107)	6.6% (9/136)	5.1% (13/254)	1.1% (1/86)
Vomiting	0/3	9.2% (6/65)	8.6% (5/58)	8.7% (11/126)	2.6% (1/38)
Abd pain	25% (1/4)	6.8% (5/73)	8.7% (6/69)	8.2% (12/146)	2.7% (1/37)
Abd pain upper	0/9	6.6% (5/76)	7.4% (7/94)	6.7% (12/179)	4.3% (2/47)
Nausea	0/10	4.3% (4/93)	3.5% (4/115)	3.7% (8/218)	4.2% (3/72)

Numerators from ISS Appendix Table 42, Denominators from ISS Appendix Table 68

Onset
Using data from the Pool A studies, Biogen showed that during the first month of treatment, the incidence of GI tolerability AEs was highest and demonstrated its greatest difference when comparing BG00012 to placebo. Below I include Biogen's graph of Pool A Incidence of GI tolerability AEs.

Incidence of gastrointestinal tolerability events by 1-month intervals: Placebo, BG00012 240 mg BID and TID in controlled MS studies (Pool A)



GI Disorder AE Risk by Sex, Age
I used the sponsor's submitted tables that stratified AEs by sex and age to look for differences in risk by these factors for select GI disorder AEs. The relative risks for diarrhea and abdominal pain upper were higher for females, while the relative risks for

the remaining events did not appear to vary markedly by sex for BG00012 compared to placebo. The relative risks for the these GI events did not appear to vary markedly age, although it is important to consider that the age range of subjects in these trials was 18-55 years.

Pool A MS Trials, GI Disorder AEs, Stratified by Sex, Age

AE	Sex	PBO	BG00012 total	RR
Any GI disorder AE	M	31% (75/243)	40% (196/495)	1.3
	F	39% (230/593)	52% (638/1225)	1.3
Diarrhea	M	11% (26/243)	11% (55/495)	1.0
	F	10% (60/593)	16% (199/1225)	1.6
Abdominal Pain	M	4% (9/243)	7% (36/495)	1.8
	F	5% (28/593)	9% (110/1225)	1.8
Abdominal pain upper	M	6% (15/243)	7% (36/495)	1.2
	F	5% (32/593)	12% (143/1225)	2.4
Nausea	M	5% (13/243)	6% (30/495)	1.2
	F	10% (59/593)	15% (188/1225)	1.5
Vomiting	M	2% (4/243)	3% (16/495)	1.5
	F	6% (34/593)	9% (110/1225)	1.5
AE	Age	PBO	BG00012 total	
GI disorder AEs	<40 yrs	33% (153/461)	46% (440/949)	1.4
	≥40 yrs	41% (152/375)	51% (394/771)	1.2
Diarrhea	<40 yrs	9% (41/461)	14% (135/949)	1.6
	≥40 yrs	12% (45/375)	15% (119/771)	1.3
Abdominal Pain	<40 yrs	4% (20/461)	8% (79/949)	2.0
	≥40 yrs	5% (17/375)	9% (67/771)	1.8
Abdominal pain upper	<40 yrs	6% (27/461)	10% (99/949)	1.7
	≥40 yrs	5% (20/375)	10% (80/771)	2.0
Nausea	<40 yrs	8% (38/461)	12% (117/949)	1.5
	≥40 yrs	9% (34/375)	13% (101/771)	1.4
Vomiting	<40 yrs	4% (19/461)	7% (71/949)	1.8
	≥40 yrs	5% (19/375)	7% (55/771)	1.4

From ISS Appendix Tables 183 and 185

Effect of food on GI events

C-1903, the randomized, 2-period crossover food-effect trial (6-10 day washout period), provides limited information about the effect of food on the occurrence of GI AEs. No participants experienced AEs of diarrhea, abdominal pain or abdominal pain upper, in either the fasting or fed state. 8% (3/36) of participants experienced nausea in the fasting state compared to 6% (2/34) in the fed state. 6% (2/36) of participants experienced vomiting in the fasting state compared to 0/34 in the fed state (C-1903 Study report, p.56).

Biogen Conclusions
Based on the relatively small number of GI SAEs, discontinuations for AEs and severe AEs, Biogen concluded that these GI AEs were primarily concerning for limiting tolerability and were not a "serious important risk." (ISS, p.189).

Infections

Reviewer summary
Despite the lymphocyte lowering effect of dimethyl fumarate, Biogen did not observe notable differences in risk for infections or serious infections when comparing BG00012 treated patients to placebo patients in the Pool A MS trials. In addition, Biogen did not identify a safety signal from their search for opportunistic infections in the clinical trials. Although the absence of such findings is somewhat reassuring, Biogen made these observations in highly selected clinical trials populations that were closely monitored. Exclusion criteria for these trials precluded participation for patients with HIV, recent use of immune modulating treatments, and low WBC counts. In addition, Biogen required discontinuation for study participants who developed low WBC counts. (b) (4) It is unclear if the apparent lack of infection risk observed in these trials will be generalizable to a real world population without the selection and monitoring employed in the clinical trials.

Methods
Biogen examined the risk of all infections and of opportunistic infections in patients treated with BG00012. As described below in the laboratory review section, BG00012 causes declines in lymphocyte counts. Biogen examined infection AE risk considering the observed declines in WBC counts and lymphocyte counts.

Results
In Pool A trials, Infection AEs were reported by 60% of BG00012 BID subjects, 60% of BG00012 TID subjects, 56% of placebo subjects and 50% of GA subjects. Biogen identified infection preferred terms where the risk among BG00012 patients was at least 2% greater (risk difference) than among placebo patients. I summarize those infection AEs in the table below.

Pool A MS Controlled Trials, Infection AEs that occurred in ≥2% and more commonly among BG00012 subjects (any dose) compared to placebo

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Infections and Infestations	34% (44)	60% (463)	60% (493)	58% (1000)	56% (469)	50% (175)
Nasopharyngitis	10% (13)	22% (170)	22% (179)	21% (362)	20% (169)	15% (51)
UTI	3% (4)	14% (107)	12% (95)	12% (206)	11% (96)	13% (46)
URTI	4% (5)	13% (99)	12% (101)	12% (205)	11% (88)	8% (27)
Sinusitis	2% (2)	5% (35)	6% (52)	5% (89)	4% (31)	3% (11)

Bronchitis	2% (3)	5% (35)	6% (49)	5% (87)	4% (32)	5% (16)

From ISS Appendix Table 24

Given the association of BG00012 with lymphopenia, I examined the AE risks for select viral infections. There did not appear to be important differences in risk for viral infections by treatment in the Pool A trials. I summarize that information below.

Pool A MS Controlled Trials, Select Viral Infection AEs

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Influenza	5% (6)	7% (54)	9% (77)	8% (137)	8% (65)	4% (15)
Oral herpes	0	3% (23)	2% (13)	2% (36)	3% (27)	2% (6)
Gastroenteritis viral	0	2% (15)	2% (20)	2% (35)	2% (17)	2% (6)
Viral infection	0	2% (18)	2% (14)	2% (32)	2% (15)	1% (5)
Viral URI	3% (4)	2% (13)	1% (10)	2% (27)	1% (12)	2% (7)
Herpes Zoster	<1% (1)	1% (8)	1% (12)	1% (21)	1% (10)	<1% (2)
H1N1 Influenza	0	<1% (2)	<1% (3)	<1% (5)	<1% (2)	<1% (2)
Genital Herpes	0	<1% (4)	0	<1% (4)	<1% (3)	<1% (1)
Herpes Simplex	0	<1% (2)	<1% (2)	<1% (4)	<1% (2)	<1% (1)
EBV infection	0	0	<1% (1)	<1% (1)	0	0
Herpes zoster neurological	0	<1% (1)	0	<1% (1)	0	0
Herpes zoster ophthalmic	0	0	<1% (1)	<1% (1)	0	0

From ISS Appendix Table 24

Infection SAEs were uncommon in Pool A studies, and the frequency of these events did not appear to vary markedly by treatment. In Pool A studies, 1% of placebo subjects experienced an infection SAE compared to 2% of BG00012 BID subjects, 2% of BG001012 TID subjects and 1% of GA subjects. In the following table, I summarize the infection SAEs that occurred in more than 1 BG00012 subject and that were more frequently reported compared to placebo.

Pool A MS Controlled Trials, Infection SAEs that occurred in >1 BG00012 subject (any dose) and more commonly compared to placebo

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Infections and Infestations	<1% (1)	2% (17)	2% (15)	2% (33)	1% (12)	1% (4)
Gastroenteritis	0	<1% (6)	<1% (3)	<1% (9)	0	0
Cellulitis	0	<1% (2)	<1% (2)	<1% (4)	0	0
UTI	0	<1% (1)	<1% (2)	<1% (3)	0	0
Viral infection	0	<1% (2)	<1% (1)	<1% (3)	0	<1% (1)

From ISS Appendix Table 52

I found no reported herpes-related SAEs in the Pool A/Pool B MS trials (ISS Appendix Table 52, Safety Update Appendix Table 22).

I read the narratives for the patients with SAEs of viral infection. The events described in the narratives were fever/weakness, fever/body aches/cough, and headache/unsteadiness, and did not suggest unusual or unexpected viral disease diagnoses.

In MS Pool A, Infection AEs led to discontinuation of <1% (n=1) of BG00012 BID patients compared to <1% (n=6) of BG00012 TID patients, <1% (n=4) placebo patients and no GA patients. No single Infection AE led to discontinuation of more than 1 BG00012 patient in Pool A MS trials. The Infection AEs that led to discontinuation of 1 BG00012 patient each were diverticulitis, gastroenteritis, gastrointestinal infection, herpes zoster, herpes zoster ophthalmic, respiratory tract infection, and urinary tract infection (ISS Appendix Table 57).

In order to assess infection AE risks over time, Biogen provided an analysis of AEs from Pool A trials that grouped events into 3 month intervals. Despite declining lymphocyte and WBC results, there did not appear to be increases in risk for infections over time, and the infection risks among BG00012 subjects did not markedly differ compared to placebo subjects (ISS Appendix Table 34).

In supplemental analyses, Biogen attempted to look for infection AE and serious infection AE risk differences, considering lymphocyte and WBC count. For these analyses, Biogen classified each patient by their minimum lymphocyte count and WBC count. Biogen then examined the infection AE and serious infection AE risks using categories of minimum lymphocyte counts and WBC counts. There appeared to be slightly increased risk of infection AEs in BG00012 patients with lower WBC/lymphocyte counts, although there are relatively few events in the lowest count categories. There did not appear to be an increased risk for serious infection AEs in patients with lower WBC/lymphocyte counts, although this analysis was based on an even smaller number of events. I summarize the results of these analyses below.

Incidence of Infections by Minimum Post-Baseline Lymphocyte Count($\times 10^9$/L)[a]

Group	<0.5	≥0.5 to <0.8	≥0.8	≥0.91[b]	Overall[c]
BG00012 BID	44/71(62%)	151/225(67%)	446/823(54%)	378/719(53%)	42/1136(57%)
BG00012 TID	30/45(67%)	126/204(62%)	540/974(55%)	473/875(54%)	698/1249(56%)

Incidence of Infections by Minimum Post-Baseline WBC Count($\times 10^9$/L)[a]

	<2.0	≥2.0 to <3.0	≥3.0	≥3.8[b]	Overall[c]
BG00012 BID	5/7(71%)	44/74(59%)	592/1038(57%)	477/863(55%)	642/1136(57%)
BG00012 TID	3/5(60%)	42/65(65%)	651/1153(56%)	537/966(56%)	698/1249(56%)

[a] 17 BG00012 BID subjects and 26 BG00012 TID subjects had no post-baseline lymphocyte or WBC values. Of these, 1 subject in the BG00012 BID group and 2 subjects in the BG00012 TID group had an infection.
[b] Lymphocytes counts <0.91 × 10^9/L and WBC counts <3.8 × 10^9/L are below the lower limit of normal.
[c] The overall incidence of infections is based on the safety population. BID = twice daily; TID = three times daily; WBC = white blood cells
Source: SU Appendix Table 29 and SU Appendix Table 31

Incidence of Serious Infections by Minimum Post-Baseline Lymphocyte Count ($\times 10^9$/L)[a]

Group	<0.5	≥0.5 to <0.8	≥0.8	≥0.91[b]	Overall[c]
BG00012 BID	0/71	5/225(2%)	23/823(3%)	18/719(3%)	28/1136(2%)
BG00012 TID	0/45	6/204(3%)	17/974(2%)	15/875(2%)	23/1249(2%)

Incidence of Serious Infections Minimum Post-Baseline WBC Count ($\times 10^9$/L)[a]

	<2.0	≥2.0 to <3.0	≥3.0	≥3.8[b]	Overall[c]
BG00012 BID	0/7	0/74	28/1038(3%)	22/863(3%)	28/1136(2%)
BG00012 TID	0/5	0/65	23/1153(2%)	18/966(2%)	23/1249(2%)

[a] 17 BG00012 BID subjects and 26 BG00012 TID subjects had no post-baseline lymphocyte or WBC values. None of these subjects had a serious infection.
[b] Lymphocytes counts <0.91 × 10^9/L and WBC counts <3.8 × 10^9/L are below the lower limit of normal.
[c] The overall incidence of serious infections is based on the safety population. BID = twice daily; TID = three times daily; WBC = white blood cells
Source: SU Appendix Table 30 and SU Appendix Table 32

Opportunistic Infections

Biogen searched for opportunistic infections using an extensive list of AE terms (ISS, p.8613). Biogen noted that no opportunistic infections were reported in BG00012 subjects from Pool A trials. One BG00012 subject had a herpes zoster infection (preferred term: herpes zoster infection neurological) that was localized to the trigeminal nerve distribution, required only topical acyclovir and resolved in 2 weeks, and therefore was not considered an opportunistic infection.

In extension trial 303, Biogen identified 2 potential opportunistic infections in BG00012 patients (both esophageal candidiasis). Biogen did not believe either case represented a true opportunistic infection. In the first case, Biogen questioned the diagnosis because it was based on observation during endoscopy, was not biopsy proven, and resolved after 5 days of oral fluconazole (usual treatment duration is 14-21 days). Biogen also identified systemic steroid use and PPI use as potential confounders for this case (ISS

p.88). For the second case, again, the diagnosis was based on an endoscopic exam, and no biopsies were taken. The infection resolved after 3 months of oral Nystatin treatment, did not require systemic treatment, and was a non-serious event. The patient continued treatment with BG00012 (SU, p.50).

Biogen Conclusions
Biogen concluded that their analyses did not demonstrate “a clear correlation between infections, serious infections, and lymphocyte counts.” Biogen also stressed that they did not find increases in infections, serious infections, or opportunistic infections in BG00012 treated patients in their safety database. (ISS, p.189)

Cardiovascular disorders

Reviewer Summary
Despite the reporting of cardiovascular AEs in small Psoriasis trials, there did not appear to be evidence of increased risk for cardiovascular AEs in BG00012 patients when viewing the much larger MS trials safety database.

Background
In BG00012 Psoriasis trials, Biogen noticed a small number of suspected and or confirmed myocardial infarctions. While none of these AEs occurred during the Psoriasis RCTs, 5 subjects had confirmed or suspected MI SAEs, and 2 subjects had coronary artery disease SAEs in Psoriasis extension trials. Even though the cases occurred in patients with cardiac risk factors, Biogen decided to evaluate in more detail cardiovascular disease risk in BG00012 patients in MS trials.

Methods
Biogen searched for ischemic heart disease and ischemic cerebrovascular disease AEs using specific SMQs. In addition, Biogen had a consultant cardiologist review AE reports suggestive of cardiovascular and cerebrovascular ischemia events.

Results
Relatively few ischemic heart disease and ischemic cerebrovascular disease events were identified by Biogen’s SMQ search search. In Pool A MS trials, ischemic AEs were reported by <1% of placebo subjects (n=4), 1% of BG00012 BID subjects (n=8), <1% of BG00012 TID subjects (n=6) and 1% of GA subjects (n=4). The ischemic heart events identified were myocardial ischemia (placebo n=1), angina pectoris (BG00012 BID n=3, BG00012 TID, n=2), and acute coronary syndrome (BG00012 TID, n=1). These cases were reviewed by Biogen’s consultant cardiologist. The consultant cardiologist felt that one of the angina pectoris cases appeared to be an ischemic event. For the remaining cases, the cardiologist identified factors such as lack of ECG abnormalities, resolution with antibiotic treatment, resolution with omeprazole and ranitidine, and clinical description of the event that did not support a diagnosis of cardiac ischemia.

The cerebrovascular events identified in the Pool A studies included cerebrovascular accident (placebo n=1), transient ischemic attack (BG00012 BID n=1; BG00012 TID, n=1), ischemic stroke (BG00012 TID n=1), and cerebrovacular disorder (GA, n=1). The cardiologist did not consider the event in the GA patient to be an ischemic event. For the remaining events, the patients had underlying conditions that predisposed to cerebrovascular ischemic events (hypercholesterolemia, smoking, DVT, hypertension, coronary artery disease, obesity).

In uncontrolled trial 303, 3 additional potential ischemic events were reported. The consultant cardiologist judged one event to be an ischemic event (acute MI). The other two events (chronic cerebrospinal venous insufficiency, asymptomatic increase in CPK) were judged not to be ischemic events.

Biogen Conclusions
Biogen noted that the incidences of ischemic cardiac and cerebrovascular events were low in Pool A and in the extension trial 303. In addition, Biogen felt that there did not appear to be increased risk of ischemic cardiac or cerebrovascular events with BG00012 treatment in subjects with MS.

Suicide and Depression

Reviewer Summary
The available AE data did not suggest an increased risk for depression/suicide AEs among BG00012 exposed patients.

Methods
Biogen explored the suicide and depression risk in the MS trials. Specifically, Biogen identified all events coded to terms in the depression/self injury SMQ for MS trials Pools A and B. These analyses are based on reported events given that these trials did not include monitoring for depression/suicidality symptoms.

Results
Biogen found no notable differences in the frequencies of these events by treatment. In the following table, I summarize the results for the Pool A trials.

Suicide and Self-injury AEs, Pool A MS trials

Depression/self-injury SMQ events	BG00012 BID n=769	BG00012 TID N=823	Placebo n=836	GA N=351
Depression	7% (53)	6% (48)	8% (70)	9% (30)
Depressed mood	2% (12)	<1% (7)	2% (19)	1% (4)
Depressive symptom	<1% (1)	<1% (2)	<1% (3)	0
Suicidal ideation	<1% (2)	<1% (1)	<1% (1)	<1% (2)
Major depression	0	<1% (2)	0	0
Suicide attempt	0	<1% (1)	0	<1% (1)
Adjustment disorder	<1% (1)	0	0	0

with depressed mood				
Dysphoria	0	0	<1% (1)	0
Completed suicide	0	0	0	<1% (1)
Intentional self injury	0	0	0	<1% (1)

From ISS, p.102

The Pool B suicide/self injury AE risk data were consistent with the data presented above for Pool A (SU Appendix Table 45). For BG00012 treated patients in Pool B trials there were 3 events of suicidal ideation, 2 suicide attempts, and 1 completed suicide.

Biogen Conclusions
Biogen felt that the incidence of events associated with depression and suicide was low and balanced across the treatment groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

I first summarize the most commonly occurring AEs in BG00012 MS clinical trials using the largest pool of integrated trials MS safety data (Pool B). I then provide comparative data for AEs using the integrated MS safety data from controlled trials (Pool A). I then provide a similar analysis using the integrated Psoriasis clinical trials data. Lastly, I summarize the common AEs in the non-integrated trials.

Integrated Controlled and Uncontrolled MS Trials (Pool B)
In the following table, I summarize the commonly occurring AEs (using a cutoff of >=5% of all BG00012 subjects) in the integrated MS trials.

MS Pool B, AEs Occurring in >=5% of all BG00012 Subjects

	BG00012			
	Low dose	240mg BID	240mg TID	Total
	N=128	N=1113	N=1227	N=2468
Any SAEs	95% (121)	91% (1013)	90% (1099)	90% (2233)
Infections and Infestations	47% (60)	54% (600)	53% (656)	53% (1316)
Nasopharyngitis	20% (26)	22% (245)	22% (270)	22% (541)
UTI	4% (5)	14% (155)	12% (149)	12% (309)
URI	7% (9)	12% (138)	12% (148)	12% (295)
Influenza	7% (9)	7% (76)	8% (99)	7% (184)
Bronchitis	2% (3)	6% (63)	7% (82)	6% (148)
Sinusitis	2% (3)	5% (59)	5% (68)	5% (130)
Gastroenteritis	2% (3)	5% (61)	4% (52)	5% (116)
Blood & Lymphatic System Disorders	6% (8)	6% (63)	7% (81)	6% (152)

Metabolism and Nutritional Disorders	2% (2)	6% (62)	6% (78)	6% (142)
Psychiatric Disorders	12% (15)	16% (179)	15% (186)	15% (380)
Depression	2% (2)	7% (81)	6% (75)	6% (158)
Nervous System Disorders	53% (68)	48% (537)	46% (564)	47% (1169)
MS Relapse	34% (44)	28% (315)	25% (316)	27% (675)
Headache	16% (21)	15% (176)	16% (194)	16% (391)
Paraesthesia	6% (8)	7% (77)	6% (81)	7% (166)
Hypoaesthesia	3% (4)	4% (49)	5% (68)	5% (121)
Dizziness	5% (6)	5% (56)	4% (53)	5% (115)
Eye Disorders	6% (8)	9% (97)	10% (118)	9% (223)
Ear and Labyrinth Disorders	8% (10)	6% (65)	7% (88)	7% (163)
Vascular Disorders	61% (78)	41% (452)	37% (455)	40% (985)
Flushing	53% (68)	33% (371)	29% (363)	32% (802)
Hot flush	6% (8)	7% (80)	8% (95)	7% (183)
Respiratory, Thoracic, and Mediastinal Disorders	11% (14)	14% (161)	14% (175)	14% (350)
Cough	4% (5)	5% (59)	5% (63)	5% (127)
Oropharyngeal pain	2% (3)	5% (55)	5% (58)	5% (116)
Gastrointestinal Disorders	40% (51)	46% (509)	49% (602)	47% (1162)
Diarrhea	11% (14)	15% (167)	16% (194)	15% (375)
Nausea	10% (13)	11% (120)	13% (159)	12% (292)
Abdominal pain upper	9% (12)	11% (120)	12% (148)	11% (280)
Abdominal pain	5% (6)	9% (105)	9% (108)	9% (219)
Vomiting	2% (3)	7% (85)	8% (97)	7% (185)
Dyspepsia	4% (5)	5% (56)	5% (60)	5% (121)
Skin and Subcutaneous Tissue Disorders	25% (32)	30% (333)	29% (358)	29% (723)
Pruritis	11% (14)	8% (94)	7% (90)	8% (198)
Rash	7% (9)	7% (75)	6% (79)	6% (163)
Erythema	2% (2)	6% (67)	6% (70)	6% (139)
Musculoskeletal and Connective Tissue Disorders	25% (32)	29% (327)	30% (364)	29% (723)
Back pain	8% (10)	12% (131)	11% (134)	11% (275)
Arthralgia	4% (5)	8% (88)	7% (91)	7% (184)
Pain in extremity	8% (10)	8% (86)	7% (85)	7% (181)
Renal and Urinary Disorders	5% (7)	17% (194)	18% (225)	17% (426)
Proteinuria	0	8% (93)	9% (107)	8% (200)
Reproductive System and Breast Disorders	4% (5)	8% (91)	8% (103)	8% (199)
General and Administrative Site Conditions	22% (28)	22% (249)	25% (302)	23% (579)
Fatigue	11% (14)	11% (126)	12% (148)	11% (288)
Pyrexia	<1% (1)	5% (52)	5% (65)	5% (118)

Investigations	11% (14)	25% (276)	25% (312)	24% (602)
ALT increased	2% (3)	6% (70)	7% (86)	6% (159)
Albumin urine present	0	6% (66)	5% (64)	5% (130)
Injury, Poisoning, Procedural Complications	9% (11)	13% (149)	14% (177)	14% (337)

From SU Appendix Table 17

Integrated Controlled MS Trials (Pool A)
The percentages of patients who experienced one or more AEs in the Pool A MS clinical trials were similar when comparing placebo (92%, 769/836), to the BG00012 low doses (89%, 114/128), BG00012 240mg BID (95%, 733/769), BG00012 240mg TID (93%, 767/823) and GA (87%, 304/351) treatment groups. Using a cutoff of at least 2%, and at least 1.5 x more frequently than placebo (any BG00012 dose group), I identify commonly occurring AEs in BG00012 treated patients.

Pool A AEs in ≥ 2% of BG00012 patients (any dose group), and at least 1.5 x more frequently than placebo

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Any AEs	89% (114)	95% (733)	93% (767)	94% (1614)	92% (769)	87% (304)
Flushing	51% (65)	34% (265)	29% (240)	33% (570)	5% (39)	2% (6)
Diarrhea	9% (11)	14% (107)	17% (136)	15% (254)	10% (86)	4% (14)
Nausea	8% (10)	12% (93)	14% (115)	13% (218)	9% (72)	5% (16)
Abdominal pain upper	7% (9)	10% (76)	11% (94)	10% (179)	6% (47)	1% (4)
Abdominal pain	3% (4)	9% (73)	8% (69)	8% (146)	4% (37)	1% (5)
Pruritis	9% (11)	8% (62)	8% (64)	8% (137)	4% (35)	2% (7)
Vomiting	2% (3)	8% (65)	7% (58)	7% (126)	5% (38)	3% (9)
Rash	6% (8)	8% (58)	7% (58)	7% (124)	3% (29)	3% (9)
Hot flush	5% (6)	7% (52)	7% (55)	7% (113)	2% (16)	1% (5)
Erythema	2% (2)	5% (36)	7% (54)	5% (92)	1% (10)	2% (6)
Sinusitis	2% (2)	5% (35)	6% (52)	5% (89)	4% (31)	3% (11)
Bronchitis	2% (3)	5% (35)	6% (49)	5% (87)	4% (32)	5% (16)
Albumin urine	0	6% (46)	4% (36)	5% (82)	3% (27)	5% (18)
Dyspepsia	2% (3)	5% (35)	5% (42)	5% (80)	3% (23)	2% (6)
Muscle spasms	<1% (1)	4% (27)	6% (50)	5% (78)	4% (35)	2% (8)
Microalbuminuria	0	5% (35)	4% (36)	4% (71)	3% (24)	4% (15)
AST increased	2% (2)	4% (33)	4% (32)	4% (67)	2% (18)	4% (14)
Gastrointestinal disorder	2% (3)	2% (18)	4% (34)	3% (55)	<1% (8)	<1% (2)
Hyperhidrosis	2% (2)	2% (17)	3% (27)	3% (46)	1% (11)	1% (5)
Abdominal discomfort	5% (6)	2% (19)	2% (15)	2% (40)	2% (13)	<1% (1)
Influenza like	4% (5)	1% (10)	2% (17)	2% (32)	2% (14)	<1% (3)

illness						
Viral URI	3% (4)	2% (13)	1% (10)	2% (27)	1% (12)	2% (7)

From Table 10, ISS, p.43.

Integrated Controlled and Uncontrolled Psoriasis Trials (Pool D)
In the following table, I summarize the commonly occurring AEs (using a cutoff of >=5% of all BG00012 subjects) in the integrated Psoriasis trials.

Pool D AEs Occurring in >=5% of all BG00012 subjects

	BG00012		
	Low dose	240mg TID	Total
	N=72	N=141	N=213
Any SAEs	74% (53)	88% (124)	83% (177)
Infections and Infestations	31% (22)	39% (55)	36% (77)
Nasopharyngitis	24% (17)	23% (32)	23% (49)
Blood & Lymphatic System Disorders	21% (15)	7% (10)	12% (25)
Nervous System Disorders	14% (10)	16% (23)	15% (33)
Headache	6% (4)	9% (13)	8% (17)
Vascular Disorders	36% (26)	45% (64)	42% (90)
Flushing	35% (25)	40% (57)	38% (82)
Respiratory, Thoracic, and Mediastinal Disorders	6% (4)	6% (8)	6% (12)
Gastrointestinal Disorders	8% (6)	48% (68)	35% (74)
Diarrhea	3% (2)	25% (35)	17% (37)
Abdominal pain upper	0	11% (15)	7% (15)
Nausea	1% (1)	8% (11)	6% (12)
Skin and Subcutaneous Tissue Disorders	14% (10)	15% (21)	15% (31)
Pruritis	7% (5)	4% (5)	5% (10)
Musculoskeletal and Connective Tissue Disorders	6% (4)	11% (15)	9% (19)
Renal and Urinary Disorders	11% (8)	2% (3)	5% (11)
Reproductive System and Breast Disorders	4% (5)	8% (103)	8% (199)
General and Administrative Site Conditions	3% (2)	9% (13)	7% (15)
Investigations	17% (12)	6% (8)	9% (20)

From Table 214, ISS, pp.7692-7701.

Integrated Controlled Psoriasis Trials (Pool C)
The percentages of patients who experienced one or more AEs in the integrated controlled Psoriasis clinical trials were lower for placebo (66%, 70/106), compared to the BG00012 low doses (74%, 53/72), and BG00012 240mg TID (88%, 124/141) treatment groups. Using a cutoff of at least 2%,(any BG00012 dose group) and at least

1.5 x more frequently than placebo, I identify the commonly occurring AEs in BG00012 treated patients.

Pool C AEs in ≥ 2% of BG00012 patients (any dose group), and at least 1.5 x more frequently than placebo

	BG00012			PBO
	Low dose	240mg TID	Total	
	N=72	N=141	N=213	N=106
Any AEs	74% (53)	88% (124)	83% (177)	66% (70)
Flushing	35% (25)	40% (57)	38% (82)	9% (10)
Nasopharyngitis	24% (17)	23% (32)	23% (49)	16% (17)
Diarrhea	3% (2)	25% (35)	17% (37)	6% (6)
Headache	6% (4)	9% (13)	8% (17)	4% (4)
Abdominal pain upper	0	11% (15)	7% (15)	3% (3)
Nausea	1% (1)	8% (11)	6% (12)	0
Pruritis	7% (5)	4% (5)	5% (10)	4% (4)
Abdominal pain	0	6% (8)	4% (8)	<1% (1)
Eosinophilia	6% (4)	3% (4)	4% (8)	0
Toothache	0	6% (8)	4% (8)	<1% (1)
Burning sensation	6% (4)	2% (3)	3% (7)	0
Vomiting	1% (1)	4% (6)	3% (7)	0
Bronchitis	0	4% (6)	3% (6)	2% (2)
RBCs urine positive	7% (5)	<1% (1)	3% (6)	4% (4)
WBCs urine positive	8% (6)	0	3% (6)	2% (2)
Cough	4% (3)	1% (2)	2% (5)	2% (2)
Dyspepsia	0	4% (5)	2% (5)	<1% (1)
Hematuria	6% (4)	<1% (1)	2% (5)	<1% (1)
Hot flush	0	4% (5)	2% (5)	<1% (1)
Leukopenia	4% (3)	1% (2)	2% (5)	2% (2)
Lymphopenia	3% (2)	2% (3)	2% (5)	0
Paresthesia	3% (2)	2% (3)	2% (5)	0
Pharyngitis	3% (2)	2% (3)	2% (5)	0
Skin burning sensation	4% (3)	1% (2)	2% (5)	<1% (1)
Feeling hot	3% (2)	1% (2)	2% (4)	0
Gastritis	0	3% (4)	2% (4)	0
Leukocyturia	6% (4)	0	2% (4)	<1% (1)
Lymphocytosis	6% (4)	0	2% (4)	<1% (1)
Respiratory tract infection	4% (3)	<1% (1)	2% (4)	0
Leukocytosis	4% (3)	0	1% (3)	0
Neutrophilia	4% (3)	0	1% (3)	0
Pyrexia	0	2% (3)	1% (3)	0

From Table 26, ISS, pp.145-146.

Non-Integrated Clinical Trials
Healthy Volunteers
In summarizing the safety results from the Phase I trials in healthy volunteers, Biogen commented that single doses of BG00012 were most frequently associated with

flushing, nausea, and pruritis and that subjects receiving repeated doses up to 6 days had increased severity of flushing and pruritis. (ISS, p.30). I read the study reports for these trials and Biogen's statement accurately reflects the AEs reported. In these trials in healthy volunteers, flushing was reported by a majority of subjects (as high as 94%-trial C-1903).

MS
Biogen reported that the most common AEs (>10%) in MS trial 109MS201 were similar to the common events in the integrated MS trials and included the following: flushing, GI events (nausea, diarrhea, abdominal distension, and abdominal pain upper), headache, URTI, fatigue, MS relapse, and nasopharyngitis (ISS, p.186). Biogen reported that in trial 109MS101 the AEs reported by >10% of subjects were flushing, headache, and vomiting. (Study Report 109MS101, Table 14-25, pp.135-6).

Psoriasis
In trial BG-PK-01/02, the most commonly reported AEs included flushing, headache, and pruritis (Study Report BG-PK-01/02, p.85).

RA
In RA trial 109RA201, the AEs reported by at least 5% of BG00012 subjects were flushing and GI events (nausea, abdominal pain, diarrhea, and vomiting), increased ALT, nasopharyngitis, pruritus, and UTI (ISS, p.186).

7.4.2 Laboratory Findings

Hematology

Reviewer Summary
BG00012 causes declines in lymphocyte counts. Evidence from both MS and Psoriasis controlled trials revealed mean declines from baseline in lymphocyte counts among BG00012 patients that were not seen in placebo patients. In addition, BG00012 patients had greater percentages of low outliers for lymphocyte counts compared to placebo. Among MS patients in the BG00012 BID group, the mean decline from baseline in lymphocyte counts at week 48 was approximately 30%. Mean lymphocyte counts in Pool A MS trials began declining at week 4 (first lab data collection in MS controlled trials), continued to decline until week 48 and exhibited little additional decline thereafter. Lab data suggested that patients' lymphocyte counts increased after stopping BG00012, but did not completely recover during the 4 week post-last dose observation period. The magnitude of the observed lymphocyte count decline with BG00012 is within the range of declines described for fingolimod and teriflunomide, two recently approved MS treatments.

In MS and Psoriasis controlled trials, BG00012 patients experienced small declines in neutrophils, hemoglobin, hematocrit and platelets compared to placebo. BG00012 use was also associated with an early, transient increase in eosinophil count during the first 4 weeks of treatment.

Results
Mean change from Baseline

Pool A MS trials
Biogen provided Table 105, which summarized the mean change from baseline for the studied hematology tests, stratified by treatment and for each visit during the Pool A trials. In the Pool A MS trials, BG00012 subjects experienced mean declines in WBCs, driven by declining lymphocytes. In addition, the data demonstrate more modest declines in neutrophils, hemoglobin, hematocrit, and platelets. I summarize the mean change data from Pool A trials in the table below.

MS Pool A, Select Hematology Lab Parameters, Mean change from Baseline

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
WBC ($x10^9$/L)					
Week 4	0.31 (730)	0.19 (777)	0.24 (1631)	0.10 (805)	0.18 (332)
Week 8	-0.29 (693)	-0.33 (727)	-0.32 (1543)	0.14 (790)	0.38 (328)
Week 12	-0.37 (697)	-0.52 (718)	-0.47 (1536)	0.12 (788)	0.14 (324)
Week 24	-0.74 (664)	-0.62 (700)	-0.72 (1475)	0.07 (756)	0.25 (315)
Week 48	-0.94 (609)	-0.87 (604)	-0.90 (1213)	0.01 (608)	-0.04 (298)
Week 60	-0.87 (594)	-0.84 (584)	-0.85 (1178)	0.16 (565)	-0.02 (286)
Week 96	-0.97 (526)	-0.88 (503)	-0.93 (1029)	0.18 (479)	0.24 (251)
Lymphocytes ($x10^9$/L)					
Week 4	-0.05 (729)	-0.10 (777)	-0.07 (1630)	0.04 (803)	-0.01 (332)
Week 8	-0.19 (693)	-0.19 (727)	-0.19 (1543)	0.04 (789)	0.04 (328)
Week 12	-0.30 (697)	-0.30 (718)	-0.30 (1536)	0.04 (787)	-0.04 (324)
Week 24	-0.49 (664)	-0.40 (700)	-0.45 (1475)	0.05 (756)	0.00 (315)
Week 48	-0.63 (609)	-0.54 (604)	-0.58 (1213)	0.02 (607)	-0.06 (298)
Week 60	-0.60 (594)	-0.53 (584)	-0.57 (1178)	0.08 (565)	0.02 (286)
Week 96	-0.66 (526)	-0.58 (503)	-0.62 (1029)	0.02 (479)	0.04 (251)
Neutrophils ($x10^9$/L)					
Week 4	0.13 (729)	0.11 (777)	0.11 (1630)	0.03 (803)	0.13 (332)
Week 8	-0.13 (693)	-0.19 (727)	-0.16 (1543)	0.07 (789)	0.21 (328)
Week 12	-0.08 (697)	-0.23 (718)	-0.18 (1536)	0.06 (787)	0.08 (324)
Week 24	-0.22 (664)	-0.20 (700)	-0.24 (1475)	0.03 (756)	0.28 (315)
Week 48	-0.25 (609)	-0.28 (604)	-0.27 (1213)	-0.01 (607)	-0.01 (298)
Week 60	-0.22 (594)	-0.28 (584)	-0.25 (1178)	0.07 (565)	-0.09 (286)
Week 96	-0.27 (526)	-0.27 (503)	-0.27 (1029)	0.15 (479)	0.15 (251)
Eosinophils ($x10^9$/L)					
Week 4	0.19 (729)	0.15 (777)	0.17 (1630)	0.00 (803)	0.06 (332)

Week 8	0.02 (693)	0.01 (727)	0.01 (1543)	0.00 (789)	0.11 (328)
Week 12	0.00 (697)	0.00 (718)	0.00 (1536)	0.00 (787)	0.08 (324)
Week 24	-0.02 (664)	-0.02 (700)	-0.02 (1475)	0.00 (756)	0.06 (315)
Week 48	-0.02 (609)	-0.02 (604)	-0.02 (1213)	0.00 (607)	0.04 (298)
Week 60	-0.02 (594)	-0.02 (584)	-0.02 (1178)	0.00 (565)	0.04 (286)
Week 96	-0.01 (526)	-0.01 (503)	-0.01 (1029)	0.00 (479)	0.04 (251)
Hemoglobin (g/L)					
Week 4	-2.65 (730)	-2.90 (777)	-2.63 (1631)	-0.45 (805)	-1.95 (332)
Week 8	-2.31 (693)	-2.52 (727)	-2.31 (1543)	-0.16 (790)	-1.90 (328)
Week 12	-1.64 (697)	-1.76 (718)	-1.64 (1536)	-0.41 (788)	-1.78 (324)
Week 24	-2.56 (664)	-2.78 (700)	-2.66 (1475)	-0.87 (756)	-1.24 (315)
Week 48	-1.53 (608)	-2.11 (604)	-1.82 (1212)	-0.06 (608)	-2.52 (297)
Week 60	-2.43 (592)	-2.06 (582)	-2.25 (1174)	-0.48 (565)	-1.65 (284)
Week 96	-1.27 (526)	-2.12 (503)	-1.68 (1029)	0.02 (479)	-1.71 (251)
Hematocrit (%)					
Week 4	-0.43 (717)	-0.48 (770)	-0.44 (1607)	0.15 (794)	-0.35 (327)
Week 8	-0.29 (688)	-0.45 (724)	-0.33 (1535)	0.18 (781)	-0.61 (326)
Week 12	-0.35 (686)	-0.51 (710)	-0.37 (1513)	-0.04 (774)	-0.60 (321)
Week 24	-0.64 (658)	-0.77 (694)	-0.63 (1462)	0.01 (745)	-0.62 (310)
Week 48	-0.35 (604)	-0.63 (601)	-0.49 (1205)	0.25 (598)	-0.03 (295)
Week 60	-0.13 (564)	-0.33 (562)	-0.23 (1126)	0.31 (517)	-0.13 (274)
Week 96	0.14 (518)	-0.20 (497)	-0.03 (1015)	0.72 (473)	0.12 (250)
Platelets ($x10^9$/L)					
Week 4	6.07 (718)	9.20 (772)	7.46 (1614)	0.12 (800)	0.76 (328)
Week 8	-2.35 (689)	-1.10 (724)	-1.90 (1535)	2.00 (783)	-0.85 (324)
Week 12	-5.74 (692)	-5.37 (713)	-6.03 (1525)	3.34 (784)	2.17 (321)
Week 24	-7.69 (657)	-6.23 (698)	-8.78 (1465)	0.46 (750)	4.62 (314)
Week 48	-9.81 (606)	-6.38 (601)	-8.10 (1207)	4.04 (603)	4.88 (294)
Week 60	-8.86 (590)	-6.93 (578)	-7.91 (1168)	5.03 (561)	-0.64 (285)
Week 96	-14.94 (524)	-13.50 (500)	-14.24 (1024)	-1.62 (478)	-1.42 (248)

Data from ISS Appendix Table 105
Although included in Table 105, the above table does not include a separate column for the low dose BG0012 subjects, but column "BG0012 Total" includes data for these n=128 subjects. In addition, I omitted data from study weeks 36, 72, 84 in the above table

Biogen noted that the mean lymphocyte count at baseline for the BG00012 BID subjects at baseline was 1.97 $x10^9$/L at baseline and was 1.34 $x10^9$/L at week 48, for a mean decline of 0.63 $x10^9$/L, which is a 30% mean decrease from baseline (ISS, p.105). The mean decline was 34% at week 96.

Pool C Psoriasis Trials
The Pool C data included fewer treated subjects, and shorter trial durations compared to Pool A. As observed in the MS Pool A data, BG00012 subjects in the Pool C Psoriasis trials experienced greater mean decreases in WBCs, lymphocytes, hemoglobin and hematocrit compared to placebo subjects. As opposed to the findings for Pool A data, Pool C trials did not demonstrate greater declines in platelets among BG00012 subjects compared to placebo. I provide those results below.

Psoriasis Pool C, Select Hematology Lab Parameters, Mean change from Baseline

Study Week	Treatment			
	BG00012 Low doses (n)	BG00012 TID (n)	BG00012 Total(n)	Placebo (n)
WBC ($x10^9$/L)				
Week 2	-0.021 (71)	0.116 (136)	0.069 (207)	-0.016 (102)
Week 4	-0.084 (70)	-0.130 (132)	-0.114 (202)	-0.004 (96)
Week 8	-0.187 (68)	-0.347 (127)	-0.291 (195)	0.091 (97)
Week 12	-0.468 (51)	-0.564 (118)	-0.535 (169)	0.095 (76)
Lymphocytes ($x10^9$/L)				
Week 2	0.021 (71)	-0.141 (130)	-0.084 (201)	0.045 (101)
Week 4	0.010 (70)	-0.164 (127)	-0.102 (197)	0.010 (95)
Week 8	-0.193 (68)	-0.208 (124)	-0.203 (192)	-0.006 (97)
Week 12	-0.299 (51)	-0.286 (114)	-0.290 (165)	0.067 (76)
Neutrophils ($x10^9$/L)				
Week 2	-0.140 (71)	0.147 (130)	0.045 (201)	-0.078 (101)
Week 4	-0.213 (70)	-0.120 (127)	-0.153 (197)	-0.097 (95)
Week 8	-0.043 (67)	-0.136 (124)	-0.104 (191)	0.047 (97)
Week 12	-0.163 (51)	-0.188 (114)	-0.180 (165)	-0.016 (76)
Eosinophils ($x10^9$/L)				
Week 2	0.042 (71)	0.045 (130)	0.044 (201)	0.024 (101)
Week 4	0.074 (70)	0.101 (127)	0.091 (197)	0.040 (95)
Week 8	0.025 (66)	-0.016 (124)	-0.002 (190)	0.023 (97)
Week 12	0.020 (51)	-0.025 (114)	-0.011 (165)	0.051 (76)
Hemoglobin (g/L)				
Week 2	-0.37 (71)	-2.93 (136)	-2.05 (207)	-0.38 (102)
Week 4	-1.46 (70)	-2.63 (132)	-2.22 (202)	-1.52 (96)
Week 8	-0.84 (68)	-1.43 (127)	-1.23 (195)	-0.76 (97)
Week 12	1.37 (51)	-0.66 (118)	-0.05 (169)	-1.21 (76)
Hematocrit (%)				
Week 2	-0.4 (71)	-0.9 (136)	-0.8 (207)	-0.3 (102)
Week 4	-0.8 (70)	-0.9 (132)	-0.9 (202)	-0.5 (96)
Week 8	-0.8 (68)	-0.6 (127)	-0.7 (195)	-0.3 (97)
Week 12	-0.2 (51)	-0.3 (118)	-0.3 (169)	-0.5 (76)
Platelets ($x10^9$/L)				
Week 2	-	5.8 (100)	5.8 (100)	-1.2 (68)
Week 4	-	4.0 (98)	4.0 (98)	-5.9 (63)
Week 8	-	4.3 (93)	4.3 (93)	-5.0 (63)
Week 12	-	-3.9 (93)	-3.9 (93)	-6.1 (60)

From ISS Appendix Table 240

Outliers

Biogen provided tables of low/high outlier risks for post baseline hematological lab results. Biogen referred to the outlier cutoffs as potentially clinically significant (PCS) values (ISS, p.109). Biogen used the following PCS values for the hematology outlier analyses:

Potentially clinically significant hematology laboratory abnormalities for Pools A-D (threshold values of: WBC: <=2.0 and >= 16 x 10^9/L; lymphocytes: <0.8, <0.5, >12 x 10^9/L; neutrophils: <=1.0, <1.5, >=12 x 10^9/L; RBC: <=3.3, >=6.8 x 10^9/L; hemoglobin: <= 100 g/L; platelet count: <=100, >=600 x 10^9/L) (ISS, p.8603)

Pool A MS Trials
Outlier analyses demonstrated that BG00012 subjects in Pool A were at greater risk for low WBC and low lymphocyte count results compared to placebo. Despite the mean change differences noted above, in Pool A there did not appear to be marked differences in risk for low outliers when comparing placebo and BG00012 subjects for neutrophils, hemoglobin, hematocrit or platelets. In order to better characterize the tails of the result distributions, I used the lab dataset ADLB03, to identify outliers using more extreme cutoff values for select parameters. I include the results of my analyses for neutrophils <0.5, hemoglobin <=80, and platelets <=75 along with the results of Biogen's analyses in the table below.

MS Pool A, Select Hematology Lab Parameters, High/Low Outlier Risks

Parameter	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
WBC(x10^9/L)	N=128	N=757	N=805	N=1690	N=830	N=347
<3.0	5% (6)	7% (54)	5% (42)	6% (102)	1% (10)	2% (7)
≥16	0	2% (15)	2% (20)	2% (35)	4% (31)	3% (10)
Lymphocytes(x10^9/L)	N=128	N=757	N=805	N=1690	N=830	N=347
<0.8	13% (16)	28% (209)	21% (170)	23% (395)	3% (22)	4% (13)
<0.5	2% (2)	6% (43)	3% (24)	4% (69)	<1% (4)	<1% (1)
>12	0	0	0	0	0	0
Neutrophils(x10^9/L)	N=128	N=757	N=805	N=1690	N=830	N=347
<1.5	2% (3)	3% (20)	3% (22)	3% (45)	2% (14)	2% (8)
≤1.0	0	<1% (6)	<1% (5)	<1% (11)	<1% (5)	<1% (3)
≤0.5	0	0	0	0	0	0
≥12	2% (2)	3% (26)	3% (27)	3% (55)	5% (42)	3% (10)
Hemoglobin (g/L)	N=128	N=757	N=805	N=1690	N=830	N=347
≤100	0	5% (36)	4% (31)	4% (67)	4% (34)	3% (12)
≤80	0	<1% (5)	<1% (6)	<1% (11)	<1% (3)	<1% (3)
Platelets (x10^9/L)	N=127	N=754	N=805	N=1686	N=830	N=345
≤100	0	<1% (6)	<1% (1)	<1% (7)	<1% (4)	<1% (3)
≤75	0	<1% (2)	0	<1% (2)	<1% (1)	0
≥600	0	<1% (2)	<1% (2)	<1% (4)	1% (10)	<1% (2)

From ISS Table 20, pp.111-112 and data set ADLB03.

Biogen did not provide an outlier analysis for eosinophils so I performed one using lab data set ADLB03. I identified those Pool A subjects with an eosinophil result ≥2x ULN of normal. Given the results of the mean change from baseline data that suggested a transient, early increase in eosinophils, I examined the results by study visit and

focused on the first 3 visits. I found that the vast majority of high outliers were reported during week 4, with few additional high outliers during the subsequent weeks of the trials. I provide the eosinophil high outlier results for weeks 4, 8, and 12 below.

MS Pool A, Eosinophil ≥2x ULN, for Study Weeks 4,8,12

	Treatment					
Study Week	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
4	2.6% (3/122)	5.5% (38/696)	3.9% (29/738)	4.5% (70/1556)	<1% (1/786)	0/313
8	<1% (1/122)	<1% (2/665)	<1% (2/707)	<1% (5/1494)	<1% (2/773)	<1% (2/305)
12	(0/120)	<1% (2/675)	(0/703)	<1% (2/1498)	(0/757)	<1% (1/304)

Reviewer analysis using ADLB03

Pool C Psoriasis Trials
Outlier analyses support that along with the mean change differences described above, BG00012 subjects in Pool C were at greater risk for low WBC and low lymphocyte count results compared to placebo. I summarize those results below. No Psoriasis subjects had a post baseline hemoglobin <=100, platelet count <=100, or >=600.

Psoriasis Pool C, Select Hematology Lab Parameters, High/Low Outlier Risks

Parameter	Treatment			
	BG00012			Placebo
	Low doses	240mg TID	Total	
WBC($x10^9$/L)	N=72	N=140	N=212	N=104
<3.0	3% (2)	2% (3)	2% (5)	<1% (1)
≥16	0	<1% (1)	<1% (1)	0
Lymphocytes($x10^9$/L)	N=72	N=140	N=212	N=104
<0.8	18% (13)	15% (21)	12% (25)	8% (8)
<0.5	0	3% (4)	2% (4)	<1% (1)
>12	0	0	0	0
Neutrophils($x10^9$/L)	N=72	N=140	N=212	N=104
<1.5	18% (13)	3% (4)	8% (17)	7% (7)
≤1.0	13% (9)	1% (2)	5% (11)	4% (4)
≥12	1% (1)	2% (3)	2% (4)	0

From ISS Table 30, p.164.

Shift analyses
The shift analyses identified subjects who “shifted” from having a normal (WNL) or low (< LLN) result for a lab test at baseline to at least one high (>ULN) result during treatment; and those who “shifted” from normal (WNL) or high (>ULN) result at baseline to at least one low (<LLN) result during treatment.

Pool A MS Trials
Biogen reported that in Pool A, compared to placebo, higher percentages of subjects in the BG00012 BID and TID groups experienced shifts to low in WBC counts (7% placebo, 21% BID, 19% TID) and lymphocyte counts (4% placebo, 37% BID, 28% TID). Also, the percentage of subjects with shifts to low in neutrophil counts was slightly higher with BG00012 than with placebo (7% placebo, 11% BID and TID).
Biogen also found that a higher percentage of subjects in the BG00012 BID and TID and GA groups than in the placebo group had shifts to high in eosinophil counts (3% placebo, 13% BID, 10% TID, GA group 9%).

Pool C Psoriasis Trials
Compared with placebo, a higher percentage of subjects in the BG00012 TID group in Pool C had shifts to low in WBC counts (5% placebo, 12% BG00012 TID), and lymphocyte percentage (14% placebo, 19% BG00012 TID). Shifts to high in monocyte percentage (25% placebo, 30% BG00012 TID) and eosinophil percentage (17% placebo, 22% BG00012 TID) were more common among BG00012-treated subjects.

Recovery of lymphocyte counts
Biogen provided 3 analyses that examined recovery of lymphocyte counts after stopping BG00012 (ISS, p.113). These results suggest improvement in lymphocyte count following discontinuation, but not complete recovery to baseline values. Given the available data, it is not possible to determine the duration of the decrement in lymphocyte counts. I summarize those results below.

In the 133 MS patients who completed 2 years of treatment in studies 301 and 302, and who had baseline, post-baseline, and 4 week post last dose lymphocyte counts, the mean percentage decrease at the last treatment visit was 31.3%. At 4 weeks post last dose, the mean percentage decrease in lymphocyte counts was 25.6%, suggesting an increase in lymphocyte counts following discontinuation of BG00012.

In those 130 MS patients who completed one year of treatment in Study 1900 (parts 1 and 2), and who had baseline, post-baseline, and 4 week post last dose lymphocyte counts, the mean percentage decrease at the last treatment visit was 28.2%. At 4 weeks post last dose, the mean percentage decrease in lymphocyte counts was 17.9%, suggesting an increase in lymphocyte counts following discontinuation of BG00012. Biogen notes that 89 of these 130 subjects received “lower doses” (120mg Q day or 120mg TID) of BG00012 in this trial.

In the 299 MS Pool A subjects who had baseline, post-baseline, and > 2 week post last dose lymphocyte counts, the mean percentage decrease in lymphocyte counts was 22.6%. At 4 weeks post last dose, the mean percentage decrease in lymphocyte counts was 19.3%, suggesting an increase in lymphocyte counts following discontinuation of BG00012.

Lymphocyte decline relative to fingolimod, teriflunomide
Fingolimod and teriflunomide, recently approved MS treatments, are also associated with declines in lymphocyte counts. In reviewing labeling and safety reviews for these drugs, I determined that the decline in lymphocyte count with BG00012 is within the range described for fingolimod and teriflunomide. In the fingolimod NDA safety review, Dr. Villalba reported that the mean lymphocyte count decline from baseline at 6 months for the 1.25mg group was -1.4 $x10^9$/L and for the 0.5mg dose group was -1.3 $x10^9$/L (Fingolimod NDA safety review p.162). In addition, an outlier analysis using a lymphocyte count cutoff of <0.2$x10^9$/L found 29% (273/943) of patients receiving fingolimod 1.25mg and 17% (142/854) receiving 0.5mg met this criterion (Fingolimod NDA safety review Table 69, p.167). The teriflunomide label explains that a lymphocyte count <0.8$x10^9$/L was observed in 7% and 10% of patients on teriflunomide 7mg and 14mg, respectively compared with 5% on placebo.

Adverse events related to hematological test results

MS Pools A and B
No BG00012 subjects in MS Pools A/B experienced an SAE related to hematological test results. Biogen reported that 4 BG00012 subjects discontinued for AEs related to low WBC or lymphocyte counts.

Subject 508-421 (trial 302), a 46 year old female, discontinued for WBC decreased. Her baseline WBC count was 4.12. Her WBC count slowly declined through the study and reached 2.87 on day 85. On the day of her last dose of study drug (day 139) her WBC count was 2.98. 54 days after stopping study drug her WBC count was 3.11.

Subject 194-302 (trial 303) a 34 year old female, discontinued for increased ALT/AST, increased LDH, increased GGT, and decreased lymphocyte count, decreased neutrophil count, decreased WBC count. This subject completed controlled trial 301 where she received placebo. During that time she experienced transient elevation of transaminases (AST 273, ALT 304) that resolved. After enrolling in open label trial 303, on study day 29, her ALT was 51 and AST 37. On study day 88, her ALT was 482, AST 276, LDH 243 and GGT 78. She also had a WBC count of 1.99, lymphocyte count of 0.59, and neutrophil count of 1.04. Study treatment was stopped on day 90. On day 144, ALT was 52 and all other LFTs and hematology tests were within normal limits.

Subject 427-302 (trial 303) a 55 year old female, completed RCT 301 and enrolled in OL trial 303. During trial 301, she received BG00012, 240mg TID. Her WBC count and lymphocyte count were normal at baseline (WBC 4.41, lymphocyte count 1.75) and decreased during the trial with the lowest recorded value for WBC count being 3.07 and lymphocyte count 0.69 (study day 562). During this trial she had an AE of lymphopenia (days 478-562) that led to treatment being temporarily held. On the last day of trial 301/first day of trial 303, her WBC count was 3.81, and lymphocyte count was 0.88.

During trial 303, on study day 171, her WBC count dropped to 3.04 and lymphocyte count to 0.63. At this time, the investigator reported lymphopenia as an AE. On study day 185, her lymphocyte count was 0.67, and on study day 252 it was 0.76. The only infection related AE that she experienced around this time was a non-serious event of bronchitis (start day 227, end day 242). Study treatment was discontinued on day 298. Approximately 1 month after discontinuation, her lymphocyte count was 0.84.

Subject 505-317 (trial 303) a 49 year old female with a history of leukopenia, completed RCT 301 and enrolled in OL trial 303. During trial 301, she received BG00012, 240mg BID. For trial 301, her baseline WBC count was 3.81 and lymphocyte count was 1.2. During trial 301, she had an AE of leucopenia (WBC 3.11, lymphocytes 1.09) on study day 27 that was not resolved at the end of the study. For trial 303, her baseline WBC count was 2.12 and lymphocyte count was 0.26. On study day 85, her WBC was 1.81 and lymphocyte count was 0.5 and the investigator recorded an AE of exacerbation of leucopenia. On study day 174, her WBC count declined to 1.47, with a lymphocyte count of 0.27, and 7 days later she was discontinued from the trial. At her follow up visit 15 days later, her WBC count was 1.91 and lymphocyte count was 0.43.

In the common AE table, hematological AEs were included in 2 separate body systems, Blood and Lymphatic System Disorders, and Investigations. In the table below, I summarize the results for declines in hematological parameters that were reported as AEs as well as for increased eosinophils. There did not appear to be robust evidence of differences in reporting by treatment for these AEs.

MS Pool A Hematological Common AEs

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Investigations	7% (9)	28% (212)	28% (228)	26% (449)	25% (205)	30%(106)
WBC dec	<1% (1)	2% (13)	2% (15)	2% (29)	<1% (1)	<1% (1)
Lymphocyte dec	0	1% (9)	<1% (8)	<1% (17)	<1% (1)	<1% (1)
Hgb dec	0	1% (8)	<1% (6)	<1% (14)	<1% (5)	<1% (1)
Hct dec	0	<1% (6)	<1% (3)	<1% (9)	<1% (4)	<1% (1)
Neutrophil dec	0	<1% (6)	<1% (2)	<1% (8)	<1% (2)	<1% (1)
Platelets dec	0	<1% (4)	0	<1% (4)	<1% (2)	<1% (3)
Eosinophils inc	<1% (1)	<1% (2)	<1% (3)	<1% (6)	<1% (2)	0
Blood & Lymphatic System Disorders	4% (5)	7% (51)	7% (59)	7% (115)	5% (40)	3% (11)
Lymphopenia	<1% (1)	2% (18)	2% (20)	2% (39)	<1% (2)	0
Anemia	<1% (1)	2% (13)	3% (21)	2% (35)	2% (15)	1% (4)
Leukopenia	0	<1% (7)	1% (11)	1% (18)	<1% (1)	0
Neutropenia	<1% (1)	<1% (1)	<1% (4)	<1% (6)	<1% (1)	0
Thrombo-cytopenia	0	<1% (2)	0	<1% (2)	0	<1% (1)

Eosinophilia	<1% (1)	<1% (3)	<1% (5)	<1% (9)	<1% (1)	0

From ISS Appendix Table 24

Psoriasis Pools C/D
No BG00012 subjects in Psoriasis Pools C/D experienced an SAE related to a hematological test result. As noted above, reasons for discontinuations were not recorded in these trials so it is not know how many subjects discontinued for hematological test result abnormalities.

In the common AE table, hematological AEs were included in 2 separate body systems, Blood and Lymphatic System Disorders, and Investigations. In the table below, I summarize the results for declines in hematological parameters that were reported as AEs as well as for increased eosinophils. There did not appear to be robust evidence of differences in reporting by treatment for these AEs.

Psoriasis Pool C Hematological Common AEs

	BG00012			PBO
	Low dose	240mg TID	Total	
	N=72	N=141	N=213	N=106
Investigations	17% (12)	6% (8)	9% (20)	10% (11)
Lymphocyte dec	0	0	0	<1% (1)
Hct dec	1% (1)	0	<1% (1)	0
Blood & Lymphatic System Disorders	21% (15)	7% (10)	12% (25)	6% (6)
Lymphopenia	3% (2)	2% (3)	2% (5)	0
Leukopenia	4% (3)	1% (2)	2% (5)	2% (2)
Neutropenia	3% (2)	1% (2)	2% (4)	6% (6)
Eosinophilia	6% (4)	3% (4)	7% (10)	0

From ISS Appendix Table 214

Chemistry
Note: I present a review of transaminases, billiubin, and ALP in the special section reviewing the potential for liver injury with BG00012. In addition, I review the kidney related lab data (creatinine, BUN, urinalysis, B2 microglobulin, and albumin) in the special section reviewing the potential for renal injury.

Reviewer Summary
BG00012 did not appear to affect sodium, potassium, magnesium, phosphorus, glucose, total cholesterol, or uric acid. The observed mean change differences for chloride and triglycerides (more negative compared to placebo) and bicarbonate (more positive early and less negative late compared to placebo) were small and did not appear to be clinically important. There did not appear to be meaningful differences in the percentages of patients with outliers for chloride (low). Despite increased percentages of BG00012 patients with outliers for bicarbonate at less extreme cutoffs (ULN-32mmol/L, 32-34 mmol/L), there did not appear to be differences using the

highest cutoff (>34mmol/L). BG00012 patients were not at increased risk of AEs related to elevated bicarbonate (nephrolithiasis, metabolic alkalosis, bone pain, or lethargy).

Results
Mean change from Baseline

MS Pool A
Biogen did not identify any notable differences in mean changes from baseline by treatment for serum chemistry tests collected during Pool A MS RCTs. I reviewed the mean change from baseline results in Appendix Table 125, and there did not appear to be important differences by treatment for sodium, potassium, magnesium, phosphorus, glucose, total cholesterol, or uric acid. Among BG00012 subjects, chloride and triglycerides had persistently more negative changes from baseline compared to placebo. Bicarbonate appeared to increase more for BG00012 subjects compared to placebo (early) and decrease less than placebo (late). I summarize those data below.

MS Pool A, Select Chemistry Lab Parameters, Mean change from Baseline

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
Chloride					
Week 4	-0.05 (734)	-0.20 (793)	-0.15 (1652)	0.12 (817)	0.13 (339)
Week 12	-0.33 (692)	-0.23 (728)	-0.25 (1543)	0.13 (786)	0.44
Week 24	-0.32 (658)	-0.42 (693)	-0.40 (1465)	0.07 (741)	0.32 (316)
Week 52	-0.46 (577)	-0.42 (576))	-0.44 (1153)	-0.01 (567)	0.29 (288)
Week 96	-0.29 (533)	-0.25 (523)	-0.27 (1056)	-0.03 (490)	-0.09 (263)
Bicarbonate					
Week 4	0.53 (731)	0.48 (787)	0.46 (1642)	0.17 (815)	0.16 (335)
Week 12	0.49 (689)	0.41 (721)	0.39 (1530)	0.13 (779)	0.11 (322)
Week 24	0.55 (654)	0.63 (686)	0.48 (1453)	0.03 (738)	0.23 (315)
Week 52	-1.27 (574)	-1.08 (572)	-1.17 (1146)	-1.48 (557)	-1.89 (286)
Week 96	-0.01 (531)	-0.06 (516)	-0.03 (1047)	-0.29 (488)	-0.25 (259)
Triglycerides					
Week 4	-0.16 (737)	-0.14 (734)	-0.15 (1471)	0.02 (756)	-0.02 (339)
Week 12	-0.14 (693)	-0.12 (671)	-0.13 (1364)	-0.03 (722)	-0.06 (328)
Week 24	-0.15 (672)	-0.13 (656)	-0.14 (1328)	0.00 (704)	-0.03 (319)
Week 48	-0.14 (625)	-0.11 (620)	-0.12 (1245)	0.06 (618)	0.00 (304)
Week 96	-0.15 (532)	-0.14 (522)	-0.14 (1054)	0.05 (491)	-0.03 (262)

Data from ISS Appendix Table 125

Although included in Table 125, the above table does not include a separate column for the low dose BG0012 subjects, but column “BG0012 Total” includes data for these n=128 subjects for some parameters. Table 125 provided data for additional study weeks, but I provide data only for select study weeks

Psoriasis Pool C
For Psoriasis Pool C data, Biogen provided mean change from baseline analyses for only sodium and potassium. The mean change from baseline for these 2 analytes were unremarkable (ISS Appendix Table 252).

Outliers
Biogen did not provide analyses of PCS chemistry results in their NDA submission. In response to a Division request, in an 8/28/12 submission Biogen provided tables of chemistry outlier results using NIH Common Terminology Criteria for Adverse Events (CTCAE). The majority of these analyses found no differences in outliers among the different treatment groups in the MS Pool A trials. Biogen noted among BG00012 patients, a slight increase in the percentage of patients with bicarbonate values> ULN-32 mmol/L (placebo 7%, BID 11%, TID 11%, GA 8%) and >32-34mmol/L (Placebo 2%, BID 5%, TID 3%, GA 2%) but no difference above 34mmol/L (8/28/12 submission, p.4). Biogen also reported that there were no differences by treatment for AEs potentially associated with increased bicarbonate (e.g., renal calculi, metabolic alkalosis, bone pain, lethargy).

Shift Analyses
In table 133, Biogen summarized shift data for chemistry parameters in MS Pool A trials. Aside from bicarbonate, there did not appear to be meaningful differences in shifts across treatments. BG00012 subjects appear more likely to shift high for bicarbonate compared to placebo or GA subjects.

MS Pool A Shift data, chemistry

Parameter	Treatment									
	BG00012 BID		BG00012 TID		BG00012 Total		Placebo		GA	
	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high
Sodium	1%	11%	2%	10%	1%	10%	<1%	9%	<1%	13%
Potassium	3%	8%	5%	8%	4%	8%	2%	6%	3%	9%
Chloride	<1%	2%	1%	2%	<1%	2%	<1%	3%	<1%	2%
Bicarbonate	8%	16%	8%	15%	8%	14%	8%	9%	10%	10%
Magnesium	<1%	0	<1%	0	<1%	0	<1%	0	0	0
Glucose	24%	40%	20%	41%	22%	40%	24%	37%	20%	34%
Cholesterol	16%	15%	18%	17%	17%	16%	16%	18%	19%	13%
Triglycerides	13%	16%	11%	17%	12%	17%	7%	22%	9%	25%
Uric acid	5%	4%	4%	5%	4%	5%	4%	4%	6%	6%

Data from ISS Appendix Table 133

Special Chemistry Tests

PTH and Vitamin D

BG00012 exposed trial subjects experienced greater mean increases in PTH and were more likely to have PTH results that were >ULN. Over 20% of BG00012 subjects had PTH >ULN compared to 17% of GA subjects and 9% of placebo subjects. BG00012 subjects were also more likely than other subjects to have elevated PTH at both study weeks 48 and 96. Analyses also demonstrated what appeared to be a dose response for these findings. In addition, BG00012 subjects experienced Vitamin D<LLN. BG00012 subjects did not experience notable differences in calcium results compared to placebo or GA subjects.

Given the lack of evidence of corresponding elevated calcium results, the elevated PTH appears to represent a secondary hyperparathyroidism. BG00012 treated subjects were more likely to have Vitamin D levels <LLN. Vitamin D deficiency resulting in hypocalcemia is a recognized etiology of secondary hyperparathyroidism, but in these BG00012 patients the two abnormalities were not commonly seen occurring at the same time in the same subject.

The clinical importance of the observed increased PTH and decreased Vitamin D are not known. There did not appear to be among BG00012 subjects an increased risk for AEs potentially associated with hyperparathyroidism. Although the difference in percentage of BG00012 patients with elevated PTH compared to placebo was notable, it was less pronounced compared to GA, which has not been previously recognized to be associated with increased PTH. Further complicating our understanding of these results is the evolving understanding of the role of Vitamin D in MS.

Background
Biogen explained that because of proliferative parathyroid changes in rats (attributed to end stage renal failure) in the 2-year carcinogenicity study, BG00012 clinical trials 109MS301 and 109MS302 included parathyroid hormone (PTH) and vitamin D measurements. Specifically, Biogen noted the following:

> As a consequence of the pathologic changes in the kidney, a dose-related increase in incidence of parathyroid hyperplasia was observed in males and females, and parathyroid adenoma was observed in 1 and 3 males in the 50 and 150 mg/kg/day groups, respectively (Table 50). Renal failure is the most common cause of secondary hyperparathyroidism and it is attributed to renal failure-induced hyperphosphatemia (Silver et al. 1997). Hyperphosphatemia results in hypocalcemia, which in turn triggers increased parathyroid gland activity, evidence of the effects of parathyroid hormone and parathyroid gland hyperplasia or neoplasia. The low number of adenomas was not statistically significant. The incidence of adenoma was within the range of the published historical control tumor data of Sprague-Dawley rats from the same vendor that provided the study animals (Table 50)(Toxicology Written Summary, p.69).

Parathyroid hormone is secreted by the parathyroid glands. Normally, low serum calcium levels stimulate release of PTH, and elevated calcium levels suppress PTH secretion. PTH acts directly to inhibit calcium excretion and phosphate and bicarbonate reabsorption by the kidney, stimulate production of Vitamin D by the kidney, and activate octeoclasts to release calcium from bone. PTH also acts indirectly, via Vitamin D, to increase intestinal absorption of calcium.

Hyperparathyroidism, a condition in which there is an increase in the secretion of parathyroid hormone, is divided into primary, secondary and tertiary categories. In primary hyperparathyroidism, the parathyroid glands inappropriately secrete PTH even though serum calcium is not low. The diagnosis is made by establishing both elevated PTH and serum calcium. Associated findings can include hypophosphatemia, increased 1,25 $(OH)_2D$, hypercalciuria, calcium nephrolithiasis, and reduced bone mineral density. The majority of primary hyperparathyroidism cases are due to a single parathyroid adenoma, with fewer cases due to multiple gland hyperplasia, and parathyroid carcinoma. Secondary hyperparathyroidism is an appropriate increase in PTH secretion in response to hypocalcemia due to Vitamin D deficiency or chronic renal failure. Patients with secondary hyperparathyroidism have elevated PTH and either eucalcemia or hypocalcemia. Tertiary hyperparathyroidism occurs in the setting of prolonged stimulation of parathyroid glands (chronic renal failure or Vitamin D deficiency) and is associated with hypercalcemia. Chronic stimulation results in parathyroid hyperplasia which can result in the parathyroid glands being resistant to the inhibitory effects of elevated serum calcium levels.[1]

Methods
Studies 109MS301 and 109MS302 required investigators to collect PTH and Vitamin D at baseline and weeks 48 and 96. Biogen provided mean change from baseline and shift tables for these parameters.

Results
BG00012 subjects had greater mean increases in PTH compared to placebo and GA at weeks 48 and 96. The BG00012 and GA subjects experienced mean declines in Vitamin D that were greater than the mean decline seen in placebo subjects. I summarize those data below. Biogen acknowledged the differences in mean changes from baseline for BG00012 and placebo but felt that “there were no clinically relevant changes in mean values for either parameter over time in the BG00012 BID and TID groups, and no meaningful differences from placebo or subjects who received GA (ISS p.125).

1 Andreoli and Carpenter’s Cecil Essentials of Medicine, 7th edition, Saunders Elsevier Copyright 2007

MS RCTs 109MS 301 and 109MS 302, Mean Change from Baseline for PTH and Vitamin D

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
PTH					
Week 48	7.97 (587)	10.40 (582)	9.18 (1169)	-0.96 (581)	3.11 (275)
Week 96	12.02 (452)	15.40 (441)	13.69 (893)	3.07 (415)	7.43 (223)
Vitamin D					
Week 48	-18.31 (561)	-24.69 (548)	-21.46 (1109)	0.58 (538)	-18.12 (270)
Week 96	-31.92 (433)	-36.17 (413)	-33.99 (846)	-20.97 (404)	-25.87 (219)

From ISS Appendix Table 141

Shift analyses demonstrated a higher percentage of BG00012 subjects who shifted to high for PTH compared to placebo or GA. Biogen did not comment on these findings. In addition, a higher percentage of BG00012 subjects shifted to low for vitamin D. I provide those results below.

MS RCTs 109MS 301 and 109MS 302, Shift from Low or Normal at Baseline to High on Treatment and from Normal or High at Baseline to Low on Treatment for PTH and Vitamin D

Parameter	Treatment									
	BG00012 BID		BG00012 TID		BG00012 Total		Placebo		GA	
	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high
PTH	<1%	19%	0	22%	<1%	21%	<1%	8%	0	17%
Vitamin D	8%	13%	10%	10%	9%	12%	5%	21%	4%	17%

From ISS Appendix Table 143

Using Biogen's ADLB05 dataset, I characterized the distribution of high outlier risk for PTH. Specifically, for those subjects with baseline and at least one on treatment PTH test result, I identified subjects that did not have elevated PTH at baseline, and that experienced one or more increased PTH >ULN, >1.5 x ULN, and >2 x ULN. BG00012 subjects had a greater frequency of high outliers for the cutoffs examined. I provide those results below.

MS RCTs 109MS 301 and 109MS 302, Percentage of Subjects by Treatment with PTH >ULN, >1.5 x ULN, and >2 x ULN

Parameter	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
PTH	n=577	n=583	n=1160	n=583	n=273
>ULN	19.8% (114)	22.8% (133)	21.3% (247)	8.6% (50)	16.8% (46)

>1.5xULN	3.5% (20)	4.6% (27)	4.1% (47)	0.9% (5)	1.5% (4)
>2xULN	1.0% (6)	0.7% (4)	0.9% (10)	0.2% (1)	0.4% (1)

Reviewer analysis using Dataset ADLB05

Since there were two scheduled on-treatment PTH measurements (Week 48 and week 96), I examined the outlier risk over time. For those patients with PTH that was not elevated at baseline, I determined the percentage, by treatment, with PTH >ULN at week 48 and at week 96. Compared to week 48, the percentage of patients with PTH above ULN at week 96 was higher in all treatment groups, with BG00012 subjects having the highest percentages of subjects with PTH>ULN. I summarize those data below.

MS RCTs 109MS 301 and 109MS 302, Percentage of Subjects by Treatment with PTH >ULN, week 48, week 96

>ULN	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
Week 48	11.1% (55/493)	12.7% (63/497)	11.9% (118/990)	3.9% (20/507)	6.6% (16/244)
Week 96	15.9% (72/454)	19.5% (92/473)	17.7% (164/927)	6.7% (30/447)	13.2% (30/227)

Reviewer analysis using Dataset ADLB05

To look for differences in persistence of elevated PTH by treatment, I identified the number of subjects with PTH>ULN at both weeks 48 and 96. A higher percentage of BG00012 subjects had a PTH>ULN at both weeks 48 and 96. I provide those results below.

MS RCTs 109MS 301 and 109MS 302, Percentage of Subjects by Treatment with PTH >ULN at both weeks 48 and 96

Parameter	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
PTH	n=454	n=473	n=927	n=447	n=227
>ULN at both weeks 48 and 96	4.4% (20)	5.9% (28)	5.1% (48)	1.3% (6)	1.8% (4)

Reviewer analysis using Dataset ADLB05

Given that the lab data support that BG0012 subjects had higher mean increases from baseline for PTH and that BG00012 subjects were more likely to have a high PTH outlier results, I examined more closely the lab results for calcium and phosphorus. In the Pool A MS studies, there did not appear to be marked differences in mean change from baseline by treatment for either calcium or phosphorus. I summarize those data below.

MS Pool A, Calcium and Phosphorus Mean change from Baseline

Study week	Treatment				
	BG00012 BID (n)	BG00012 TID (n)	BG00012 Total (n)	Placebo (n)	GA (n)
Calcium (mmol/L)					
Week 4	0.00 (712)	-0.01 (711)	0.00 (1423)	-0.01 (726)	-0.02 (336)
Week 12	0.01 (671)	0.01 (654)	0.01 (1325)	-0.01 (695)	-0.02 (325)
Week 24	0.00 (639)	0.00 (620)	0.00 (1259)	-0.02 (659)	-0.04 (315)
Week 48	-0.01 (587)	-0.02 (591)	-0.02 (1178)	-0.03 (586)	-0.06 (293)
Week 96	-0.01 (520)	-0.03 (512)	-0.02 (1032)	-0.03 (477)	-0.03 (260)
Phosphorus (mmol/L)					
Week 4	-0.01 (711)	-0.02 (709)	-0.01 (1420)	0.00 (725)	-0.03 (336)
Week 12	0.01 (670)	-0.02 (653)	-0.01 (1323)	-0.01 (695)	-0.03 (325)
Week 24	0.01 (638)	0.01 (618)	0.01 (1256)	0.00 (658)	-0.02 (314)
Week 48	0.01 (585)	0.00 (591)	0.00 (1176)	0.00 (585)	-0.03 (293)
Week 96	-0.01 (518)	-0.01 (511)	-0.01 (1029)	-0.01 (477)	-0.01 (260)

Data from ISS Appendix Table 125
Although included in Table 125, the above table does not include a separate column for the low dose BG0012 subjects, but column “BG0012 Total” includes data for these n=128 subjects for some parameters. Table 125 provided data for additional study weeks, but I provide data only for select study weeks

The shift analyses did not support differences by treatment in the percentages of patients that shifted higher or lower for calcium or phosphorus. I summarize those data below.

Pool A MS Trials, Calcium Shift from Low or Normal at Baseline to High on Treatment and from Normal or High at Baseline to Low on Treatment

	BG00012 BID		BG00012 TID		BG00012 Total		Placebo		GA	
	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high	Shift low	Shift high
Calcium	1%	8%	1%	6%	1%	7%	1%	5%	3%	7%
Phosphorus	6%	5%	8%	4%	7%	4%	7%	4%	6%	2%

Data from ISS Appendix Table 133

Given that the above analyses did not suggest differences in calcium results by treatment, for the overall Pool A population I decided to focus on patients with PTH>ULN. I examined calcium results in the subset of subjects with PTH>ULN. For the subjects with PTH>ULN at weeks 48 and 96, I identified their calcium test results from the same study weeks and examined the mean change from baseline and low and high outlier risk.

For subjects with PTH>ULN, there did not appear to be notable differences by treatment in calcium mean change from baseline, and the changes observed in this group were

similar to the changes seen in all study subjects at these visits (see above). I summarize those results below.

MS RCTs 109MS 301 and 109MS 302, Calcium Mean change from Baseline at Weeks 48 and 96 for subjects with PTH>ULN at those Visits

Study week	Treatment			
	BG00012 BID (n)	BG00012 TID (n)	Placebo (n)	GA (n)
Week 48	-0.02 (55)	-0.05 (63)	-0.03 (20)	-0.02 (336)
Week 96	-0.04 (72)	-0.05 (91)	-0.05 (29)	-0.06 (30)

Reviewer analysis using Datasets ADLB01 and ADLB05

In addition, I reviewed the datasets and determined that none of the subjects with PTH >ULN at weeks 48 or 96 had a calcium result that was >ULN or <LLN.

Since there were 2 scheduled on-treatment Vitamin D measurements (Week 48 and week 96), I examined the outlier risk over time. For those patients with Vitamin D that was not low at baseline, I determined the percentage, by treatment, with Vitamin D<LLN at week 48 and at week 96. Compared to week 48, the percentage of patients with Vitamin D <LLN at week 96 was higher in all treatment groups, with BG00012 subjects having the highest percentages <LLN. I summarize that data below.

MS RCTs 109MS 301 and 109MS 302, Percentage of Subjects by Treatment with Vitamin D<LLN, week 48 and week 96

>ULN	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
Week 48	4.2% (24/573)	4.8% (27/557)	4.5% (51/1130)	3.2% (19/585)	1.8% (5/284)
Week 96	6.9% (38/547)	7.8% (42/538)	7.4% (80/1085)	3.7% (20/542)	3.3% (9/274)

Reviewer analysis using Dataset ADLB05

To examine the association of PTH results and Vitamin D, I determined the percentage of BG00012 patients with post baseline PTH>ULN who also experienced post baseline Vitamin D<LLN. I provide those results below.

MS RCTs 109MS 301 and 109MS 302, Percentage of Subjects by Treatment with PTH >ULN at week 48 and at week 96 who also had Vitamin D<LLN

>ULN	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
Week 48	9.1% (5/55)	7.9% (5/63)	8.5% (10/118)	10% (2/20)	(0/16)
Week 96	11.1% (8/72)	13.0% (12/92)	12.1% (20/164)	6.7% (2/30)	13.3% (4/30)

Reviewer analysis using Dataset ADLB05

For all treatment groups, in patients with elevated PTH, a relatively small percentage also had Vitamin D<LLN.

AEs Related to Hyperparathyroidism
I searched for AE terms that can be associated with hyperparathyroidism. Despite the PTH lab results described above, I did not find robust evidence in the Pool A trials of differences in the frequency of AEs potentially related to hyperparathyroidism. I summarize those results below.

AEs potentially related to hyperparathyroidism, MS Pool A Trials

	BG00012				PBO	GA
	Low dose	240mg BID	240mg TID	Total		
	N=128	N=769	N=823	N=1720	N=836	N=351
Hyperparathyroidism	0	<1% (1)	<1% (1)	<1% (2)	<1% (1)	0
Hyperparathyroidism 1°	0	0	<1% (1)	<1% (1)	0	0
Hyperparathyroidism 2°	0	<1% (1)	0	<1% (1)	0	0
Vitamin D deficiency	0	<1% (5)	<1% (8)	<1% (13)	<1% (7)	<1% (3)
Osteopenia	0	<1% (2)	<1% (2)	<1% (4)	<1% (2)	<1% (1)
Osteoporosis	0	<1% (3)	<1% (1)	<1% (4)	<1% (5)	0
Spinal compression fracture	0	<1% (2)	0	<1% (2)	0	0
Wrist fracture	0	0	<1% (2)	<1% (2)	<1% (2)	0
Femur fracture	0	<1% (1)	<1% (1)	<1% (2)	0	<1% (1)
Nephrolithiasis	0	<1% (5)	<1% (8)	<1% (13)	<1% (8)	<1% (1)
Parathyroid tumor benign	0	0	0	0	<1% (1)	0
Hypercalcemia	0	0	0	0	<1% (1)	0
Blood PTH increased	0	2% (15)	2% (17)	2% (32)	<1% (6)	<1% (2)
Vitamin D decreased	0	<1% (5)	<1% (2)	<1% (7)	<1% (2)	<1% (1)
Vitamin D increased	0	0	<1% (4)	<1% (4)	<1% (2)	0
Blood calcium dec	0	<1% (1)	0	<1% (1)	<1% (1)	<1% (1)
Blood calcium inc	0	0	<1% (1)	<1% (1)	<1% (2)	<1% (1)
Blood PTH abnormal	0	0	<1% (1)	<1% (1)	0	0
Blood PTH decrease	0	0	0	0	<1% (1)	0

From ISS Appendix Table 24

I also examined the AE table for MS Pool B trials to determine if additional events in the above table were reported during the MS extension trials. Investigators reported few additional AEs potentially associated with hyperparathyroidism. The additional events were Nephrolithiasis (11 new events), Vitamin D deficiency (8 new events), Vitamin D decreased (5 new events), osteoporosis (5 new events), wrist fracture (2 new events), blood PTH increased (1 new event), osteopenia (1 new event), and Vitamin D increased (1 new event) (SU Appendix Table 16).

Discussion
BG00012 exposed trial subjects experienced greater mean increases in PTH and were more likely to have PTH results that were >ULN. Over 20% of BG00012 subjects had PTH >ULN compared to 17% of GA subjects and 9% of placebo subjects. BG00012 subjects were also more likely than other subjects to have elevated PTH at both study weeks 48 and 96. Analyses also demonstrated what appeared to be a dose response for these findings. In addition, BG00012 subjects experienced Vitamin D<LLN. The majority of subjects with increases in PTH did not also experience Vitamin D<LLN. BG00012 subjects did not experience notable differences in calcium results compared to placebo or GA subjects.

Given the apparent lack of evidence of corresponding elevated calcium results, the elevated PTH appears consistent with secondary hyperparathyroidism. As described above, BG00012 treated subjects were more likely to have Vitamin D levels <LLN. Although Vitamin D deficiency resulting in hypocalcemia is a recognized etiology of secondary hyperparathyroidism, the results in these subjects do not strongly support that relationship. Vitamin D<LLN was seen about half as frequently as PTH>ULN, and as noted above, the two abnormalities were not commonly seen occurring at the same time in the same subject.

The clinical importance of the observed increased PTH and decreased Vitamin D are not known. There did not appear to be among BG00012 subjects an increased risk for AEs potentially associated with hyperparathyroidism or related bone disorders. Although the difference in percentage of BG00012 patients with elevated PTH compared to placebo was notable, it was less pronounced compared to GA, which has not been previously recognized to be associated with increased PTH. Adding to the difficultly in interpreting these results is the evolving understanding of the relationship between MS and Vitamin D. Vitamin D deficiency has been cited as a risk factor for MS and examined as a potential treatment.[2,3] In addition, publications have examined low vitamin D and high PTH in MS patients. In a longitudinal study, Soilu-Hanninen et al[4] found lower vitamin D levels and higher PTH levels among MS patients during relapses than in remissions. In another publication, Nieves et al measured bone mineral density and biochemical indices of bone metabolism in females with MS. The authors found in their sample of MS patients, lower BMD compared to a reference population, with

2 Faridar A, Eskandari G, Sahraian MA, Minagar A, Azmi A. Vitamin D and multiple sclerosis: a critical review and recommendations on treatment. Acta Neurologica Belgica 2012, DOI: 10.1007/s13760-012-0108-z
3 Soloman AJ, Whitham RH. Multiple Sclerosis and Vitamin D: A Review and Recommendations. Current Neurology and Neuroscience Reports. Vol.10, Number 5 (2010), 389-396.
4 Soilu-Hänninen M, Laaksonen M, Laitinen I, Erälinna JP, Lilius EM, Mononen I. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. Mult Scler. 2007 Jun;13(5):670-2. Epub 2007 Feb 16.

vitamin D deficiency in 23% and elevated PTH in 13%[5] of their MS patients. These publications suggest possible important differences in Vitamin D, PTH, and bone metabolism among MS patients. It is unclear if the observed changes in PTH and Vitamin D in these clinical trials reflect direct effects of BG00012 or alterations in the underlying disease process. Regardless, the similarity of PTH results for BG00012 patients and GA patients, and the lack of apparent increased risk for AEs related to hyperparathyroidism among BG00012 patients are reassuring.

7.4.3 Vital Signs

The vital sign data collected during the BG00012 trials did not suggest notable differences in temperature, pulse or blood pressure across treatments. In summarizing the vital sign data, I focus on the data collected during the MS controlled trials (Pool A).

Temperature
The mean changes from baseline for temperature were small and similar across treatment groups. For example, the temperature mean change at week 4 for BG00012 BID patients was 0.01 compared to 0.02 for the BG00012 TID patients, -0.02 for the placebo patients and -0.04 for the GA patients (ISS Appendix table 163). For the remainder of the study visits, the temperature mean changes from baseline did not appear to vary considerably when comparing across treatments.

Biogen also demonstrated that <1% of patients in any treatment group met the potentially clinically significant criteria for temperature (>38 C with >=1 C increase from baseline) (ISS Appendix table 166).

Pulse
BG00012 patients experienced slightly greater mean increases from baseline for pulse compared to placebo and GA patients. At week 4, the mean increase in pulse for BG00012 BID patients was 2.5 bpm compared to 2.9bpm for BG00012 TID patients, 1.2bpm for placebo patients and 0.1bpm for GA patients. The mean changes from baseline were similar for the remainder of the study. For example, at week 52, the mean increase in pulse for BG00012 BID patients was 2.1 bpm compared to 1.9bpm for BG00012 TID patients, 0.3 bpm for placebo patients and -0.5 bpm for GA patients (ISS Appendix Table 163).

5 Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. Neurology. 1994 Sep;44(9):1687-92.

There did not appear to be meaningful differences by treatment in the percentages of patients with PCS results for pulse. Biogen considered patients as having a PCS result for pulse if they experienced an increase in pulse >120bpm and their pulse was <=120 bpm at baseline, or if they had an increase of 20bpm >baseline. Biogen also considered patients who experienced a decrease in pulse to <50bpm, if their pulse was >=50 bpm at baseline, or who had a decrease of >20bpm from baseline as having a PCS result. I summarize the results for Biogen's analyses in the following table.

Potentially Clinically Significant Results, Pulse, Pool A Trials

Pulse PCS criteria	Treatment					
		BG00012			Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
>120bpm, if pulse was <=120 bpm at baseline, or who had an increase of 20bpm >baseline	10% (13/128)	26% (198/761)	25% (204/811)	24% (415/1700)	23% (194/831)	20% (71/347)
<50bpm, if their pulse was >=50 bpm at baseline, or who had a decrease > 20bpm from baseline	5% (6/128)	8% (63/761)	9% (76/811)	9% (145/1700)	12% (103/831)	13% (36/347)

From ISS Appendix Table 166

Blood pressure

BG00012 patients experienced slight mean declines from baseline in systolic and diastolic blood pressure that were more negative compared to the mean changes seen in placebo and GA patients. I summarize those results below.

Blood Pressure Mean Change from Baseline by Treatment for Select Study weeks, Pool A MS Trials

	Treatment				
	BG00012 BID	BG00012 TID	BG00012 Total	Placebo	GA
Systolic Blood Pressure, mean change from baseline					
Week 4	-0.8	-1.1	-0.9	0.4	0.0
Week 12	-1.2	-1.6	-1.2	0.3	-0.1
Week 48	-1.7	-1.8	-1.7	-0.6	-0.8
Week 96	-0.5	-2.0	-1.3	-0.1	0.0
Diastolic Blood Pressure, mean change from baseline					
Week 4	-0.5	-0.9	-0.6	0.1	0.0
Week 12	-1.0	-0.6	-0.6	0.4	-0.3
Week 48	-1.2	-1.2	-1.2	-0.4	-0.9
Week 96	-1.0	-1.1	-1.0	0.4	-0.1

From ISS Appendix Table 163

There did not appear to be meaningful differences by treatment group for the percentages of patients who met Biogen's criteria for PCS result for systolic or diastolic blood pressure. Biogen used the following criteria for PCS blood pressure changes:

> Post baseline SBP >180, if SBP was <=180 at baseline or increase in SBP of >40
> Post baseline SBP <90, if SBP was >=90 at baseline or decrease in SBP of >30
> Post baseline DBP >105, if DBP was <=105 at baseline or increase in DBP of >30
> Post baseline SBP <50, if SBP was >=50 at baseline or decrease in SBP of >20

I summarize the results for this analysis below.

Potentially Clinically Significant Results, Blood Pressure, Pool A MS Trials

BP PCS criteria	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
Systolic Blood Pressure						
Post baseline SBP >180, if SBP was <=180 at baseline or increase in SBP of >40	0/128	1% (11/760)	2% (20/811)	2% (31/1699)	2% (16/831)	3% (9/347)
Post baseline SBP <90, if SBP was >=90 at baseline or decrease in SBP of >30	6% (8/128)	11% (86/760)	11% (91/811)	11% (185/1699)	8% (67/831)	9% (31/347)
Diastolic Blood Pressure						
Post baseline DBP >105, if DBP was <=105 at baseline or increase in DBP of >30	(0/128)	3% (24/760)	3% (27/811)	3% (51/1699)	4% (33/831)	3% (12/347)
Post baseline SBP <50, if SBP was >=50 at baseline or decrease in SBP of >20	2% (2/128)	14% (104/760)	14% (110/811)	13% (216/1699)	12% (101/831)	13% (45/347)

From ISS Appendix Table 166

Body weight
In MS trials 301 and 302, at week 96, the mean change in body weight for the placebo group was -0.12kg compared to -0.10kg for the BG00012 BID group, 0.17kg for the BG00012 TID group and 0.9kg for the GA group (ISS appendix table 180).

7.4.4 Electrocardiograms (ECGs)

Through QT Study
Biogen conducted a thorough QT study (Trial 109HV101). The FDA interdisciplinary review team (IRT) reviewed the results of this trial in an 8/31/07 memo. The IRT commented that "No significant effect of BG00012 administration on the QT interval was detected in this thorough QT study." The IRT did note that the effects of BG00012 were assessed for only 8 hours after dosing and that some drugs can have a delayed effect after Tmax. The IRT recommended that Biogen submit the ECGs from this trial that were recorded at 24 hours post dose for evaluation to exclude a delayed effect. Biogen submitted those data and IRT reviewed the information. In a 9/6/12 memo, the IRT concluded that Biogen adequately addressed the previous concerns. The IRT found no effect of BG00012 on the QT interval in the 24 hour ECG data.

Clinical Trial ECG analyses
Biogen required ECGs at baseline and at 12 week intervals in trial 1900, and at baseline and every 24 weeks in trials 301 and 302. For their pooled analyses of quantitative data, Boigen included ECG results from trials 1900, 301 and 302 (Pool A). For qualitative data, Biogen included ECG data only from trials 301 and 302. Biogen did not include data from trial 1900 in their pooled analysis of qualitative data due to the use of different qualitative rating methodologies and centers to evaluate ECGs.

There did not appear to be meaningful differences by treatment when comparing mean change from baseline for various ECG parameters. In the table below, I provide the mean change from baseline data for select ECG parameters.

Select ECG Parameters, Mean Change from Baseline, Pool A MS Trials

ECG Parameters	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
Heart Rate						
Week 24	0.1	1.9	2.5	2.1	-0.3	-0.5
Week 48	-	1.8	1.7	1.8	0.6	-1.3
Week 72	-	1.5	2.2	1.9	0.1	-1.3
Week 96	-	1.9	1.8	1.9	-0.2	-1.7
PR Interval						
Week 24	-0.3	0.0	-0.7	-0.4	0.2	-0.1
Week 48	-	0.3	-0.5	-0.1	-1.3	0.4
Week 72	-	0.6	-0.8	-0.1	-0.2	-0.6
Week 96	-	0.6	0.2	0.4	-1.2	-0.5
QT uncorrected						
Week 24	-0.4	-5.3	-5.2	-4.9	2.5	2.5
Week 48	-	-3.6	-3.7	-3.6	2.7	5.1
Week 72	-	-3.6	-3.9	-3.7	4.7	6.6
Week 96	-	-1.8	-0.1	-0.9	6.1	8.3

QTcB						
Week 24	0.1	0.1	2.0	1.0	2.1	1.3
Week 48	-	1.5	1.4	1.5	4.7	1.7
Week 72	-	0.9	2.7	1.8	5.5	3.3
Week 96	-	3.5	5.3	4.4	5.9	3.9
QTcF						
Week 24	0.0	-1.8	-0.5	-1.0	2.3	1.7
Week 48	-	-.2	-0.4	-0.3	4.1	2.9
Week 72	-	-0.6	0.4	-0.1	5.2	4.4
Week 96	-	1.6	3.4	2.5	6.0	5.4

From ISS Appendix Table 169

In addition to mean change analyses, Biogen provided outlier analyses of ECG data (QTc absolute values and increases from baseline). There did not appear to be notable differences in QTc outliers by treatment. I summarize those analyses below.

Select ECG Parameters, Outliers, Pool A MS Trials

Outliers	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
QTcB						
>450	3% (3)	9% (63)	10% (74)	9% (140)	11% (84)	10% (32)
>480	0	<1% (7)	<1% (2)	<1% (9)	<1% (4)	<1% (1)
>500	0	0	0	0	0	0
QTcB increase fromBL						
>30	7% (8)	18% (125)	18% (133)	17% (266)	20% (151)	18% (59)
>60	<1% (1)	1% (10)	1% (10)	1% (21)	1% (9)	1% (4)
QTcF						
>450	<1% (1)	2% (18)	2% (15)	2% (34)	3% (21)	4% (12)
>480	0	0	0	0	<1% (1)	0
>500	0	0	0	0	0	0
QTcF increase fromBL						
>30	7% (8)	7% (50)	10% (76)	9% (134)	12% (94)	13% (41)
>60	0	0	<1% (2)	<1% (2)	0	0

From ISS Appendix Table 170, 171

7.4.5 Special Safety Studies/Clinical Trials

All trial data are discussed above.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Biogen's MS clinical trials examined two different BG00012 dosing regimens, 240mg BID and 240mg TID. Biogen intends to recommend in labeling only the 240mg BID regimen. The above presentations of safety data have included the different dose regimens used in the clinical trials, and therefore I present no additional dose-related analyses in this section.

7.5.2 Time Dependency for Adverse Events

I presented the relevant time related analyses in the sections examining the AEs of special interest above.

7.5.3 Drug-Demographic Interactions

I presented analyses of drug-demographic interactions for flushing and GI AEs above. This section will summarize the general findings of Biogen's analyses for drug-demographic interactions

Age
The MS clinical trials included patients between ages 18 and 65 years, so there are no safety data for patients in younger or older age groups. Biogen's analyses of safety data by age compared AE risks in patients <40 to >=40years. For these age groupings, I summarize overall AE risk and the AEs that occurred >5% of BG00012 subjects and >1.5x placebo (excluding flushing related and GI, which were reviewed above). There did not appear to be robust evidence of differences in risk by age.

MS Pool A, AEs that occurred in >5% of BG00012 subjects and >1.5x placebo, stratified by age (<40, >=40 years)

	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
<40 years						
One or more AE	70% (90)	95% (410)	94% (411)	94% (891)	92% (424)	87% (187)
Sinusitis	3% (2)	4% (19)	6% (28)	5% (49)	4% (17)	2% (4)
Bronchitis	4% (3)	5% (20)	6% (27)	5% (50)	4% (20)	6% (3)
Albumin urine	0	7% (31)	4% (16)	5% (47)	3% (16)	6% (12)
Muscle spasms	1% (1)	3% (11)	6% (28)	4% (40)	2% (11)	<1% (1)
>=40 years						
One or more AE	88% (44)	96% (323)	93% (356)	94% (723)	92% (345)	87% (117)
Sinusitis	0	5% (16)	6% (24)	5% (40)	4% (14)	5% (7)
Bronchitis	0	4% (15)	6% (22)	5% (37)	3% (12)	7% (10)

Albumin urine	0	4% (15)	5% (20)	5% (35)	3% (11)	4% (6)
Muscle spasms	0	5% (16)	6% (22)	5% (38)	6% (24)	5% (7)

From ISS Appendix Table 183

Sex
I summarize overall AE risk and the AEs that occurred >5% of BG00012 subjects and >1.5x placebo (excluding flushing related and GI, which were reviewed above) for males and females. There did not appear to be robust evidence of differences in risk by sex.

MS Pool A, AEs that occurred in >5% of BG00012 subjects and >1.5x placebo, stratified by sex

	Treatment					
	BG00012				Placebo	GA
	Low doses	240mg BID	240mg TID	Total		
Males						
One or more AE	83% (35)	93% (211)	91% (204)	91% (450)	88% (215)	83% (86)
Sinusitis	2% (1)	2% (4)	4% (8)	3% (13)	3% (7)	3% (3)
Bronchitis	2% (1)	2% (5)	<1% (2)	2% (8)	<1% (2)	5% (5)
Albumin urine	0	7% (16)	2% (5)	4% (21)	3% (7)	7% (7)
Muscle spasms	0	6% (3)	3% (7)	3% (13)	4% (10)	6% (6)
Females						
One or more AE	88% (44)	96% (323)	93% (356)	94% (723)	92% (345)	87% (117)
Sinusitis	1% (1)	6% (31)	7% (44)	6% (76)	4% (24)	3% (8)
Bronchitis	2% (2)	6% (30)	8% (47)	6% (79)	5% (30)	4% (11)
Albumin urine	0	6% (30)	5% (31)	5% (61)	3% (20)	4% (11)
Muscle spasms	1% (1)	4% (21)	7% (43)	5% (65)	4% (25)	<1% (2)

From ISS Appendix Table 185

Race
I do not present the AE risks stratified by race because >80% of patients in the Pool A trials were White, making analyses stratified on this variable of limited usefulness.

7.5.4 Drug-Disease Interactions

Biogen did not examine AE risks stratified by underlying disease to look for drug-disease interactions.

7.5.5 Drug-Drug Interactions

As noted earlier, Biogen felt that the potential of DMF and MMF for drug-drug interactions appears to be low for several reasons. Neither DMF nor MMF inhibited CYP2D6 or CYP3A4 at clinically relevant concentrations, and the induction potential of MMF was low. In addition, DMF and MMF have relatively low protein binding. Because metabolism of DMF and MMF is through the TCA cycle, Biogen conducted no formal drug-drug interaction studies with BG00012 (ISS, p.180).

Biogen did summarize safety data for select medications co-administered with BG00012 in clinical trials.

Avonex
Biogen reported that in trial 109HV103 BG00012 PK was not altered in the presence of Avonex, and no new safety signals were identified in healthy volunteers administered BG00012 240 mg TID for 3 days in combination with a single dose of Avonex. (ISS, p.180)

Glatiramer acetate
Biogen reported that in trial 109HV104, BG00012 PK was not altered in the presence of GA, and no new safety signals were identified in healthy volunteers administered BG00012 240 mg TID for 2 days in combination with a single dose of GA. (ISS, p.180)

Aspirin
Biogen reported that in trial 109HV106, no new safety concerns were detected in 56 healthy volunteers who received repeated doses of either BG00012 (total daily doses ranging from 480 to 720 mg) or placebo with or without ASA for 4 days. (ISS, p.180)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Reviewer Summary
The available data do not suggest that BG00012 is associated with an increased malignancy risk. The overall malignancy risk in the MS clinical trials was not elevated compared to SEER data. Biogen reported increased renal tumors in their preclinical carcinogenicity study. The incidence of renal cell cancers from MS clinical trials was elevated compared to incidences from SEER data and from an insurance claims database, but this comparison was based on only 2 cases in BG00012 patients, and the confidence intervals for the risk estimates overlapped. The renal cell cancer incidence in the BG00012 database is similar to the incidence observed in the teriflunomide NDA database. As with most NDAs, the exposure (number of patients and durations) limits any assessment of human carcinogenicity.

Background
Biogen notes that BG00012 may be considered an immunomodulator and that with such drugs there is a potential for increased malignancy risk (ISS, p.96). Biogen also reported development of renal tumors in the 2-year preclinical carcinogenicity studies.

Methods
Biogen provided analyses to assess the relationship between BG00012 and the development of malignancies in general and specifically for renal cell cancers. Biogen

identified potential malignancy AEs using the SMQ for malignant or unspecified tumors. Biogen assessed the identified individual cases to determine if the diagnoses described malignant neoplasms. Biogen included the malignant neoplasm cases in their analyses. Biogen's analyses included comparisons of malignancy risk in the Pool A RCTs (up to 2 years duration). In addition, Biogen compared malignancy AE risk in MS Pool B BG00012 patients to SEER data and managed care claims data.

Results
MS Pool A
Malignant neoplasms occurred at similar frequency across treatment groups in the MS Pool A RCTs. Biogen reported that <1% (n=3) placebo subjects had a malignant neoplasm, compared to <1% (n=2) BG00012 BID subjects, <1% (n=2) BG00012 TID subjects, and 1% (n=4) GA subjects (ISS, p.96). The malignancies in the placebo group were breast cancer (n=2), and basal cell cancer. In the BG00012 BID group the reported malignancies were transitional cell carcinoma of the renal pelvis and basal cell cancer of the skin, and in the BG00012 TID group were breast cancer and cervical cancer. The malignancies reported in the GA group were cervical cancer, endometrial cancer, thyroid cancer, and basal cell cancer of the skin.

MS Pool B
Through the 120 day SU there were 19 reported malignancies in 18 BG00012 patients (4 from MS RCTs discussed above, and 15 from MS extension trials) (SU, p.53). The reported malignancies from the extension trials were breast cancer (n=3), malignant melanoma (n=2), breast cancer in situ, rectal cancer, papillary renal cell carcinoma, renal cell cancer, squamous cell carcinoma of the lung, salivary gland cancer, mesothelioma, endometrial cancer, glioma, and cervical cancer.

Biogen calculated an incidence for all malignancies in the Pool B MS trials of 375.4/100,000PY. Biogen compared the incidence of malignancy in their Pool B trials to the incidence of all malignancies (excluding BCC and SCC) of 456.7/100,000PY that was based on 2008 SEER data.

Given the preclinical carcinogencity findings, Biogen compared the incidence of the kidney related cancers in Pool B to the SEER incidences and incidences in MS patients and controls derived from the (b) (4) database. Biogen concluded that the incidences for these malignancies in MS Pool B patients were comparable to the incidence in the SEER and managed care databases. I provide those data below.

Incidence Rate/100,000PY (95% CI) for Malignancies of the Kidney (Excluding Pelvis), Renal Pelvis (Only), and Kidney and Renal Pelvis Combined

Site	BG00012 (Pool B)	US SEER 2008	(b) (4) Claims data	
			MS	Control
Kidney (excluding pelvis)	44.10 (5.34, 159.31)	14.5 (14.3, 14.8)	(b) (4)	
Renal Pelvis (only)	26.29 (0.67, 146.50)	1.0 (0.9, 1.03)		

From ISS table p.98 and SU table p.59

The above comparison is based on two renal cell malignancies and a single malignancy of the renal pelvis (transitional cell) from the Pool B trials. Biogen provided narrative summaries for the 3 BG00012 patients with the malignancies noted above. Biogen commented that the patient with the renal pelvis malignancy (transitional cell) had a risk factor of a 40 pack year smoking history. One patient with renal cell cancer had received BG00012 for 35 months and was diagnosed with the malignancy during an evaluation of RUQ pain. Biogen noted that this patient had risk factors of hypertension and borderline obesity (ISS, p.97). The second patient with renal cell cancer had the malignancy diagnosed as an incidental finding during evaluation for concomitant endometrial cancer after 14.6 months of BG00012 (SU, p.58).

Biogen felt that the renal cell malignancies diagnosed during the clinical trials were likely present in the BG00012 patients prior to initiating BG00012. This conclusion was based on data from the literature regarding growth rates in renal masses detected during active surveillance. Biogen considered these growth rate data applicable because the renal cell cancers from the clinical trials were detected incidentally during evaluations for abdominal pain, in one case, and for endometrial cancer, in the second (SU, p.58). Biogen did not have baseline imaging data to support that these malignancies arose prior to treatment with BG00012.

Biogen discussed the incidence of renal cell cancers in the general population. Biogen cited publications that described the increasing incidence for renal cell cancers over the past 20 years. Biogen notes that the increase in renal cell tumor diagnoses is at least partially attributable to increased detection as a result of increased use of imaging techniques.

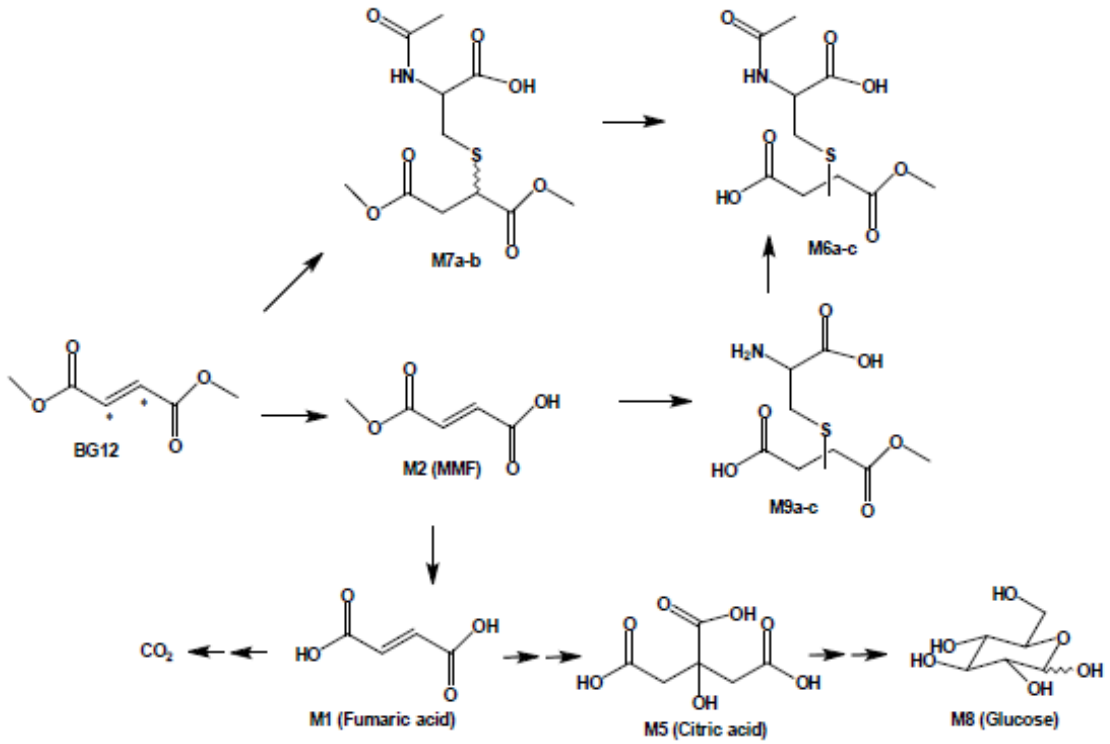
Biogen Conclusions
Biogen feels that the incidence of renal cell tumors in the BG00012 studies is compatible with incidences in the general population and in the MS population in the US. Biogen concluded that “there is no evidence of a causal relationship between the development of renal cancers and BG00012 treatment” (SU, p.58).

Fumarate as an Oncometabolite
While reviewing the medical literature related to this application, I identified publications that discussed the role of fumarate in renal cell cancers and other tumors. These publications refer to fumarate as an oncometabolite. These publications merited further consideration given that DMF is metabolized to fumarate and then further metabolized by the TCA cycle.

Metabolism of Dimethyl fumarate
Dimethyl fumarate is metabolized to fumarate and then further metabolized by the TCA cycle. I provide Biogen's diagram of the metabolic pathways of dimethyl fumarate below:

Figure 3: Proposed Metabolism Pathways of BG00012

(* = ^{14}C label)



Source: Derived from Figure 35, CSR 109HV102, Appendix 16.1.10.1, Metabolic Profiles and Identification

I also provide the sponsor's table 9 that summarizes the relative abundance of metabolites. In this table, fumarate is grouped with citrate (M1+M5).

Table 9: Summary of Abundance of Metabolites, Study 109HV102

	Urine	Expired Air	Plasma
Total Time Period of Collection Sample Analyzed for Metabolites Compound (as % of Dose or % of Sample)	0 to 168 h 0 to 48 h	0 to 96 h 0 to 96 h	0 to 168 h 2 to 24
Males:			
% of Total Dose Excreted (0-168 h) Parent (BG00012)	15.5 0.06	39.7 to 58.6 -	NA
M1[1]+ M5[2]	-	-	
M2 (MMF)		27.5	
M6a[3]	0.23	-	4.93
M6b[3]	1.77	-	
M6c[3]	0.17	-	
M7a[4]	0.16		
M7b[4]	1.40		
M8[5]	0.62		
M9a-b[6]		-	
M9c[6]		60.5	
CO_2	4.64		-
Unknown[7]	0.91		-

[1] Fumarate
[2] Citrate
[3] N-acetylcysteine conjugate of monomethyl succinate
[4] N-acetylcysteine conjugate of dimethyl succinate
[5] Glucose
[6] Cysteine conjugates of monomethyl succinate
[7] Including multiple other minor radioactivity peaks
Source: Derived from CSR 109HV102, Table 14-7, and Table 10, Appendix 16.1.10.1, Metabolic Profiles and Identification.

Background
Pollard et al[6] describe the evidence for consideration of fumarate as an oncometabolite. Fumarate is metabolized to malate by fumarate hydratase (FH), via the TCA cycle. The authors explain that mutations in the genes coding for this enzyme can result in impairment of FH function, resulting in increased intracellular fumarate levels. Accumulation of intracellular fumarate may result in a variety of potentially deleterious effects including inhibition of 2-oxoglutarate-dependent oxygenases, including the hypoxia-inducible factor (HIF) hydroxylases, thus activating oncogenic HIF pathways; non-enzymatic modification of cysteine residues (succination) that could lead to disruption or loss of protein functions; dysfunctional cell metabolism and cell signaling;

6 Yang, M, Tomoyoshi S, Pollard P, Adam J. The emerging role of fumarate as an oncometabolite. Front Oncol. 2012;2:85.

and activation of Nrf2 resulting in tolerance to oxidants, which promotes tumor survival. I include the following illustration of potential effects resulting from increased fumarate levels that was included in the above publication.

Patients with FH mutations can develop the hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. This syndrome is characterized by benign cutaneous and uterine leiomyomata, renal cysts and aggressive collecting duct and Type 2 papillary renal tumors.

The Division asked Biogen to provide a discussion of the medical literature regarding the deleterious effects of increased intracellular fumarate levels and its role as an oncometabolite, the implications for dimethyl fumarate, with consideration of the preclinical findings of increased renal cell cancers and the two renal cell cancers identified in the clinical trials database.

In their response to our inquiry, Biogen provided information obtained from their search of the medical literature. In the following paragraphs I discuss Biogen's response. In addition, I provide information identified from the literature but not included in Biogen's response.

Evidence supporting that fumarate is an oncometabolite comes from investigation of deficiencies of fumarate hydratase (FH) the TCA cycle enzyme that catalyzes the conversion of fumarate to malate. Mutations in the genes coding for FH result in reduction in FH function and increases in intracellular fumarate.

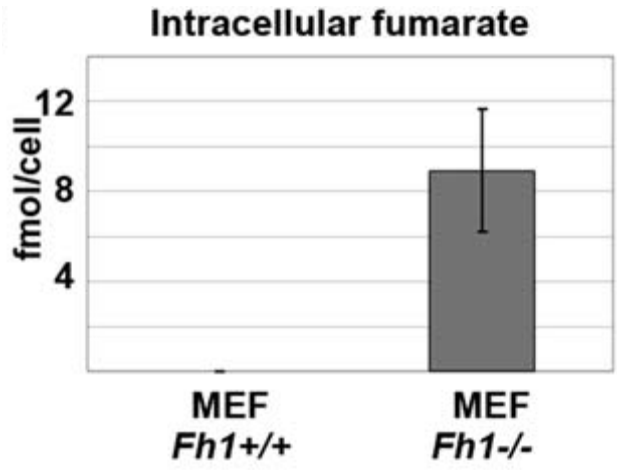
Disease manifestations in patients with FH mutations are variable and depend on the nature of the mutations. Fumarate Hydratase deficiency, a recessive disorder characterized by bi-allelic loss of FH function at birth, results in gross neuroanatomical malformation, profound developmental delay, and death within the first decade of life. Alternatively, individuals can inherit a single mutant copy of the gene and subsequently experience alteration of the wild type copy (two hit model) resulting in loss of FH function. These individuals develop hereditary leiomyomatosis and renal cell cancer, bladder cancer, collecting duct tumors, and possibly adult Leydig cell tumors. Investigators have documented a number of different mutations to the genes coding for FH and have demonstrated differences in FH activity resulting from these mutations[7]. In one publication, the authors reported that cutaneous and uterine leiomyomas are the most common clinical manifestations of HLRCC and renal cell cancers less common, with only 5 of 35 identified families with HLRCC having members with renal cell cancer.[8]

Biogen reported that the literature suggests the exact mechanism of the increased malignancy risk is unknown. Furthermore, Biogen makes the distinction that it is unclear if the observed outcomes are due to a true oncogenic response, or a result of promotion of favorable conditions for tumor growth.

FH activity, fumarate levels
O'Flaherty et al found elevated cellular fumarate levels in FH-/-mouse embryonic fibroblasts compared to FH+/+ fibroblasts9. That information is summarized in the following graph.

7 Pollard PJ, Brie`re JJ, Alam NA, Barwell J, Barclay E, Wortham NC, Hunt T, Mitchell M, Olpin S, Moat SJ, Hargreaves IP, Heales SJ, Chung YL, Griffiths JR, Dalgleish A, McGrath JA, Gleeson MJ, Hodgson SV, Poulsom R, Rustin P, Tomlinson IPM. Accumulation of Kreb's cycle intermediates and over-expression of HIF 1α in tumours which result from germline HF and SDH mutations. Human Molecular Genetics, 2005, Vol.14, No.15, 2231-2239.
8 Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, Stewart L, Duray P, Tourre O, Sharma N, Choyke P, Stratton P, Merino M, Walther MM, Linehan WM, Schmidt LS, Zbar B. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003 Jul;73(1):95-106. Epub 2003 May 22.

9 O'Flaherty L, Adam J, Heather LC, Zhdanov AV, Chung YL, Miranda MX, Croft J, Olpin S, Clarke K, Pugh CW, Griffiths J, Papkovsky D, Ashrafian H, Ratcliffe PJ, Pollard PJ. Dysregulation of hypoxia pathways in fumarate hydratase-deficient cells is independent of defective mitochondrial metabolism. Hum Mol Genet. 2010 Oct 1;19(19):3844-51. Epub 2010 Jul 21.



Biogen states that with low or absent FH activity, the there is significant accumulation of cellular fumarate with levels achieving an approximate 500-fold increase over normal concentration range. Biogen cited data from a publication by Pollard et al as the source of this information. The authors measured succinate and fumarate in 4 HLRCC fibroids and in 2 normal myometrial samples (one from HLRCC patient and 1 from non HLRCC patient). Those results are provided below.

The authors also reported that skin fibroblasts from 4 patients with recessive disorder fumarase deficiency had enzyme activity that ranged from 2.4%-13%.

DMF metabolism and fumarate
In explaining the metabolism of DMF, Biogen states the following:
in preclinical and clinical studies utilizing oral dimethyl fumarate dosing, no elevations in fumarate (fumaric acid) levels were detected in circulation or in tissues. DMF ultimately

gets metabolized and is predominately eliminated in expired air as CO2. DMF is ultimately metabolized through the TCA cycle, suggesting fumarate is formed at some point, but this species does not appear to accumulate. To support these statements, Biogen referenced their PK summary and their Summary of Clinical Pharmacology, contained in their NDA submission. I reviewed the referenced sections. The sections in the PK Summary documented that following a single dose in both rats and dogs, no fumaric acid (fumarate) was detected in plasma samples. Biogen referenced 3 sections in the Summary of Clinical Pharmacology that included fumaric acid level data. In the first reference, section 2.1.1, they noted that in trial IKP/ID33, following a single oral dose of dimethyl fumarate, no DMF and no fumaric acid were detected in plasma. The second reference (2.2.1) cited information from study FG-PK-03/04. In the study report for FG-PK-03/04, the sponsor noted that in patients dosed with 720mg and 1440 mg of DMF, fumaric acid concentrations were below the limit of quantification (p.68). In this analysis the lower limit of quantification appeared to be 0.27mg/L (p.306). The third reference (2.4.1) cited information from study FG-PK-02/02, a crossover food effect trial where subjects were dosed with 240mg of DMF. In the study report for FG-PK-02/02 the investigators reported that fumaric acid could not be quantified in any of the samples (lower limit of quantification was 0.27mg/L) (p.6).

Comparisons of fumarate in HLRCC tumors from FH-deficient patients to DMF levels from BG00012 trial data

Biogen noted that Pollard et al found that in HLRCC-derived tumors from FH-deficient individuals, fumarate levels have been reported to reach 72,000 µg/ml. Biogen then noted that after oral dosing of 240 mg DMF, maximal plasma concentrations of MMF achieve a concentration of approximately 2,000µg/ml. Biogen stated that the tissue distribution properties of MMF are not amenable to study in humans, so they relied on preclinical data, which suggest that tissue levels of MMF after an oral DMF dose were significantly lower than plasma concentrations. The reference provided for this statement pointed to data from report Rsch-2001-027. In that study, investigators measured plasma, brain and CSF levels of MMF in rats with malonate-induced striatal lesions, 30 minutes after last dose of DMF. I provide those results below.

Biogen felt that these findings support that human tissue exposures to MMF would potentially be less than the plasma concentration of 2,000 µg/ml. Biogen went on to state that "Even if a 1:1 ratio of plasma to tissue MMF concentration ratio was speculated, the tissue concentration of MMF after 240 mg DMF dosing would be 36-fold less than that which occurs due to deficiencies in FH activity. As tumors are only associated with a profound loss of FH activity (i.e. bi-allelic inactivation) and subsequent accumulation of excessive cellular fumarate, it is reasonable to speculate that the tissue and cellular exposures of MMF after oral dosing of 240 mg DMF do not achieve the fumarate levels necessary for neoplastic conversion or for promotion of tumor growth and survival."

Fumarate and purported oncogenic mechanisms
Yang et al identified several possible mechanisms for increased malignancy risk due to fumarate elevations and Biogen provided information related to these possible mechanisms.

Biogen noted that preclinical transcriptional profiling studies that utilized dosing DMF in both acute and chronic (3 month) paradigms, found no indication that HIF downstream target genes were upregulated. To support this statement, Biogen referenced a rat study in which they reported that there was no evidence of up-regulation of any HIF-alpha transactivated downstream genes (increased expression of VEGF, TSP1, and BNIp1). (NDA 2.6.6, section 3.2.1).

Biogen also felt that the constitutively high levels of cellular fumarate that result from genetic FH deficiencies were not likely comparable to the pulsatile exposure achieved through twice or three times daily dosing with DMF with regards to Nrf2 activation. Biogen explained that the relative fumarate levels and constitutive versus pulsatile delivery will almost certainly result in differential Nrf2 pathway induction. Biogen felt that genetic FH deficiencies would result in more robust and persistent activation of the pathway, as compared to the more transient responses after DMF dosing. Therefore, if Nrf2 activation has a causative role in promoting deleterious effects in FH deficient cells and tumors, it is unlikely that this type of activation profile is comparable to the activation that occurs after DMF dosing. It is also important to note that if fumarate itself, as compared to dimethyl or monomethyl fumarate, is the causative pathogenic agent in the described FH deficiency studies, preclinical and clinical evidence has demonstrated that circulating and tissue levels of fumarate (as fumaric acid) were unchanged after an oral dose of DMF compared to baseline and vehicle/placebo controls.

Biogen comments on preclinical and clinical data
Biogen attributed the DMF-related preclinical renal cell cancer risk to rodent specific chronic progressive nephropathy (CPN) and therefore not relevant to humans. Biogen stated that the renal tumors “have no physiological or mechanistic linkage to the tumors reported in FH-deficient subjects.”

Biogen also maintains that there was no increased risk of renal tumors in clinical trials. I provide a table of the renal cell malignancy risk from BG00012 MS clinical trials that was included above.

Incidence Rate/100,000PY (95% CI) for Malignancies of the Kidney (Excluding Pelvis), Renal Pelvis (Only), and Kidney and Renal Pelvis Combined

Site	BG00012 (Pool B)	US SEER 2008	(b) (4) Claims data	
			MS	Control
Kidney (excluding pelvis)	44.10 (5.34, 159.31)	14.5 (14.3, 14.8)	(b) (4)	
Renal Pelvis (only)	26.29 (0.67, 146.50)	1.0 (0.9, 1.03)		

From ISS table p.98 and SU table p.59

In an 11/30/12 response to a Division request, Biogen replied that they had no access to tumor tissue samples from the 2 BG00012 patients with renal cell cancer in order to test for FH activity/mutations.

I refer the reader to the Post marketing section of this review for a discussion of data for Fumaderm, a product that includes DMF and that is approved in Germany. Biogen reported that Fumaderm post marketing data included 4 renal cell cancer reports in an estimated 159,000 person years of exposure. This yields a reporting rate of renal cell

cancers (2.4/100,000PY) that is below the Globocan 2008 reference data (8.6/100,000/yr).

Renal cell cancer incidence with Teriflunomide
The data from the teriflunomide NDA included 3 cases of renal cell cancer in 6,000 patient years yielding an incidence of 50/100,000 person years. This incidence of renal cell cancer is similar to the incidence for BG00012.

Incidence of leiomyomas in BG00012 MS trials
As noted above, leimyomata appear more frequent clinical sequelae of FH deficiency In the Pool A studies, the incidence of uterine leiomyoma was similar for placebo (1%, 4/836), BG00012 240mg BID (<1%, 2/769), BG00012 240mg TID (<1%, 4/823) and GA (<1%, 2/351) (ISS Table 24). An additional 7 uterine leiomyomas were reported during the extension study (7 in each the 240mg BID and 240mg TID groups) (SU Table 17). No skin leiomyomas were reported in the MS pooled trial data.

Other sources of exposure to fumarate
Fumarate is present in a number of products including the salt for various drugs (quetiapine, bisoprolol, etc.), in foods (recognized as GRAS), and as dietary supplements. Unfortunately, I could not identify information about the pharmacokinetics of fumarate from these sources and therefore, it is not clear if ingestions of these forms result in similar exposures to those seen with fumaric acid esters.

Reviewer Discussion
Genetic mutations causing alterations in FH function result in increased intracellular levels of fumarate. Increased intracellular levels of fumarate are presumed to be responsible for the sequelae of leiomyomata and renal cell cancers seen in the HLRCC syndrome. The threshold level/safe intracellular level of fumarate is not known. The exact mechanism resulting in these events is under study and several potential pathways have been proposed as being responsible the increased risk for tumor development.

BG00012 is metabolized to MMF and then fumarate. Fumarate is then metabolized by the TCA cycle enzyme FH. We lack information to determine if ingesting BG00012 results in increased intracellular levels of fumarate. Fumarate was not detected in plasma levels of patients administered BG00012, but this does not necessarily preclude the possibility of increased intracellular levels. Preclinical data suggests that HIF downstream genes are not upregulated following exposure to DMF, but DMF does activate Nrf2.

There was no credible evidence of increased risk for leiomyomata among DMF treated patients in the NDA database. Although elevated compared to SEER and insurance database estimates, the point estimate for renal cell cancer risk in BG00012 treated MS

patients was based on only 2 cases and it was comparable to the renal cell cancer risk observed in the NDA database for a recently approved MS drug.

Despite the lack of information about intracellular fumarate levels, the absence of affirmative evidence for an increased risk for leiomyomata or renal cell cancer in BG00012 exposed patients is sufficiently reassuring that treatment with BG00012 is not associated with the outcomes seen with HLRCC. Even though the NDA doesn't support an increased risk for leimyomata and renal cell cancers, as part of the pharmacovigilance monitoring for BG00012, Biogen should monitor post marketing reports for cases of leiomyomata and or renal cell cancers in patients treated with BG00012.

7.6.2 Human Reproduction and Pregnancy Data

Biogen did not conduct trials of BG00012 in pregnant women. Through the safety update, there have been 35 pregnancies in women taking BG00012. One pregnancy occurred in a healthy volunteer following 2 single doses of BG00012 and the remaining pregnancies were in women with MS.

Of the 35 pregnancies in women taking BG00012, 15 resulted in live births, 3 were spontaneously aborted, 7 were terminated electively, and outcomes are not known for 10.

No fetal anomalies were reported for the 15 live births. Thirteen of the 15 live births were full term pregnancies (>37 weeks) and 2 were 35 week pregnancies. In these 2 cases, the women had not taken BG00012 for 60 days prior to their last menstrual period.

Of the 3 BG00012 spontaneous abortions, one occurred in a woman who stopped BG00012 4 months prior to the event. She was being treated with Avonex at the time of the spontaneous abortion. Subject 516-306 was 31 years old and exposed to BG00012 TID until 4 weeks gestation; the outcome occurred at 9 weeks. The spontaneous abortion was considered possibly related to BG00012 by the Investigator. Subject 842-406 was 35 years old and exposed to BG00012 TID until 6 weeks gestation; the outcome occurred at 10 weeks gestation. The spontaneous abortion was considered unrelated to BG00012 by the Investigator.

Biogen reported 7 elective pregnancy terminations in women treated with BG00012 (subjects 148-301, 184-404, 283-301, 650-222, 820-407, 976-402, and 988-401). Biogen noted that no adverse prenatal testing was reported prior to the terminations (SU, pp. 80-81).

7.6.3 Pediatrics and Assessment of Effects on Growth

Biogen did not study BG00012 in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose of BG00012 have been reported in the clinical studies performed to date. Biogen felt that the clinical trial adverse events were not consistent with rewarding effects or other abuse-related behaviors. Biogen searched the clinical trial adverse events using a list of MedDRA terms potentially related to drug abuse (e.g., mood elevation, euphoria, hallucination, sedation, somnolence, insomnia, cognitive disorder, anxiety). Biogen noted that the majority of these AEs occurred in <1% of BG00012 exposed patients. Based on the chemical properties, mechanism of action, and clinical study AE data, Biogen felt that BG00012 has a low potential for potential abuse and should not be considered a controlled substance (SU, p.82).

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Reviewer Summary
BG00012 is not yet approved by a regulatory authority, so to support the BG00012 NDA, Biogen provided foreign post marketing data for Fumaderm, a product that includes dimethyl fumarate. Fumaderm is approved in Germany for the treatment of Psoriasis and estimated exposure is 159,000 person years. Biogen's summary of post marketing reports and the medical literature demonstrates that the most commonly reported AEs with Fumaderm (lymphopenia, GI adverse events and flushing) are the AEs commonly reported in BG00012 clinical trials. There appeared to be relatively few hepatic or renal adverse events for Fumaderm and for the reported events, it was not clear if BG00012 had a causal role. Fumaderm did not appear to be associated with increases in malignancy risk, although post marketing data have limited value for such assessments. There were relatively few reports of infections, but Biogen did identify 3 reports of PML, 2 of which had identified confounding factors.

Background
At the time of the NDA filing, dimethyl fumarate had not been approved for use in any country, so there are no post marketing data. Biogen noted that Fumaderm, a drug that contains dimethyl fumarate in combination with 3 different salts of monoethyl fumarate, was approved in 1994 in Germany for the treatment of moderate and severe Psoriasis. Biogen provided post marketing safety data for Fumaderm. Biogen's post marketing safety review for Fumaderm included a summary of information from the medical literature as well as a review of the Fumaderm post marketing safety database.

Exposure
Biogen lacks precise post marketing use data for Fumaderm. Using sales data and assumptions regarding daily dose (120mg TID) and duration of therapy (one year), Biogen estimates that through 9/2011, there have been 159,000 person years of exposure and 159,000 patients exposed to Fumaderm. Biogen provide no data to support the assumptions upon which the use estimates were based (ISS Appendix 3, p.8627).

Literature Review
Biogen noted that a review of the published medical literature found that the most common AEs with Fumaderm were vasodilatory reactions (ex. flushing, headache), and gastrointestinal events (ex. abdominal pain, diarrhea, flatulence). Biogen stated that these events generally were non serious and diminished over time but that occasionally patients discontinued treatment for these events.

Other AEs observed with Fumaderm use were decreased lymphocyte counts and reduction in neutrophils. Biogen also noted reports of transient eosinophilia in some patients.

Biogen summarized safety monitoring recommendations from publications. Biogen noted that regular measurement of leukocytes with differential cell counts and discontinuation of treatment is recommended, if persistent clinically significant abnormalities are present. In addition, regular testing of urine for protein and blood serum for creatinine is recommended because of reports of very rare toxic effects of fumarates on renal proximal tubular cells. Regular measurement of hepatic enzymes is also recommended, although Biogen reports that significant liver damage during treatment with Fumaderm is very rare (ISS Appendix 3, p.8628).

Post Marketing Safety Database Review
In their Executive Summary of post marketing events, Biogen reported that the Fumaderm safety database most commonly included reports of flushing, headaches and gastrointestinal symptoms, as well as reports of decreased lymphocyte counts. Biogen noted that the majority of these events were not serious.

In a 7/30/12 response to a Division request, Biogen provided a detailed summary of the AE reports included in the Fumaderm post marketing safety database. Biogen noted that the Fumaderm post marketing safety database includes 1432 unique reports with 2697 AEs. Of the 2697 AEs, 2381 were considered non-serious (7/30/12 Response, p.1).

The highest number of cases and AEs are reported for the GI SOC (423 reports, 683 AEs). Other SOCs with more than 100 AEs are Blood and lymphatic system disorders (n= 390 AEs), Investigations (n= 386 AEs), Skin and Subcutaneous Tissue Disorders (n= 255 AEs), Vascular Disorders (n= 170 AEs), Nervous System Disorders (n= 128

AEs), General Disorders and Administration Site Conditions (n= 123 AEs), and Renal and Urinary Disorders (n= 101 AEs) (7/30/12 Response, Appendix A Table 1).

The most frequently reported adverse events (>=50) by PT were diarrhea (n=217), lymphopenia (n=142), abdominal pain upper (n=116), flushing (n=108), eosinophilia (n=95), abdominal pain (n=86), nausea (n=67) and leukopenia (n=60). Infrequent, but potentially concerning reported AEs included agranulocytosis (n=1), pancytopenia (n=2), acute pancreatitis (n=4), necrotizing pancreatitis (n=1), drug induced liver injury (n=1), hepatic steatosis (n=1), cholestatic hepatitis (n=1), hepatitis toxic (n=1), drug hypersensitivity (n=2), hypersensitivity (n=2), herpes zoster (n=6), PML (n=3), rhabdomyolysis (n=1), suicide attempt (n=2), Fanconi syndrome (n=1), glomerulonephritis chronic (n=1), glomerulonephropathy (n=1), ketonuria (n=1), renal failure (n=9), nephropathy toxic (n=2), renal failure acute (n=2), renal tubular acidosis (n=1), tubulointerstitial nephritis (n=5), angioedema (n=1) (7/30/12 Response, Appendix A Table 2).

The most frequently reported serious adverse events by PT were breast cancer (n=7), lymphopenia (n=6), renal failure (n=6), alanine aminotransferase increased (n=5) and myocardial infarction (n=5).

Serious Hepatic Events
Biogen identified 12 reports (23 event terms) of serious liver event AEs. The serious events reported were ALT increased (n=5), AST increased (n=4), GGT increased (n=4), transaminases increased (n=2), hepatic cirrhosis (n=2), cholecystitis acute, cholelithiasis, drug induced liver injury, hepatitis cholestatic, liver disorder, and liver function test abnormal. There were no events coded to the terms acute hepatic failure, hepatic failure, or liver failure.

Biogen felt that several of the serious hepatic event reports included alternative explanations for the events (primary biliary cirrhosis, hepatitis C, and cirrhosis in a patient with previous hepatitis B). Additional reports included confounding medication use (allopurinol, female hormones in a case of cholestatic jaundice).

Among the serious reports of elevated liver transaminases, the patients had no other reported liver related symptoms, or concomitant elevation of bilirubin (7/30/12 Response, p. 2).

Serious Renal Events
Biogen identified 20 reports (28 event terms) of serious renal event AEs. The events reported were renal failure or acute renal failure (n=8), creatinine increased (n=4), proteinuria (n=4), hematuria (n=3), tubulointerstitial nephritis (n=3), nephropathy toxic (n=2), osteomalacia (n=2), Fanconi Syndrome, and glycosuria. I summarize selected events using data from the submitted MedWatch forms.

Renal Failure, Acute renal failure
Biogen submitted 8 reports of serious events coded as renal failure or acute renal failure. There did not appear to be affirmative evidence that Fumaderm caused these events, but this assessment was limited by the lack of information. These events occurred in 5 females and 3 males. The age range for the patients in these reports was 68-76 years (2 not reported). The reports generally included few clinical details about the events and none had baseline BUN or creatinine data. Three reports included only the diagnosis and no other details. One report noted a BUN of 52 mg/dL and a creatinine of 1.62mg/dL in a 76 year old male. One report noted a creatinine of 1.4mg/dL and a GFR of 55 (no units) in a 68 year old female. Two reports described patients with worsening renal function but also mentioned confounding factors (underlying vascular disease, hypertension). One report described a patient who experienced dehydration in the setting of nausea, and diarrhea, and the event resolved with hydration and withholding all medications.

Creatinine increased
Biogen submitted 4 reports of serious events coded as creatinine increased. These reports included few details, and none of the cases had baseline BUN or creatinine data. The events occurred in males aged 30-53 years. One event was identified as post-renal failure (obstruction). Another event occurred in the setting of dehydration, and diarrhea and resolved with hydration and discontinuation of Fumaderm. In one event, the 30 year old patient experienced increased creatinine (1.27-1.44 mg/dL). In the last event, the 53 year old had creatinine results that increased from 1.39 to 2.03 (no units) over a 4-year period.

Tubulointerstitial nephritis/Nephropathy toxic
Two patients had serious adverse events of both tubulointerstitial nephritis and nephropathy toxic and one patient had a serious event of only tubulointerstitial nephritis. Biogen noted that these 3 serious reports (identified from the medical literature) most likely involved other preparations of fumaric acid formulations, since the dates on the articles (1989 and 1990) preceded the date of marketing authorization of Fumaderm®. In these cases, the patients were treated with concomitant oral formulations of fumaric acid, fumaric acid ointment and fumaric acid baths.

In the first case, a 36 year old female with a creatinine of 83mcmol/L was started on treatment with fumarates and 6 weeks later developed nausea, vomiting, and fever, and stopped the fumarate therapy. She was evaluated and treated with amoxicillin for WBCs in her urine. Her condition worsened and 4 days later she was admitted to a hospital. She had a serum creatinine of 2770 mcmol/L, proteinuria, glucosuria, urinary WBCs (10-20/HPF), and granular casts. She also had anemia and a positive indirect Coombs test. She received hemodialysis for 2 weeks. A kidney biopsy documented normal glomeruli, widespread necrosis of tubular cells, with eosinophils, consistent with tubular interstitial nephritis. Nine months after this event, creatinine clearance was 56mL/min and urine was negative for protein, glucose, and casts.

The remaining 2 cases involved sisters, and the events were described in a single publication. A 25 year old treated with fumarates experienced flushing symptoms and on day 4, developed fever. Fumarates were stopped after 2 weeks for GI complaints and general clinical side effects. She was evaluated and found to have proteinuria (2.65 grams), urinary WBCs (60 cells/mm3), granular casts, hematuria, and developed an elevated creatinine (2.2mg/dL) and low creatinine clearance (44mL/min). A renal ultrasound demonstrated kidney enlargement. Her abnormal renal function tests and urinary findings resolved within 3 weeks. The patient's 29 year old sister experienced a similar course. This patient also developed a fever within 4 days of starting fumarates and stopped treatment after 16 days for GI and other AEs. Her creatinine rose (highest 2.5mg/dL) and creatinine clearance fell to 27mL/min. She also experienced proteinuria, urinary WBCs, and hematuria. The authors reported that these abnormalities resolved in 3-4 weeks.

Fanconi's Syndrome
A serious literature report of acquired Fanconi's syndrome and osteomalacia described a patient with a 10 year history (from 1989-1999) of treatment with oral fumaric acids, fumaric acid ointment and potentially Fumaderm. This 48 year old female with bilateral coax vara deformities initially presented in 1996 with a pathological left femoral neck fracture. She underwent bilateral corrective osteotomies. In 1999 she presented with tibial and fibular fractures. She was subsequently diagnosed with osteomalacia. Evaluation revealed hypophosphatemia, proteinuria, aminoaciduria, glucosuria, and creatinine clearance of 55 mL/min. She was diagnosed with Fanconi syndrome. All fumaric acid treatments were stopped and within 3 months proteinuria, glycosuria, and aminoaciduria were improved and serum phosphate and Vitamin D were nomal. Biogen felt that the other serious case report of osteomalacia with limited data appeared to overlap with the information in this case and may be a duplicate.

Biogen identified 30 post marketing report cases of proteinuria. Biogen felt that these reports would be expected given that urine testing is commonly performed in patients treated with fumarates.

Lymphopenia/Infections
Biogen reported that 15% of the post marketing reports for Fumaderm described lymphopenia or decreased lymphocyte count. Biogen did not feel that there was evidence of increased risk of infection associated with these cases. Biogen did examine the safety database for opportunistic infections and identified occasional reports of such cases. Biogen noted that there have been 3 cases of PML reported for Fumaderm. Biogen felt that Fumaderm was not involved in one case because the onset of PML was within 1 month of starting Fumaderm. In this case, Biogen felt PML was more likely related to underlying sarcoidosis requiring treatment with steroids and methotrexate. In a second case, Biogen identified potential confounding factors such as prior treatment with efalizumab, history of melanoma, and decreased immunoglobulins of unknown etiology. In the 3rd case, a 74 year old male was diagnosed with PML after 3 years of

Fumaderm treatment, which included decreased lymphocyte counts <500 for over 2 years. This patient had previously been treated for psoriasis with acitretine and methotrexate. Biogen felt that this single case of PML without clear risk factors in 159,000 person years of use was consistent with the background rate of PML in patients with autoimmune diseases. In addition to PML, Biogen identified one report of tuberculosis and one of Kaposi sarcoma in their database.

In addition to the Fumaderm PML cases described above, Biogen provided information about a PML case that occurred in a Psoriasis patient treated with compounded dimethyl fumarate and copper monoethyl fumarate. In a submission dated 12/10/12, Biogen provided a summary of the limited available information for this case. This event occurred in a 42 year old female from the Netherlands. She was treated with dimethyl fumarate and copper monoethyl fumarate for 6-7 years. She presented with neurological symptoms including involuntary movements of her right thumb, and weakness of the right hand. An MRI demonstrated a demyelinating lesion of the white matter of the left pre-central gyrus affecting the U fibers. Her initial diagnosis was MS and she was treated with methyprednisolone without improvement. She subsequently developed right hemiparesis. A follow up MRI, at an MS center, showed that the lesion progressed and was not typical for MS. A CSF sample was positive for JCV, and serology was positive for JCV and negative for HIV. Her lymphocyte count was 200. Her fumarate treatment was stopped and she is being followed. Biogen will provide additional information about this case as it becomes available.

Biogen noted that if no confounding factors are identified for this case, then it is possible that compounded fumarate had a contributory role in the development of PML, in the setting of severe lymphopenia. Biogen also noted that there was no evidence of increased risk for opportunistic infections, and no PML cases in the BG00012 NDA and therefore, this case does not change the risk profile for BG00012.

Malignancies
Biogen also reviewed available post marketing data regarding malignancy risk with Fumaderm.

Biogen found relatively few publications about malignancy risk with Fumaderm. Biogen identified a publication that discussed a possible link between Fumaderm and squamous cell carcinoma and another with melanoma. Biogen also identified a publication that indicated dimethyl fumarate impaired melanoma growth and metastasis in animals.

Biogen found 50 serious reports (51 events) and 15 non-serious reports of malignancies in their Fumaderm post marketing database. Biogen did not explain why some of these malignancy cases were classified as non-serious. The malignancies reported at least 3 times were breast (n=9), leukemia (n=7), colon/rectum (n=5), lymphoma (n=4), prostate (n=4), renal (n=4), basal cell carcinoma of the skin (n=3), squamous cell carcinoma of

the skin (n=3), and melanoma (n=3). Using their estimated exposure to Fumaderm (159,000 person years) Biogen calculated reporting rates for malignacies and then compared the reporting rates to Globocan 2008 incidences for malignancies. The Globocan data is derived from malignancy incidences in developed countries/regions (North America, Europe (northern, southern, western, and eastern), Japan, and Australia and New Zealand). The individual malignancy reporting rates with Fumaderm were all lower than the corresponding Globocan incidences. Based on 4 reports, the reporting rate of renal cell cancers (2.4/100,000PY) was below the Globocan 2008 reference data (8.6/100,000/yr). Biogen recognized the limitations of these comparisons, specifically, likely underreporting of events with Fumaderm and the lack of adjustment for age and gender (7/30/12 Response, p.6).

Biogen also noted that a number of publications report increased rates of malignancy in psoriatic patients compared to non-psoriatic patients (Margolis et al 2001, Boffetta et al 2001, Ji et al 2009), which impacts interpretation of the above comparisons. Biogen noted that Brauchli et al compared incidence rates of individual malignancies in psoriatic and non-psoriatic patients using data in General Practice Research Database and found increased risk in patients with psoriasis for hematological malignancies (0.75/1000 pyrs), for gastrointestinal malignancies (1.00/1,000 pyrs), for renal or bladder malignancies (0.36/1000 pyrs) and for breast malignancies in women (1.79/1000 pyrs). Biogen felt that the available data suggest that the reports of malignancies received from patients with Fumaderm represent background events and do not suggest an increased malignancy risk with Fumaderm.

PTH/Vitamin D
There were no reports of hyperparathyroidism or elevated PTH, and one report of Vitamin D deficiency with Fumaderm.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

Labeling recommendations to be presented and discussed during review team meetings.

9.3 Advisory Committee Meeting

Not Applicable

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/s/

GERARD A BOEHM
01/04/2013

SALLY U YASUDA
01/09/2013

CLINICAL REVIEW

Application Type	NDA
Application Number	204063
Priority or Standard	Standard
Submit Date	2-27-2012
Received Date	2-27-2012
PDUFA Goal Date	3-27-2013
Division / Office	DNP/OND 1/ ODE 1
Reviewer Name	Heather Fitter, M.D.
Review Completion Date	11-08-2012
Established Name	BG00012 (BG-12)
(Proposed) Trade Name	Tecfidera
Therapeutic Class	Dimethyl Fumarate
Applicant	Biogen Idec
Formulation	Oral
Dosing Regimen	240 mg bid
Indication	(b) (4)
Intended Population	Relapsing forms of Multiple Sclerosis

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

I recommend approval of the BG-12 240 mg dose to be taken orally twice daily for the treatment of patients with relapsing forms of multiple sclerosis (b) (4)

1.1 Recommendation on Regulatory Action

The pivotal clinical efficacy trials demonstrated that BG-12 is effective for the treatment of patients with relapsing forms of multiple sclerosis (b) (4) The two efficacy trials, 109MS301 and 109MS302 were adequate and well controlled trials that compared two doses of BG-12 to placebo on clinically relevant endpoints in multiple sclerosis patients over the course of 2 years. Trial 109MS301 was a placebo controlled randomized double blind trial in patients with relapsing remitting multiple sclerosis (RRMS) that evaluated the safety and efficacy of BG-12 240 mg twice daily (bid), BG-12 240 mg three times daily (tid) and placebo in patients with RRMS. The primary endpoint was the proportion of patients relapsing at 2 years, and the key secondary endpoints were the number of new and newly enlarging T2 hyperintense lesions, the number of Gd-enhancing lesions, the annualized relapse rate (ARR) and the delay of disability progression sustained for 12 weeks. The second trial 109MS302 was of similar design except it included an additional treatment arm of an active comparator, Copaxone (GA), in an open label rater blinded only fashion. This arm is not considered a well controlled arm and therefore data from this arm is not considered to contribute to substantial evidence of effectiveness to support comparative claims for BG-12 over Copaxone. Trial 109MS302 evaluated the primary endpoint of the ARR and included key secondary endpoints of the number of new and newly enlarging T2 hyperintense lesions, the number of new T1 hypointense lesions, the proportion of subjects relapsing at 2 years and the delay of disability progression sustained for 12 weeks. Both trials reported very robust findings on the primary clinical measures of relapse and were associated with p values of <0.0001 for all comparisons of active study treatment to placebo. These robust findings were further supported by multiple relevant sensitivity analyses such as the per protocol population, worst case scenario analyses on dropouts and on the ITT including data after patients switched to alternative medications. In addition, all key secondary MRI endpoints for the active treatment vs. placebo comparisons in both trials were highly supportive (p<0.0001) of efficacy.

The pre-specified analysis for trial 109MS301 was supportive of efficacy on the delay of disability progression for both doses studied, yet the disability progression analysis for 109MS302 was not. In trial 109MS301, the proportion of subjects that progressed by 2 years was 0.271, 0.164 and 0.177 for the placebo, BG-12 bid and BG-12 tid groups, respectively. This represented a reduction in the risk of confirmed disability progression by 38% (p=0.005) and 34% (p=0.0128) for the BG-12 bid and BG-12 tid comparison to placebo, respectively. The proportion of patients that progressed by 2 years in trial 109MS302 was 0.169, 0.128 and 0.130 in the placebo, BG-12 bid and BG-12 tid groups, respectively. These differences between the placebo group and the active treatment groups on this endpoint did not represent a statistically significant effect of BG-12 over placebo. The sponsor proposes that an effect of disability

progression was not seen in 109MS302 because the placebo group had a low progression rate as compared to that of the placebo group in trial 109MS301. Although this may be the case, this fact isn't sufficient to invalidate the disability progression analysis from trial 109MS302. The fact is that the placebo group in this second pivotal trial is relatively well balanced to the other treatment groups and as such, should be adequate to demonstrate a treatment effect on this endpoint if one exists. Therefore, in summary we have one pivotal trial that shows a positive treatment effect on disability progression for BG-12 over placebo and one pivotal trial that does not. Many products that have been studied for the treatment of MS have demonstrated an effect on relapse but were not able to show an effect on disability progression. In order to show an effect on disability progression either longer studies or studies with larger number of patients are often required. Pooling of the data in this case gives us the opportunity to assess the strength of the evidence through another analysis.

When the data from the two pivotal trials are pooled, the proportion of patients that progressed at 2 years was 0.222, 0.146 and 0.125 in placebo, BG-12 bid and BG-12 tid, respectively. These differences represented statistically significant treatment effects for both the placebo vs. BG-12 bid comparison (p=0.0034) and for the placebo vs. BG-12 tid comparison (p =0.0059). Further substantiation of this endpoint is provided by the robust effect on relapse and MRI lesion load reduction which are related clinical endpoints. I conclude that the data provided in this submission on the effect of BG-12 over placebo on disability progression sustained over 12 weeks represent substantial evidence of effectiveness when the data is considered from trial 109MS301 and the pooled analysis from trials 109MS301 and 109MS302.

Both doses studied in these efficacy trials, BG-12 240 mg bid and 240 mg tid, had very comparable efficacy on the primary endpoints and all key secondary endpoints. Since the 240 mg tid dose offered no additional efficacy to the 240 mg bid dose, I recommend approval of the 240 mg bid dose only. The higher dose would offer no clear additional benefit and would be associated with poorer tolerability and safety.

1.2 Risk Benefit Assessment

The BG-12 development program for RRMS has demonstrated efficacy in both decreasing the rate of relapses and the proportion of subjects relapsing in both pivotal efficacy trials, as well as, in delaying disability progression in one pivotal placebo controlled trial and in the pooled analysis of both pivotal efficacy trials. In addition, this product showed robust effects on the reduction of MRI lesion burden through the reduction of new and newly enlarging T2 hyperintense lesions, new Gd-enhancing lesions and new T1 hypointense lesions in patients enrolled in these trials. Therefore, benefit of this product has clearly been demonstrated for patients with RRMS. With adequate safety monitoring recommended in the product's label this product should have an acceptable risk/benefit ratio. Please refer to Dr. Gerard Boehm's safety review for a more detailed discussion of the risk assessment of this product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend the requirement of a postmarketing trial for pediatric patients age 10 -17 conducted as a randomized, controlled parallel group superiority trial to evaluate the single and multiple dose pharmacokinetics of BG-12 and the safety and efficacy of BG-12 compared to control/placebo for the treatment of relapsing remitting multiple sclerosis followed by a long term extension study. I do not recommend a requirement to study patients under age 10 due to the small numbers of patients with MS in this age range, making the study of this these younger patients highly impractical.

2 Introduction and Regulatory Background

Multiple Sclerosis (MS) is a progressive neurologic illness with a distinctly variable phenotype and course in different individuals. The etiology remains unknown, although several factors, such as genetic susceptibility, autoimmune mechanisms, viral infection and sun exposure up to adolescence are thought to contribute to the development of MS in an individual. This illness is thought to trigger an autoimmune response that leads ultimately to demyelination in the central nervous system (CNS). More recently, data is accumulating to suggest that there also is a significant degree of gray matter involvement. Treatment for MS is generally directed in three areas 1) reduction of relapses, 2) delay of disability progression and/or 3) symptomatic relief. The development program for BG-12 has explored this medication's utility to reduce relapses and delay disability progression. Currently there are several other first or second line therapies with this target. Most are injectable products yet two newer products are administered orally. One product, Gilenya, received marketing authorization in December 2010, is associated with multi-organ safety signals and requires six hours of monitoring in a clinic after administration of the first dose. The other oral product, Teriflunamide, has two safety signals described in a black box warning namely, hepatotoxicity and the risk of teratogenicity. BG-12 , if marketed, will provide another oral alternative to patients with MS.

2.1 Product Information

BG -12 is a fumarate ester drug product formulation that contains the active ingredient dimethyl fumarate (DMF). DMF is rapidly metabolized to its primary active metabolite, monomethyl fumarate (MMF). BG-12 is a new molecular entity (NME), and as such, has not been marketed in any region including the United States (US). A product that includes DMF in combination with other salts of monoethyl fumarate, Fumaderm, has received marketing authorization in 1994 for the treatment of moderate to severe psoriasis in Germany.

The BG-12 product is formulated as (b) (4) a size 0 hard gelatin capsule and will be available in two dosage strengths, 120 mg and 240 mg capsules if

marketed. The recommended dose will be 240 mg bid, yet patients will be instructed to use 120 mg bid for the first week and then increase the dose up to 240 mg bid to prevent common adverse events (AEs) with initiation of this product including gastrointestinal discomfort and flushing.

2.2 Tables of Currently Available Treatments for Proposed Indications

Please refer to Table 1 below.

Table 1: Table of currently available treatments for proposed indications

	Indication	Effect on exacerbation (exac) rate		Effect on disability progression	Safety issues (of concern)	Approved dose
Avonex (RMS)	Decrease clinical exac, slow physical disability	32% reduction (rn)		37% rn	decreased blood counts, hepatic injury, flu like symptoms	30 mcg IM q week
Betaseron (RMS)	Decrease clinical exac	30% reduction		None described in label	injection site necrosis, flu like symptoms	0.25 mg sq qod
Rebif (RMS)	Decrease clinical exac, delay physical disability	22 mcg 29% rn	44 mcg 32 % rn vs. placebo and Avonex*	27% rn	hepatic injury, flu like symptoms, injection site reaction	22 mcg or 44 mcg tiw
Copaxone (glatiramer acetate) (RMS)	Reduce relapses including patients with CIS	75% rn in first trial (n=48) 29% rn in second trial (n=251)		None described in label	Post injection reaction, transient chest pain, skin necrosis	20 mg sq q d
Mitoxantrone (SPMS or worsening RRMS)	Reduce neurologic disability and/or relapses	60% rn exacerbations; Primary outcome: 86% rn in new enhancing lesions		64% rn	Cumulative cardiotoxicity, AML[1]	12mg/m2 IV q 3 months
Tysabri (natalizumb) (RMS)	To delay physical disability and reduce exac	61% rn		33% rn	PML[2], immunosuppression, hepatotoxicity	300 mg IV q 4 weeks
Gilenya (fingolimod) (RMS)	Decrease ARR and reduce disability progression	54% rn		30% rn	Bradycardia, macular edema, infection	0.5 mg po q day
Teriflunamide	Treatment of RMS	32% rn		26% rn for 14 mg	Hepatotoxic, Teratogenic	7 mg or 14 mg po q d

[1] acute myelogenous leukemia
[2] progressive multifocal leukoencephalopathy
*32% reduction in proportion of Rebif patients who experienced relapses compared to Avonex.

Four classes of agents are approved as first line treatment for the prevention of clinical relapses in relapsing forms of MS. The first class is recombinant interferon-b (IFN-b), which includes

three formulations, specifically Avonex, Betaseron and Rebif. IFN-b is hypothesized to exert many effects at critical points in MS pathogenesis. It induces the expression of a number of genes and effects major histocompatability complex (MHC) gene expression, antiviral and antiproliferative actions and monocyte activation in vitro. The exact mechanism that leads to improvement in MS patients is not well understood[1]. Another first line compound is glatiramer acetate (GA), which is a random polypeptide made up of four amino acids in a specific molar ratio that resembles myelin basic protein. This compound is thought to exert its immunomodulatory effect due to altered T cell activation and differentiation[2]. Fingolimod (gilenya) is a third class of agent approved as first line treatment for MS. This product was the first oral agent approved for this indication and has a proposed mechanism related to its ability to sequester lymphocytes in lymph nodes, thereby reducing the number of circulating lymphocytes. This product is a sphingosine 1 phosphate receptor modulator and requires that the first dose be administered under medical supervision due to the associated risk of bradycardia. In addition, multiple safety concerns including the development of macular edema, case reports of sudden death, AV blocks, lymphopenia, infection, reduced pulmonary function tests and PML (generally following Tysabri use) have led to a cautious approach concerning the use of this product by the community. Teriflunomide was approved recently, September, 2012, and is another oral agent that reduces the frequency of relapses and delays the accumulation of physical disability (at the 14 mg dose) in patients with relapsing MS. This product acts as an immunomodulator with both antiproliferative and anti-inflammatory effects. It blocks de novo pyrimidine synthesis and has a cytostatic effect on proliferating T and B cells in the periphery. The blockage is proposed to prevent activated lymphocytes from entering the central nervous system. This product has been associated with hepatotoxicity and teratogenicity.

Mitoxantrone (Novantrone), an alkylating chemotherapeutic agent, is considered a second line treatment option because of its potential cumulative cardiotoxicity, which limits the individual maximum dose. Mitoxantrone intercalates into DNA, resulting in cross links and strand breaks[3]. In addition, this product interferes with the enzyme topoisomerase II that forms double strand breaks when DNA is altered during replication. Therefore, mitoxantrone is thought to affect replication predominantly in rapidly dividing cells. As a result of this effect, there are secondary effects on the immune system, including interference with antigen presentation, proinflammatory cytokines and attenuation of leukocyte migration[4].

Natalizumab (Tysabri) is another second line treatment option. Because of a risk for progressive multifocal leukoencephalopathy (PML), natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their

1 Markowitz, CE. Interferon-beta: mechanism of action and dosing issues. Neurology 2007;68:S8-11.
2 Menge T et al, Disease-Modifying agents for Multiple Sclerosis: Recent advances and future prospects. Drugs 2008; 68: 2445-2468.
3 Durr FE, Wallace RE, Citarella RV. Molecular and biochemical pharmacology of mitoxantrone. Cancer Treat Rev 1983; 10 Suppl. B 3-11.
4 Neuhaus O, et al. Multiple sclerosis: mitoxantrone promotes differential effects on immunocompetent cells in vitro. J Neuroimmunol 2005; 168: 128-137.

counter receptors. Disruption of these molecular interactions is proposed to prevent transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. The specific mechanism by which Tysabri exerts its effects in multiple sclerosis has not been fully defined. PML occurs in approximately 1/1000 patients treated with Tysabri. This opportunistic infection is thought to be caused by reactivation of a clinically latent JC polyomavirus infection. Risk of developing PML can be stratified based on several factors including treatment duration, prior immunosuppressant use and the presence of anti-JC virus antibodies. At this time, Tysabri is available only through a special restricted distribution program.

Several other drugs are used off label in clinical practice, including cyclophosphamide, azothioprine, methotrexate and cyclosporine.

2.3 Availability of Proposed Active Ingredient in the United States

BG-12 is not marketed in the US and is an investigational product for the treatment of MS.

2.4 Important Safety Issues with Consideration to Related Drugs

Fumaderm is a product that contains DMF as well as three other salts of monoethyl fumarate and has been marketed in Germany since 1994 for the treatment of moderate to severe forms of psoriasis.

The medical literature on Fumaderm/fumarates indicate that the most common adverse reactions involve vasodilatory effects (flushing and headaches), as well as GI effects (diarrhea, abdominal pain, flatulence), most of which occur early in treatment, are non-serious in nature, and diminish with continuing treatment. However, some patients find these effects intolerable and discontinue further treatment. A reduction in the lymphocyte count is a common laboratory finding with Fumaderm treatment, affecting up to 50% of patients. Mild transient eosinophilia is also reported to occur in some patients.

As of September 2011, the estimated postmarketing exposure was 150,000 person-years. Review of the Biogen Idec's safety database for Fumaderm reveals that the most commonly reported adverse reactions are flushing, headache, GI symptoms, and reports of decreased lymphocyte counts, the vast majority of which are non serious. Reports of small increases in one or more liver enzymes have been reported, but only rare serious hepatic events (5 cases), all of which had alternative etiologies, have been reported.

There are a relatively large number of reports (30) of cases of suspected adverse reactions of proteinuria reported, and few reports (6) of renal failure as a serious suspected adverse drug reaction. No deaths or transplantations resulted in any of these cases.

Reports of lymphopenia or decreased lymphocyte count represent nearly 15% of the reports of suspected adverse reactions in the Fumaderm safety database, but there was no evidence of any increase of reports of infections in general associated with these cases. The safety database contains very rare reports of opportunistic infections, mostly in patients with risk factors or

alternative etiologies for these events. Three cases of PML have been reported. Confounding factors in 2 of these cases (efalizumab treatment and malignancy, sarcoidosis treated with MTX and steroids) preclude a definitive role for Fumaderm. There was 1 case of PML without clear risk factors in 159,000 person-years of Fumaderm exposure.

There are relatively few reports of malignancies in the Fumaderm safety database. The most commonly reported malignancies were breast carcinoma, leukemia, gastrointestinal carcinoma, melanoma, lymphoma, and renal carcinoma.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A preIND meeting was held September 1, 2005.The sponsor expressed their plans to open the IND with a QT study and provided details in the meeting package with a list of nonclinical and clinical questions. The Agency responded to the questions as follows: The Agency stated that the nonclinical studies done with Fumaderm were insufficient to support the initiation of the phase 3 studies with BG-12, as the Agency considered this product a first in class product. The sponsor also asked that the battery of in vitro genotoxicity studies be conducted with MMF, the primary metabolite of DMF. The Agency agreed with the proposed dosing for the QT study. Several study design issues were discussed, such as placebo controlled, active comparator and alternative designs, such as all comers, add on or fixed combination. If a placebo controlled trial was selected, it would have to accommodate the ethical issues expressed by the MS Society for a placebo controlled trial. If an active comparator trial was selected such a trial would be acceptable if superiority was observed, but the trial would be uninterpretable if this was not achieved. The Agency stated that they were concerned about the early onset of forestomach carcinomas in the 13 week rat study and stated that the relevance to humans is uncertain since there is no forestomach equivalent in humans, yet the Agency asked that the sponsor provide their rationale for why these findings are not relevant to humans in the IND opening submission.

The investigational new drug (IND) application was submitted on February 22, 2006 and was placed on hold after the first review cycle. The main issues were related to safety, as there was insufficient information in the submission about patients previously exposed to BG-12 that developed cardiac and liver toxicity. In addition, insufficient safety information was provided for the phase 2 dose finding trial (C-1900). The sponsor addressed these issues and the clinical hold was lifted June 14, 2006.

On August 30, 2006, the sponsor held an EOP2 meeting with the division to discuss the continued development of BG-12. The Agency recommended that the sponsor conduct the pre and postnatal developmental toxicity study using rats rather than rabbits, as proposed. The Agency also recommended that screening for drug interaction potential involving CYP2C8 and P-glycoprotein inhibition by BG-12 should be conducted to support the NDA application. In addition, the Agency requested more details of the (b) (4) formulation (MR), and suggested investigating the potential dose dumping effect of a possible interaction between the MR formulation and alcohol. The Agency recommended that the sponsor include a population PK program to help detect potential drug-drug interactions with concomitant medications and/or other factors that could contribute to variability. In addition, the Agency mentioned that if the

sponsor studies patients with RRMS in their trial, the indication would likely be RRMS. In order to have this indication extend to patients with relapsing forms of MS, a substantial number of patients with progressive relapsing MS should be included. A discussion followed about the proposed primary endpoint and methodology to allow efficacy to be assessed onto the second year of the trial. The dose of 240 mg tid was discussed. The Agency agreed that due to tolerability issues, the dose selected was an adequate maximum dose, but they recommended that the sponsor also look at a lower dose, such as 240 mg bid or 120 mg tid. The sponsor proposed stopping the trial if an interim analysis at the time when all patients had a minimum of 1 year of treatment showed a statistically significant treatment effect. The Agency disagreed with this plan because they were concerned that if there were a large number of dropouts or early escapes, there would be very limited data on patients after 1 year of treatment. This would limit both the efficacy and safety analysis. In addition, the sponsor proposed offering patients an option of taking open label study drug if they had a relapse during the study. The Agency stated that the drug proposed for patients relapsing during the study should be one of the approved MS drugs, not the investigational drug for which efficacy and safety have not been definitively established.

On October 27, 2006 the sponsor submitted a special protocol assessment for their phase 3 trials 109-MS-301 and 109-MS-302. A "no agreement" letter was issued December 11, 2006 in response to both protocols. The main clinical issues for trial 301 were as follows:

The sponsor proposed the primary endpoint in trial 301 as proportion of relapse free estimated by Kaplan Meier estimate. This change did not address the Agency's concern about the maintenance of efficacy in the second year, but considering that trial 302 has the ARR as the primary endpoint which takes into account all relapses, the Agency believes that time to first relapse can be an acceptable endpoint for trial 301. The Agency suggested that the log rank test for the time to first relapse, as originally proposed, was a better test than the Kaplan Meier estimate since it takes into account all time points rather than a single time point at 2 years. Additional clinical comments were made as follows: the inclusion criteria as proposed allows for MRI criteria alone to determine eligibility. The Agency proposed that the inclusion criteria be based on clinical relapse, not radiological relapse. In addition, the Agency recommended that MRI with gadolinium be done in all subjects if they plan to make a claim for this endpoint and that the sponsor make disability progression a key secondary endpoint in both trials. The Agency recommended that since the sponsor's estimate of the dropout rate was 20%, they should provide a plan indicating how dropouts will be handled.

Similar comments were shared in the "no agreement" letter for trial 302, yet since the proposed primary endpoint was different in this trial, the comments about the primary endpoint varied. The Agency mentioned that they did not agree with the sponsor proposal that the final 2 year analysis should be done when 50% of the subjects reached 2 years. They believed this analysis should be done when all patients reached 2 years. The Agency stated that although the proposed efficacy analysis model is the Poisson regression model that includes three covariates, the Agency was not certain that the relapse data would follow the Poisson distribution. The Agency recommended that the sponsor reconsider the covariates to be included in the model since the currently proposed baseline EDSS and baseline relapse rate are correlated which may complicate

interpretation. Rather than use age as a covariate, the age effect can be evaluated in a sub group analysis instead.

On August 8, 2007 a teleconference took place between the sponsor and DNP. The sponsor acknowledged that they had withdrawn the two SPA requests and resubmitted the modified protocols. The trials were already initiated because the sponsor believed they had addressed the Agency's concerns.

A pre-NDA meeting occurred on January 25, 2012. The discussion at the pre-NDA meeting focused on the following topics: the adequacy of the safety and efficacy data from the two phase 3 trials, the criteria for selecting narratives and CRFs to be submitted with the NDA, the presentation of electronic data and datasets for the key studies, the approach to integrate efficacy and safety data, the plan for pediatric studies and whether the Agency expected the need for an Advisory Committee to discuss this application. In general the discussion of these points represented an exchange of information with no controversial issues arising. In addition, the sponsor mentioned that they planned to provide a rationale for priority review for this product, and the Agency said that at this point they did not anticipate designating this application for priority review, but that the sponsor should submit their rationale and the Agency would consider their arguments. The Agency stated that since other products with similar clinical profiles were available, their product did not appear to address an unmet medical need. The Division asked the sponsor what their plan was for the presentation and handling of the Copaxone data in trial 302 in terms of a comparison to the other study treatment arms in that trial, since Copaxone was given in an open label fashion unlike the 3 other arms, which were double blind, placebo controlled. The sponsor stated that they would provide the data and make efficacy comparisons to the other treatment arms in the study, but did not intend to reach definitive conclusions regarding comparisons between the study drug and Copaxone.

3 Ethics and Good Clinical Practices

The sponsor's submission was of acceptable quality. FDA's inspections by the Division of Scientific Investigations (DSI) revealed certain problems which will be described below for two sites in which 483s were issued. Overall, this reviewer concludes that these deficiencies would not affect the integrity of the data or the conclusions drawn from the data in a significant way. The sponsor exercised due diligence in obtaining financial disclosure on required investigators.

3.1 Submission Quality and Integrity

In the reviewer's opinion, the quality of the overall submission was acceptable. The information required for the review of BG-12 was easily found within the submission. Additional information requested during the review process was provided in a timely fashion by the sponsor.

3.2 Compliance with Good Clinical Practices

The sponsor reports that their clinical data was collected in compliance with good clinical practices as required by the International Conference on Harmonization (ICH) "Guideline for Good Clinical Practice" (GCP) and with the Declaration of Helsinki.

The sponsor conducted meetings with the investigators and site visits to ensure understanding of the trial procedures and requirements for data collection. The sponsor also conducted site audit visits to ensure compliance with GCP guidelines. During these audits, the sponsor identified three sites in trial 301 that were not compliant with GCP guidelines. When this was identified by the sponsor, the sites were closed. The sponsor provided sensitivity analyses of the primary and key secondary outcomes without the patients from these sites. The specific guidelines that were not followed at each site are listed below:

Site 198 (15 patients)/ US
The Investigator applied her dated signature to clinical source data that were not personally generated by her.

Site 240 (4 patients)/ Mexico
The site personnel did not have adequate oversight for the study and as a result there was deviation from the protocol and inappropriate delegation of responsibilities. Informed consent was not adequately being administered. Adverse events were not correctly documented in the source documents.

Site 188 (4 patients)/US
The Investigator did not demonstrate adequate oversight for the study. There was repeated non compliance with the protocol and inadequate source documentation.

The Division of Scientific Investigations (DSI) at the FDA was asked to inspect four sites that participated in the pivotal efficacy trials. Please refer to Dr. Antoine El-Hage's inspection report for details. Of the four sites investigated, one 483 was issued for site 516 in Poland and one 483 was issued for site 413 in Serbia.

Site 516 enrolled 45 patients in trial 109MS302. Although most of the deficiencies would not significantly effect the integrity of the data, there is one that could. The Investigator states that for 7.75% (32) of the visits identified as visit, 3, 6, 9, 12, 15, 18, 21, 24, the assessments for the primary endpoint were conducted outside of the recommended visit window. Although this is a high percentage of visits that were not conducted at the right time, the report states that the two that were farthest out from the required window was 15 and 24 days. This reviewer believes that the assessment would still be interpretable and contribute valuable information about efficacy even in the case of a delayed assessment. The main concern from this data is that it appears this site was sloppy in its ability to adhere to the protocol; therefore, there is not a high level of confidence that other errors were not made. Due to this concern, the Agency statistician performed an efficacy analysis on the primary endpoint of trial 109MS302 excluding site 516

and demonstrated that the efficacy results remained very robust for the BG-12 bid vs. placebo ($p<0.0002$) and BG-12 tid vs. placebo ($p<0.0001$) comparisons.

Site 413 enrolled 24 patients in trial 109MS301. The deficiencies that were most concerning from an efficacy evaluation perspective were the following: Six patients did not have INEC confirmation of relapses properly recorded on the source documents. In addition 2 patients had visit dates listed that did not correspond to the actual dates that the subjects were seen. The Agency statistician performed an efficacy analysis on the primary endpoint of trial 109MS301 excluding site 413 and demonstrated that efficacy results for this endpoint remained very robust without this site included in the analysis.

Site 451 and site 514 had no serous deficiencies on inspection.

3.3 Financial Disclosures

The sponsor provided adequate financial disclosure information on the following 3 clinical studies, C-1900, 109-MS-301 (this trial will also be referred to as 301 in this review) and 109-MS-302 (302).

In trial C-1900 the following Investigators disclosed financial interest: (b) (6) at (b) (6) (b) (6) for clinical trial investigator fees ($59,000), (b) (6) ($67,000) at ((b) (6), (b) (6) ($116,000) at (b) (6) (b) (6) ($54,000) at (b) (6) for consulting or speaking engagements.

In trial 301 there were 20 Investigators/sites that received over $100,000 in funds for speaking, consulting, teaching and or research. Please see Table 2 for a listing of sites where Investigators/sites earned over $100,000 and enrolled ≥ 5 patients. The Agency statistician did an analysis of the primary endpoint, proportion relapsing, eliminating the highest earning sites that enrolled ≥ 5 patients and determined that efficacy was preserved without these patients in the analysis.

Table 2: Financial disclosure trial 301, earnings over $100,000 and enrollment ≥ 5

Site number	Earnings in $	# Enrolled subjects	Direction of treatment effect	Activities
(b) (6)	655,869	(b) (6)	Positive	Consulting, speaking, training
	619,145		Positive in bid, negative in tid	Consulting, investigator initiated trial
	503,669		Positive	Consulting, speaking, training
	264,933		Neutral	Speaking, grant to hospital
	221,271		Positive	Consulting, speaking, research
	194,222		Positive bid, negative tid	Consulting, speaking, training
	167,135		Positive	Consulting, speaking
	127,708		Positive	honorarium
	101,800		Positive for bid, neutral for tid	Consulting, speaking

Refer to Table 3 for a list of the sites on trial 302 where Investigators earned over $100,000 and enrolled ≥ 5 patients with one exception. The table also includes the highest earning site in the trial at $1,226,221 although only 3 patients were enrolled. The Agency statistician performed the primary analysis on the ARR for trial 302 excluding the sites in the table below and this analysis revealed that efficacy was preserved without these subjects.

Table 3: Financial disclosure trial 302, earnings over $100,000 and enrollment ≥ 5 subjects, with one exception.

Site number	Earnings in $	# Enrolled subjects	Direction of treatment effect	Activities
(b) (6)	1,226,221	(b) (6)	Neutral	Consulting, speaking, preceptor
	715,703		Negative	Consulting, speaking, preceptor
	569,290		Positive	Consulting, speaking, grants, research, preceptorship
	202,834		Neutral	Consulting, speaking
	181,063		Neutral bid, Negative tid	Consulting, speaking
	115,177		Neutral	Consulting, speaking, training

Adequate records were provided showing that the sponsor practiced due diligence in their attempts to get financial disclosure on Investigators in the trials, even in the cases where financial disclosure was not obtained.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the Dr David Claffey's review for a comprehensive Agency CMC review of this submission.

BG-12 is being developed by Biogen Idec as a first line monotherapy for the treatment of relapsing forms of multiple sclerosis. BG-12 drug product is formulated in gelatin capsules for oral administration.

4.2 Preclinical Pharmacology/Toxicology

Please refer to the Agency nonclinical pharmacology/toxicology review by Dr. Melissa Banks for a comprehensive review. The following is a summary of the findings described by the sponsor.

In vitro and in vivo experiments with BG-12 support a mechanism of action related to activation of the nuclear factor related factor 2 (Nrf2) pathway, through the promotion of an anti-inflammatory and antioxidant response. The safety pharmacology studies did not identify any potential adverse effects on the CNS, respiratory, or CV systems.

The pharmacokinetics studies revealed that DMF is rapidly absorbed from the gastrointestinal tract and is presystemically converted to MMF in preclinical species. The primary route of elimination of 14C-DMF was due to exhalation of CO_2 followed by urine. The metabolism of DMF is mediated by the high capacity esterases and the enzymes involved in the TCA cycle pathways resulting in the formation of endogenous compounds common to all mammals. There were no apparent gender related differences in the metabolic profiles. All of the metabolites identified in humans were also found in the rat.

Acute toxicity was evaluated in the rat and mouse, and repeat dose toxicity was evaluated in the rat, dog and monkey. These trials revealed that the NOAELs for the mouse and rat in the repeat dose studies were driven by findings in the forestomach that were observed at all dose levels. Target organs identified in repeat dose toxicology studies include the liver (rat), forestomach (mouse and rat), testes (rat and dog), and kidney (mouse, rat, dog, and monkey).

The repeat dose toxicology findings are summarized below. The liver and forestomach, changes were concluded to be of limited concern in human risk. The liver changes observed with DMF administration were considered to be rodent specific as they were only observed in the 6-month rat study, were not associated with any changes in clinical chemistry, and were not observed in any other study, in any other species, and as such were not considered to be toxicologically significant.

Inflammation and tumors of the forestomach were considered to be rodent specific. Tissues analogous to the rodent forestomach are found in the epithelial cells lining the pharynx and esophagus of non-rodents (dogs and monkeys) and humans, and no DMF-findings were observed in these tissues in dogs or monkeys in studies up to 11-12 months of duration. As there is no human gastric homologue for the rodent forestomach and the clinical formulation is specifically designed to avoid release in acidic environment (i.e. the stomach), lesions of the forestomach in rodents are of limited concern for human safety

In the rat, interstitial (Leydig) cell hyperplasia and adenoma of the testis was observed.
In the 11 month dog study a decrease in the testis and epididymis weights was observed with microscopic correlates of degeneration of the seminiferous tubules of the testis at exposures approximately 3 fold higher than the RHD and hypospermia in the epididymis at exposures approximately 7 fold higher. These findings were observed in dogs that also had weight loss,

particularly the high dose animals which had lost greater than 15% of their initial body weight during the first few weeks of dosing. The findings in the testes were decreased in incidence and/or severity in both dose groups following a 28 day treatment free period, indicating a trend towards recovery once drug treatment was stopped. DMF related findings were not observed in the testes of monkeys.

Minimal to mild multifocal interstitial cell hyperplasia was also observed in the testes of DMF treated rats in the male fertility study without any adverse effects on fertility. This was not seen in the monkey. Degeneration of the seminiferous tubules, Leydig cell hyperplasia and interstitial cell adenoma were observed in the 2 year carcinogenicity study in rats.

DMF related changes were observed in the kidney of the mouse, rat, dog and monkey in the repeat dose toxicology studies. These changes were observed in multiple species with low safety margins, relative to the therapeutic exposure in humans. Investigational studies with DMF in the rat identified urinary albumin as a noninvasive biomarker of the kidney injury which led to the inclusion of urinary biomarkers, microalbumin and 2-microglobulin into the phase 3 clinical trials. Renal tumors were observed at a low incidence in mice and rats in the 2 year carcinogenicity studies.

Neither DMF nor MMF was found to be genotoxic in the standard battery of in vitro and in vivo genotoxicity assays.

Two year carcinogenicity studies were performed in the rat and the mouse with daily oral lavage of DMF. Treatment related carcinogenic findings were observed in both the rat and mouse in the nonglandular stomach, testis (rat) and parathyroid (rat) and kidney.

The reproductive effects of DMF have been thoroughly evaluated in fertility, developmental, and peri- and post-natal development toxicology studies. DMF was not found to be teratogenic, nor have any effects on male or female fertility. Findings (reduced fetal weight, reductions in ossification, delays in male sexual maturity and increased abortions) were apparent at maternally toxic doses resulting in reduced maternal weight.

As nephrotoxicity was observed in all of the toxicology species at exposures similar to the human therapeutic exposure, the sponsor considered the identification of noninvasive biomarkers that correlated with the early DMF renal injury to be very important to the human risk assessment, given the utility of such markers to identify early renal changes in the clinic. Investigational studies were conducted in the rat to determine potential biomarkers for DMF renal toxicity. The investigative studies evaluated 4 urinary markers for renal tubule injury; albumin, ß-N Acetylglucosaminidase (NAG), 2-microglobulin (2m), and Kidney Injury Molecule 1 (KIM-1). In addition, the studies included immunohistochemical evaluation of kidney tissue with Ki67, a marker of cellular proliferation. These studies in the rodent demonstrated that urinary albumin was an early marker for renal injury at a time when DMF related kidney changes were reversible.

4.3 Clinical Pharmacology

Please refer to the Agency review by Dr. Jagan Parepally for a comprehensive review of the Clinical Pharmacology data in this application. The following is the Sponsor's summary of the clinical pharmacology information as it relates to this application.

4.3.1 Mechanism of Action

BG-12 is an orally administered product with a novel mechanism of action for the treatment of relapsing MS. BG-12 pharmacodynamic responses appear to be mediated through activation of the nuclear factor (erythroid-derived 2)-related factor 2 (Nrf2) antioxidant response pathway, which is the primary cellular defense system for responding to a variety of potentially toxic stimuli through upregulation of antioxidant response genes. In preclinical in vitro studies, BG-12 significantly reduced macrophage activation and subsequent pro-inflammatory cytokine release in response to inflammatory stimuli. BG-12 also demonstrated therapeutic efficacy in multiple types of in vivo inflammatory insults, such as the collagen induced arthritis (CIA) model and multiple rodent experimental autoimmune encephalomyelitis (EAE) models. Ex vivo studies with human and animal immune cells suggest that BG-12 may promote a transition in the cellular responses from pro-inflammatory (TH1, TH17) to anti-inflammatory (TH2) cytokine expression profiles. Preclinical studies collectively indicate that BG-12 activation of the Nrf2 pathway works along multiple fronts to reduce inflammatory responses in both peripheral and central cells and to promote cytoprotection of CNS cells against toxic insults. The exact mechanism by which BG-12 exerts its therapeutic effects in MS is not fully understood.

4.3.2 Pharmacodynamics

Activation of the Nrf2 Pathway
DMF and MMF dependent activation of endogenous antioxidant response elements (ARE) has been confirmed in primary cells from humans, rats and mice in which treatment increased transcription and protein levels of several Nrf2 target genes. Activation of the ARE is proposed to regulate expression of antioxidant and stress response associated genes.

Flushing
The sponsor conducted a study to evaluate potential mediators of BG-12 induced flushing (trial BG-PK-01/02). Analysis of this PD data showed an increase of PGD2 and PGF2α and plasma serotonin during flushing. Plasma histamine and TNFα did not increase. In addition, the sponsor conducted a trial to look at the PK/PD relationship between plasma, MMF and flushing (109HV106). Flushing was highest in patients on day 2, following dosing and occurred most during the first month of treatment and then decreased thereafter.

Gastrointestinal Effects
Although patients frequently report GI related adverse events (nausea, vomiting, diarrhea, abdominal pain, dyspepsia, gastritis) with administration of BG-12, the sponsor was unable to identify a relationship between PK parameters and GI symptoms. GI events occurred most during the first month and decreased substantially afterwards.

Lymphopenia/Eosinophilia
Over the first year of treatment mean WBC count decreases by 10-30%. In the overall controlled and uncontrolled clinical trial database, WBC counts <3.0 x 10^9/L were observed in 6% of patients on BG-12 bid and 5% on BG-12 tid. In patients with reduced lymphocyte counts, lymphocytes begin to recover 4 weeks after discontinuation. A transient increase in eosinophils was seen over the first 2 months of therapy.

4.3.3 Pharmacokinetics

Orally administered DMF is rapidly and completely converted to its major metabolite MMF after oral administration. DMF is rapidly cleaved by hydrolysis to MMF which is also pharmacologically active. As a result, DMF is not quantifiable in plasma following oral administration of BG-12, so PK analyses were performed with MMF plasma concentrations in BG-12 clinical studies.

The single and multiple oral dose PK of BG-12 was characterized with sampling schemes in healthy volunteers (HV) as well as in patients with MS. The exposure (by Cmax and AUC) was generally dose proportional across the dose range (120 mg to 360 mg) and the dosing frequencies (bid and tid) tested. No accumulation of exposure was detected with multiple dosing due to rapid elimination of the drug. The PK in subjects with MS was similar to that observed in HV. Body weight was identified as the main covariate of exposure, but did not affect the safety and efficacy measures evaluated in the pivotal phase 3 studies. Food effect on exposure was partial and weak (with high fat diet and on Cmax only). The effect of food on the PK was evaluated in 2 studies in which HV were administered a single 240 mg dose with a low fat or high fat diet. These studies together, showed that the high fat diet resulted in a moderate decrease in Cmax without affecting the overall exposure as measured by AUC. These findings suggest that food should not have a clinically significant effect on exposure.

Single dose studies were performed in HV with oral doses of 120 mg, 240 mg and 360 mg. Despite the high inter-individual variability of the MMF concentration time profiles, the overall exposure after a single and multiple oral dose of BG-12, as characterized by AUC, was consistently dose proportional across studies and dose levels. The terminal half life is 0.5-1.2 hours. Most of the concentration levels fall below detection by 8-12 hours.

Multiple dose studies were performed in HV and MS subjects with bid and tid dosing for up to 4 days. The concentration time profiles in MS subjects were consistent with those for HV. In MS subjects the median Tmax values were 5 hours (bid) and 7.5 hours (tid), whereas the median Cmax values were 1.72 mg/L (bid) and 1.93 mg/L (tid). The overall MMF exposure was dose proportional with median AUC (0-24) values of 8.02 h.mg/L (bid) and 12.3 h.mg/L (tid).

An open-label study to investigate the absorption, metabolism and excretion of a single oral dose of 14C-labelled BG-12 was performed in healthy male subjects. The major metabolites of BG-12 in plasma were MMF, fumaric acid, citric acid, and glucose. Primary metabolites in urine differed from those identified in plasma with the most abundant being cysteine and N-acetylcysteine conjugates of monomethyl and or dimethyl succinate. Metabolism of BG-12 to

MMF is mediated by esterases in the gut, blood and tissues prior to reaching systemic circulation. The downstream metabolism of DMF and MMF and their metabolites occurred through the TCA cycle, with exhalation of CO_2 serving as the major route of elimination (60% of dose). Renal elimination (15.5% of dose) was the secondary and minor route of elimination. Therefore, the sponsor believed that an evaluation of the PK in individuals with renal impairment was not necessary due to the low renal elimination of BG-12. Data suggests that BG-12 has low potential for CYP440 hepatic metabolism therefore, the evaluation of PK in individuals with hepatic impairment was considered not necessary by the sponsor. No dose adjustment for patients with renal or hepatic impairment is recommended.

The influence of various demographic factors on exposure were evaluated in a phase 1 study of MS subjects. An analysis of variance (ANOVA) showed that weight had a statistically significant effect on AUC and Cmax and that gender and age had a marginal, but not statistically significant, impact on Cmax only. Although weight appears to inversely affect exposure, results from the pivotal phase 3 efficacy trials indicate that body weight did not have an effect on the efficacy or safety of BG-12. Therefore, no dose adjustment for weight is recommended.

5 Sources of Clinical Data

All documents and datasets for review of this NDA were in electronic format. This information can be found in the electronic document room at the following link:
\\cdsesub5\EVSPROD\NDA204063\0000

5.1 Tables of Studies/Clinical Trials

Table 4 below provides a listing of the clinical studies which contributed to this efficacy review. The dose finding trial is referred to as C-1900 and the two pivotal efficacy trials are 109MS301 and 109MS302. In this review, these two trials will also be referred to as trials 301 and 302. The long term extension trial, 109MS303 (303), is described although it provides mostly safety, rather than efficacy data.

Table 4: List of BG-12 trials that contributed to efficacy analysis

Study Number	Study Design	Treatment Regimens
C-1900	Phase 2, randomized, multicenter, placebo-controlled, double-blind, parallel-group, dose-ranging study	• Placebo (during Part 1) • BG00012 120 mg QD • BG00012 120 mg TID • BG00012 240 mg TID
109MS301	Pivotal Phase 3 randomized, multicenter, double-blind, rater-blind, placebo-controlled, dose-comparison study designed to determine the efficacy and safety	• Placebo • BG00012 240 mg BID\ • BG00012 240 mg TID
109MS302	Pivotal Phase 3 randomized, multicenter, double-blind, rater-blind, placebo-controlled, active reference comparator, dose-comparison study designed to determine the efficacy and safety	• Placebo • BG00012 240 mg BID • BG00012 240 mg TID • GA 20 mg QD SC
109MS303	Phase 3 multicenter, parallel-group, randomized, dose blind, rater-blind, dose-comparison extension study	• BG00012 240 mg BID • BG00012 240 mg TID

BID (twice daily); GA (glatiramer acetate); TID (three times daily); QD (once daily); SC (subcutaneous)

5.2 Review Strategy

Two large phase 3 trials contributed the bulk of the efficacy data in this submission; a single two year randomized placebo controlled double blind trial, and a second two year randomized placebo controlled double blind trial with an active reference comparator open label arm. The Sponsor also presents one year data from an open label extension trial and data from a phase 2 dose finding trial.

The phase 3 trials used the clinical endpoints of relapse (ARR, proportion relapsing) and disability progression, supported by MRI measures of disease inflammatory activity of the central nervous system (CNS). The early evaluation of efficacy in the phase 2 trial was based on MRI measures of disease inflammatory activity, supported by relapse and other clinical endpoints.

5.3 Discussion of Individual Clinical Trials

5.3.1 Protocol C-1900

Title: Double blind, placebo-controlled, dose ranging study to determine the efficacy and safety of BG-12 in subjects with relapsing remitting multiple sclerosis.

Study Objectives

The primary objective of this study was to determine the efficacy of three dose levels of BG-12 on brain lesion activity as measured by magnetic resonance imaging (MRI) in patients with relapsing remitting multiple sclerosis (RRMS) when compared to placebo.

The primary endpoint was the total number of new gadolinium (Gd)-enhancing lesions over 4 scans at weeks 12, 16, 20, and 24 (calculated as the sum of these 4 MRI scans).

The secondary objectives of this study were to determine whether BG-12, when compared to placebo was effective in reducing the:

- the cumulative number of new Gd-enhancing lesions from baseline to week 24
- the number of new or newly enlarging T2 hyperintense lesions at week 24 compared to baseline.

Study Design

This was a multicenter, placebo controlled double blind, randomized, parallel group, dose ranging study composed of two parts: a 24 week double blind, placebo controlled safety and efficacy phase (part 1) followed by a by a 24-week dose blinded, safety extension phase (part 2). In part 1, patients were randomized in a 1:1:1:1 ratio to receive one of three doses of BG-12 (120 mg qd; 120 mg tid, or 240 mg tid) or placebo for 24 weeks. In part 2, patients who received placebo in part 1 switched to BG-12, 240 mg tid; the remaining patients continued on their same BG-12 dosing regimen. The patients' original treatment assignments remained blinded for the full duration of the study, except for the 5 members of the sponsor's unblinded team who were unblinded to individual results at week 24 to perform an evaluation of efficacy and were no longer involved in ongoing management of the dose-blinded, safety extension phase.

Inclusion/Exclusion criteria

Inclusion and exclusion criteria were identical to those of the phase 3 pivotal trials. Please refer to section 5.3.2 for these details.

5.3.1.1. Efficacy Results Trial C-1900

5.3.1.1.1 Trial Population

Demographics and baseline disease characteristics

This study was comprised of 256 patients randomized at 43 sites and ranging from 18-54 years of age (median 36); of whom 164 (64%) were women and 250 (98%) were Caucasian. A total of approximately 91% of patients completed part 1 through the week 24 visit. Demographics of the 4 dosing groups were well matched, except the proportion of males was higher in the placebo group, 29 (45%), than in the BG-12 groups, 22 (34%) for the 120 mg qd group; 20 (31%) for the 120 mg tid group; and 21 (33%) for the 240 mg tid group.

Other differences existed as follows:

- Fewer patients randomized to the BG-12, 240 mg tid group (35%) had Gd-enhancing lesion activity on the baseline MRI than those in the other groups (42% in the placebo group, and 53% in both the BG-12 120 mg qd and the 120 mg tid groups).

- Median time from most recent relapse: 7 months for the placebo group vs. approximately 5 months for the BG-12 dose groups.
- Fewer patients in the placebo group, 17 (26%), had taken prior MS medications as compared to the combined BG-12 dose groups, 75 (39%) patients, 24 (38%) patients in the 120 mg qd group, 24 (38%) in the 120 mg tid group, and 27 (43%) in the 240 mg tid group.

5.3.1.1.2 Efficacy Analysis

Two analysis data sets were defined for the efficacy analyses: the ITT data set and the efficacy evaluable data set. The ITT group included 256 patients (65, 64, 64, 63 from placebo, 120 mg qd, 120 mg tid, 240 mg tid groups respectively) who were randomized and received at least 1 dose of study drug.

The efficacy evaluable data set was defined as patients with no missing data from MRI scans at weeks 12, 16, 20 and 24, whose scans were performed per protocol and who did not take prohibited alternate MS medications. This population included 223 patients (54, 59, 56, 54 from the placebo, BG-12 120 mg qd, 120 mg tid, 240 mg tid, respectively).

Efficacy Results

The primary endpoint, total number of new Gd enhancing lesions from MRI scans at weeks 12, 16, 20 and 24, was calculated as the sum of new Gd-enhancing lesions seen on these 4 scans. The analysis performed on the efficacy evaluable data set was considered the primary and the evaluation on the ITT population was considered to be a supportive analysis.

MRI (efficacy-evaluable population)

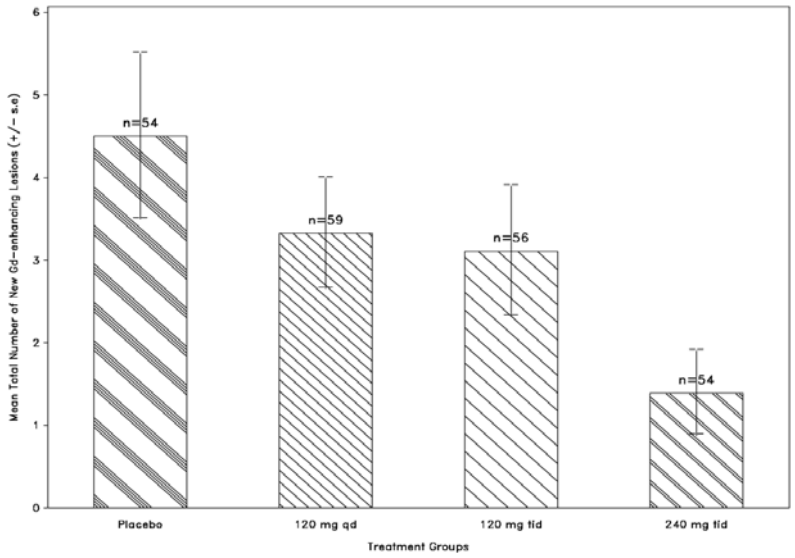
- At the highest dose of 240 mg tid, BG-12 reduced the total number of new Gd-enhancing lesions accumulated over 4 scans from week 12 through week 24 by 69% (4.5 for placebo, 1.4 for BG-12 240 mg tid; $p<0.001$) when compared to placebo, and showed significant effects on all secondary MRI endpoints versus placebo, including mean cumulative number of new Gd-enhancing lesions ($p=0.002$), the number of new or newly enlarging T2 hyperintense lesions ($p<0.001$), and the number of new T1 hypointense lesions ($p=0.014$).
- BG-12 at doses of 120 mg qd and 120 mg tid did not demonstrate a significant effect as compared with placebo on any MRI endpoint, although it approached nominal significance on the primary comparison of the total number of new Gd-enhancing lesions ($p=0.068$, 4.5 for placebo, 3.1 for BG-12 120 mg tid).
- The comparison of BG 120 mg q d to placebo yielded a p value = 0.266 (4.5 for placebo: 3.3 for 120 mg q).

Please see the results for the primary and key secondary endpoints in Table 5 and Figure 5 below. For all MRI endpoints displayed below, the 240 mg tid dose demonstrated the most favorable efficacy.

Table 5: Study C-1900 summary of key efficacy results (efficacy evaluable population)

Endpoint	Placebo	120 mg QD	120 mg TID	240 mg TID
Primary				
Number of new GdE lesions Mean number (SD) [a] Week 12-24	4.5 (7.4)	3.3 (5.1) p=0.266[a]	3.1 (5.9) p=0.068	1.4 (3.8) p<0.001
Mean number (SD) [a] Week 4-24	6.6 (11.4)	6.2 (8.9) p=0.943	6.7 (10.9) p=0.801	3.7 (11.2) p=0.002
Secondary (listed in descending rank order)				
New or newly enlarging T2 hyperintense lesions (Mean number[SD]) [a]	4.2 (5.4)	3.8 (4.7) p=0.965	4.1 (5.7) p=0.839	2.2 (5.4) p=0.0006
New or newly enlarging T1 hypointense lesions (Mean number [SD]) [a]	1.7 (2.5)	1.3 (1.8) p=0.732	1.5 (2.0) p=0.836	0.8 (2.0) p=0.014
Annualized relapse rate [b] (95% CI) Weeks 0-24	0.65 (0.43-1.01)	0.42 (0.24-0.71) p=0.196	0.78 (0.52-1.16) p=0.572	0.44 (0.26-0.76) p=0.272

Figure 1: Mean (+/- S.E.) number of new Gd-enhancing lesions (observed values) from scans at week 12 to week 24: efficacy-evaluable population



The results from the ITT population were consistent with those of the efficacy evaluable population. The mean total number of lesions was 4.8 for the placebo group. In the 3 individual BG-12 dose groups the mean values for the total number of lesions were 4.0, 3.0, and 1.3 for the 120 mg qd, 120 mg tid, and 240 mg tid groups, respectively. Compared to the placebo group, these means represent reductions of 17%, 40%, and 73% for the 120 mg qd, 120 mg tid, and 240 mg tid groups, respectively. The comparison between 120 mg tid vs. placebo and 240 mg tid vs. placebo were both nominally significant (p=0.036 and p<0.001, respectively). The median number of lesions was also reduced in all BG-12 groups compared to the placebo group.

Clinical efficacy
Although the study was not powered to evaluate the effects of BG-12 on clinical measures, clinical efficacy endpoints of the ITT population were evaluated as exploratory measures. There were no statistically significant differences between any of the BG-12 dose groups and the placebo dose group on clinical endpoints of ARR, percent relapse free, or EDSS.

However, C-1900 demonstrated a trend toward a reduction in ARR (calculated with 6-month data) for the BG-12 240 mg tid dose as compared to placebo (0.44 vs. 0.65, p=0.272), and BG-12 120 mg q d vs. placebo (0.42 vs. 0.65, p=0.196, but not for the BG-12 120 mg tid group comparison with placebo (0.78 vs. 0.65, p=0.572).

5.3.2 Protocol 109MS301

Study Title: A randomized, multicenter, double-blind, placebo-controlled, dose-comparison study to determine the efficacy and safety of BG-12 in subjects with relapsing-remitting multiple sclerosis.

Objectives
The primary objective of this study was to determine whether BG-12, when compared with placebo, was effective in reducing the proportion of relapsing subjects at 2 years.

The secondary objectives of this study were to determine whether BG-12, when compared with placebo, was effective in:

- Reducing the total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans in a subset of subjects at 2 years.
- Reducing the total number of Gd-enhancing lesions on brain MRI scans taken at 2 years in a subset of subjects.
- Reducing the rate of clinical relapses at 2 years.
- Slowing the progression of disability at 2 years as measured by at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from baseline EDSS≥ 1.0 that was sustained for 12 weeks, or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks.

Study Design
This was a phase 3, randomized, multicenter, double-blind, placebo-controlled, dose-comparison study designed to determine the efficacy and safety of BG-12 in subjects with RRMS.

Following the screening visit and a pre-treatment period lasting up to 6 weeks, subjects who met the study entry criteria were randomly assigned to 1 of 3 groups in a 1:1:1 ratio. Randomization was stratified by site.

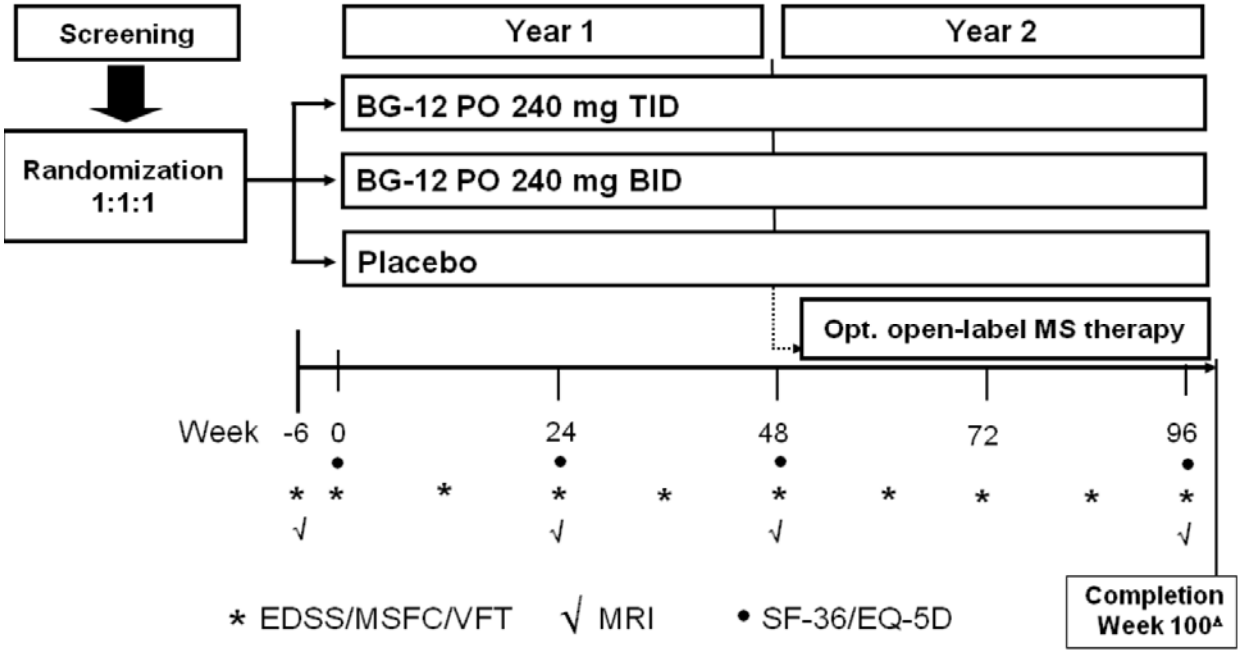
- Group 1: BG-12 240 mg bid
- Group 2: BG-12 240 mg tid
- Group 3: Placebo

The duration of blinded study treatment administration was to be 96 weeks. Clinic visits occurred every 4 weeks, with the end of study visit occurring at week 100. An overview of the study design is shown in Figure 2.

Subjects in each group were to take 2 capsules of blinded study treatment orally tid, except during the first week, when they were to take 1 capsule orally tid. Study treatment was to be taken with food. For subjects who were unable to tolerate the study treatment due to flushing and/or gastrointestinal (GI) disturbances, a 1-month dose reduction to 1 capsule tid was allowed. Subjects who experienced significantly elevated liver or renal function tests or significantly decreased white blood cells (WBCs) that were confirmed on re-testing were to have their dose temporarily withheld. If the abnormalities persisted beyond 4 weeks or occurred a second time later in the study, or if a subject experienced abnormalities in more than 2 different laboratory parameters, the study treatment was to be discontinued permanently. Other safety-related findings requiring permanent discontinuation from the study treatment included the development of renal dysfunction based on a nephrology consult or the occurrence of positive urine cytology (following hematuria of unknown etiology on 2 consecutive visits). Subjects who discontinued the study treatment prematurely for any reason were to remain in the study, continuing with an abbreviated visit schedule (see Table 10).

All study management and site personnel, Investigators, and subjects directly involved in the study were blinded to subject treatment. To protect against perceived unblinding of subjects' treatment assignments, separate study personnel were designated to treat subjects and conduct efficacy assessments. These included primary and backup treating neurologists responsible for the management of the neurological care of the subject and for performing safety and MS relapse assessments, as well as primary and backup examining neurologists who obtained EDSS scores based on detailed neurological examinations performed at protocol defined time points, but who were not involved in any other aspect of subject care.

Figure 2: Study design trial 301



In light of ethical considerations arising from the use of placebo as the comparator, the study design included defined rescue treatment options for subjects who relapsed or experienced confirmed disability progression. Subjects could be treated for a relapse with protocol defined intravenous methylprednisolone (IVMP) at the discretion of the treating neurologist, but only after being evaluated by the examining neurologist. If the relapse was confirmed by INEC and occurred at or after week 24 and the subject had completed 48 weeks of blinded study treatment, the subject was given the option of:

- Remaining on blinded study treatment;
- Discontinuing blinded treatment and switching to open-label treatment with an alternative approved MS medication, in accordance with local practices and managed by the Investigator, while remaining in the study, or
- Discontinuing blinded treatment, declining alternative MS medication, and remaining in the study.

Subjects who experienced protocol defined, confirmed disability progression at any time during the study were given the same options. Subjects who experienced an INEC-confirmed relapse or disability progression were required to re-consent in order to continue in the study.

Subjects who completed the study according to the protocol requirements were eligible to enroll in an extension study in which all subjects received BG-12. The extension study was conducted under a separate, independent BG-12 protocol, 109MS303.

Key Inclusion criteria:

- Age 18-55 years old at the time of informed consent.

- Diagnosis of RRMS according to McDonald criteria 1-4[5].
- Baseline EDSS 0-5, inclusive.
- 1 relapse within the 12 months prior to randomization, with a prior brain MRI demonstrating lesion(s) consistent with MS, or have shown evidence of Gd-enhancing lesions of the brain on an MRI performed within the 6 weeks prior to randomization.

Key Exclusion criteria:

- Primary progressive, secondary progressive or progressive relapsing MS[6]. These conditions require the presence of continuous clinical disease worsening over a period of at least 3 months. Subjects with these conditions could also have had superimposed relapses, but were distinguished from relapsing remitting subjects by the lack of clinically stable periods or clinical improvement.
- Inability to perform the Timed 25-Foot Walk (T25FW), Nine-Hole Peg Test (9HPT) with both upper extremities, and the paced auditory serial addition test 3 (PASAT 3).
- Inability to perform visual function tests (VFTs).
- History of abnormal laboratory results indicative of any significant endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, renal, and/or other major disease that would preclude participation in a clinical trial.
- History of clinically significant cardiovascular, pulmonary, gastrointestinal, dermatologic, psychiatric, neurologic (other than MS), and/or other major disease that would preclude participation in a clinical trial.
- An MS relapse that occurred within the 50 days prior to randomization and/or the subject had not stabilized from a previous relapse prior to randomization.
- Leukocytes $<3500/mm^3$, eosinophils $>0.7 \times 10^3/uL$ or $>0.7GI/L$
- Urine test abnormalities such as proteinuria 1+ or greater, hematuria without known etiology or glycosuria without known etiology.
- Previous treatment with total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody with the exception of natalizumab
- Prior treatment within 1 year prior to randomization of mitoxantrone or cyclophosphamide.
- Prior treatment within 6 months prior to randomization of cyclosporine, azathioprine, methotrexate, natalizumab, mycophenolate mofetil, IV immunoglobulin, plasmapheresis or cytapheresis.
- Prior treatment within 3 months prior to randomization of subcutaneous or oral GA, interferon alpha, interferon beta.
- Prior treatment within 50 days prior to randomization of steroids or 4-aminopyridine.

Permanent Discontinuation of Study Treatment was required for these conditions:

- The subject became pregnant.
- The subject experienced a medical emergency that necessitated unblinding of the subject's treatment assignment.

[5] Polman, 2005
[6] Lublin and Reingold, 1996

- The subject developed >3 ULN elevations in ALT (SGPT) or AST (SGOT) that were sustained for 4 consecutive weeks after blinded study treatment was withheld.
- The subject developed >1.2 ULN elevation in creatinine that was sustained for 4 consecutive weeks after blinded study treatment was withheld.
- The subject developed decreased WBC <2000/mm3 that was sustained for 4 consecutive weeks after blinded study treatment was withheld.
- The subject experienced more than 1 deviation of the same laboratory parameter that met the threshold limits defined in protocol.
- The subject receiving blinded study treatment experienced more than 2 different deviations of laboratory parameters that met the threshold limits defined in protocol. On a third occasion, the subject was required to discontinue dosing for the remainder of the study.
- The subject experienced positive urine cytology following hematuria of unknown etiology at 2 consecutive visits.
- The subject developed renal dysfunction based on a nephrologist's evaluation.
- The subject received any of the disallowed concomitant medications.
- At the discretion of the Investigator for medical reasons or for non-compliance.

Treatments administered

Investigational drug
BG-12: Each capsule contained 120 mg DMF. Patients were instructed not to take a dose within 4 hours of a study visit, and to return all drug wallets, used or unused, to the study site at each visit.

Placebo
The matched placebo for this study was supplied as enteric coated microtablets in blue and white gelatin capsules for oral administration.

Timing of doses
All subjects were either assigned to placebo, BG-12 bid, or BG-12 tid for up to 96 weeks. Capsules were to be taken tid. The study treatment was to be administered with food, because co- administration resulted in improved tolerability although it had no effect on total exposure as measured by area under the concentration time curve (AUC).

Dosing interruption for abnormal laboratory values
Blinded study treatment was required to be temporarily withheld or permanently discontinued when laboratory values met the threshold limits defined in Table 6.

Table 6: Laboratory criteria requiring withholding or permanent discontinuation of blinded study treatment

Laboratory Parameter	Laboratory Result	Required Action
AST (SGOT) or ALT (SGPT)	>3 × ULN confirmed upon re-testing[1]	Withhold study treatment
	>3 × ULN for ≥4 weeks after study treatment withheld	Permanently discontinue study treatment
Creatinine	>1.2 × ULN confirmed upon re-testing[1]	Withhold study treatment
	>1.2 × ULN for ≥4 weeks after study treatment withheld	Permanently discontinue study treatment
White blood cells (WBCs)	<2000/mm^3 confirmed upon re-testing[1]	Withhold study treatment
	<2000/mm^3 for ≥4 weeks after study treatment withheld	Permanently discontinue study treatment
Urine cytology (to be performed on any subject with hematuria of unknown etiology on 2 consecutive visits)	Positive	Permanently discontinue study treatment (added per Amendment 2, dated 20 March 2007)

Patients that developed urine laboratory abnormalities of urinary cases, proteinuria 1+ or greater, b2-microglobulinuria, urinary microalbuminuria or glycosuria in the setting of normal serum glucose, had to have these tests repeated in 2 weeks.

Dose reductions

Dose reduction was allowed only for subjects who were unable to tolerate blinded study treatment due to flushing and/or GI disturbances. (Dose reductions were not allowed for abnormal laboratory values). Subjects who could not tolerate blinded study treatment were to reduce their dose by taking 1 capsule tid for 1 month. After 1 month at the reduced dose, subjects were to resume taking 2 capsules tid. If the subject was still unable to tolerate the study treatment, the subject was required to discontinue study treatment.

Blinding

All study staff was to be blinded to subjects' randomized treatment assignments. Study staff was not to be informed of any subject's treatment assignment except in the event of a medical emergency. In addition, to protect against perceived unblinding of subjects' treatment assignments, separate study personnel were designated to conduct efficacy assessments and treat subjects as described below.

In order to maintain the blind, subjects were instructed not to take a dose of study treatment within the 4 hours prior to their scheduled appointment. This should prevent any drug-induced symptoms from being observed by study personnel during the evaluation and prevent possible unblinding of study personnel.

Primary and Backup Treating Neurologist's Responsibilities:

- 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 study treatment needed to be temporarily withheld or permanently discontinued.

Primary and Backup Treating Nurses (or study coordinator) responsibilities:

- 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 and informing the treating neurologist if a subject experienced protocol defined disease progression.

Primary and Backup Examining Neurologists Responsibilities:

- Obtaining an EDSS score based on a detailed neurological examination at the scheduled time points required in the protocol and every unscheduled relapse assessment visit if referred by the treating neurologist due to a possible relapse.

The communication of new neurologic findings by the examining neurologist to the treating neurologist was permitted as these could be relevant to the subject's medical care.

Primary and Backup Examining Technician Responsibilities:

- Administering the components of the MSFC and the VFT. The examining technician was to remain blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the treatment assignment.

MRI Technician Responsibilities:

- Performing brain MRI scans with and without Gd at all protocol specified time points.

Blinding of Study Treatment

To maintain the blind, this study used placebo capsules that matched BG-12 capsules in size, shape, color, and taste. Additionally, all subjects (including those receiving placebo) were to be dosed with the same number of capsules tid, according to the dosing scheme shown in Table 7. To ensure that the appropriate treatment was provided to each subject, the study treatment supplied to subjects consisted of drug wallets that were prepared for each treatment group. The drug wallets accounted for the fact that during the first week of double-blind treatment (days 1 to 7), subjects were to take 1 capsule of study treatment tid, and that starting on day 8, subjects were to take 2 capsules orally tid.

Table 7: Blinded study treatment dosing regimen

Treatment Group / Dose	Week 1 (Days 1-7)			Week 2+ (Day 8+)		
	Morning	Midday	Night	Morning	Midday	Night
Group 1: 240 mg BID	1 Active	1 Placebo	1 Active	2 Active	2 Placebo	2 Active
Group 2: 240 mg TID	1 Active	1 Active	1 Active	2 Active	2 Active	2 Active
Group 3: Placebo	1 Placebo	1 Placebo	1 Placebo	2 Placebo	2 Placebo	2 Placebo

Allowed concomitant therapy

- While a subject was receiving blinded study treatment, the only protocol approved treatment for relapse in this study was either 3 or 5 days with IVMP 1000 mg/day. Subjects were allowed to refuse relapse treatment. Any deviation from this recommended treatment was to be discussed first with the Biogen Idec Medical Director or designee. Steroid re-treatment of the same relapse was not allowed unless approved.
- Only under the circumstances that allowed for rescue medication were eligible subjects permitted to take alternative MS medication during the study.
- Steroids administered by nonsystemic routes (e.g., topical, inhaled) were allowed.
- Symptomatic therapy, such as treatment for spasticity, depression, or fatigue, was not restricted, but was to be optimized as early as possible during screening in an attempt to maintain consistent treatment for the duration of the study.

Prohibited concomitant medication

- Any alternative drug treatments directed toward the treatment of MS, such as long-term immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to interferon-beta, interferon-alpha, GA, natalizumab, cyclophosphamide, methotrexate, azathioprine, 4-aminopyridine or related products), with the exception of acute management of relapse as described above.
- 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-approved treatment of relapses as described above.
- Total lymphoid irradiation, cladribine, T-cell or T-cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, intravenous immunoglobulin, plasmapheresis, or cytapheresis.

Study Activities and Assessments: Efficacy, Pharmacodynamic and Safety

Please see Table 8, Table 9 and Table 10 below for the study schedules.

Table 8: Trial 301 study activities, visit 1-12, chart 1/3

Tests and Assessments[1]	Pre-Treatment Phase Prior to Randomization		Baseline Visit (Day 1)	Visit1 (Week 4±5d)	Visit2 (Week 8±5d)	Visit3 (Week 12±5d)	Visit4 (Week 16±5d)	Visit5 (Week 20±5d)	Visit6 (Week 24±5d)	Visit7[8] (Week 28±5d)	Visit8[8] (Week 32±5d)	Visit9 (Week 36±5d)	Visit 10[8] (Week 40±5d)	Visit 11[8] (Week 44±5d)	Visit 12 (Week 48±5d)
	Screening Visit (within 6 Weeks of Baseline)	3 Practice Tests within 6 Weeks													
Informed Consent	X								X[9]			X[9]			X[9]
Randomization			X												
Medical History	X														
Physical Examination	X		X						X						X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG			X						X						X
Hematology	X		X	X	X	X			X			X			X
Blood Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid Profile	X		X	X	X	X	X	X	X			X			X
Parathyroid Hormone, Vitamin D Levels			X												X
Hepatitis C antibody and HBsAg	X														
Serum Pregnancy Test[2]	X														
Urine Pregnancy Test[2]			X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
Brain MRI[3] scan ± Gd	X[10, 13]								X[13]						X[13]
EDSS	X		X			X			X			X			X
MSFC	X[5]	X[11]	X[6]			X			X			X			X

Tests and Assessments[1]	Pre-Treatment Phase Prior to Randomization		Baseline Visit (Day 1)	Visit1 (Week 4±5d)	Visit2 (Week 8±5d)	Visit3 (Week 12±5d)	Visit4 (Week 16±5d)	Visit5 (Week 20±5d)	Visit6 (Week 24±5d)	Visit7[8] (Week 28±5d)	Visit8[8] (Week 32±5d)	Visit9 (Week 36±5d)	Visit 10[8] (Week 40±5d)	Visit 11[8] (Week 44±5d)	Visit 12 (Week 48±5d)
	Screening Visit (within 6 Weeks of Baseline)	3 Practice Tests within 6 Weeks													
Visual Function Test	X[5]	X[11]	X[6]			X			X			X			X
Visual Analogue Scale			X			X			X			X			X
SF-36 and EQ-5D			X						X						X
Pharmacogenomic Sample			X[7]												
RNA Analysis[4]			X			X									X
Dispense Study Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy, Adverse Events	Monitor and record throughout the study														

Table 9: Trial 301 study activities: visits 13-25, chart 2/3

Tests and Assessments[1]	Visit13[8] (Week 52±5d)	Visit14[8] (Week 56±5d)	Visit15 (Week 60±5d)	Visit16[8] (Week 64±5d)	Visit17[8] (Week 68±5d)	Visit18 (Week 72±5d)	Visit19[8] (Week 76±5d)	Visit20[8] (Week 80±5d)	Visit21 (Week 84±5d)	Visit22[8] (Week 88±5d)	Visit23[8] (Week 92±5d)	Visit24 (Week 96±5d)	Visit25 (Week 100±5d)/ End of Study Visit
Informed Consent			X[9]			X[9]			X[9]				
Physical Examination						X							X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG						X						X	X
Hematology			X			X			X			X	X
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid Profile			X			X			X			X	X
Parathyroid Hormone, Vitamin D Levels												X	
Urine Pregnancy Test[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
Brain MRI[3] scan ± Gd												X[13]	
EDSS			X			X			X			X	
MSFC			X			X			X			X	
Visual Function Test			X			X			X			X	
Visual Analogue Scale			X			X			X			X	
SF-36 and EQ-5D												X	
RNA Analysis4						X						X	
Dispense Study Treatment	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Therapy, Adverse Events	Monitor and record throughout the study												

Table 10: Trial 301 study activities with premature study withdrawal visit and unscheduled relapse visit, chart 3/3

Tests and Assessments[1]	Premature Study Withdrawal Visit	Unscheduled Relapse Assessment Visit[14](1 to 14 days)
Informed Consent		X[15]
Telephone Questionnaire		X
Physical Examination	X	X
Vital Signs	X	X
12-Lead ECG	X	
Hematology	X	X[16]
Blood Chemistry	X	X[16]
Lipid Profile	X	X
Parathyroid Hormone, Vitamin D Levels	X	
Urine Pregnancy Test[2]	X	X
Urinalysis	X[12]	X
EDSS	X	X
MSFC	X	
Visual Function Test	X	
Visual Analogue Scale	X	
Relapse Assessment		X
SF-36 and EQ-5D	X	X
RNA Analysis[4]	X	X
Concomitant Therapy, Adverse Events	Monitor and record throughout the study	

Efficacy Assessments

Clinical Efficacy

- Relapse Assessment
- EDSS
- MSFC
- Visual function test

Definition of a relapse: A new or recurrent neurologic symptom not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. New or recurrent neurologic symptoms that evolved gradually over months were to be considered disease progression, not an actual relapse. New or recurrent neurologic symptoms that occurred fewer than 30 days following the onset of a relapse as defined above were to be considered part of the same relapse.

Procedure to be followed if a suspected relapse occurred: Subjects who experienced new neurologic symptoms were to contact the treating nurse or neurologist within 48 hours of the onset of symptoms to complete a telephone questionnaire to determine the necessity of an unscheduled relapse assessment visit. If required, the subject was then to be evaluated in person by the treating neurologist within 72 hours of the onset of the potential relapse and by the examining neurologist within 5 days of the onset of the symptoms. The examining neurologist was to perform a relapse assessment and obtain an EDSS score, and then report his/her examination findings to the treating neurologist. The treating neurologist then determined whether new objective findings (i.e., an objective relapse) had occurred, based on the neurological examination performed by the examining neurologist. Only after the examining neurologist completed the evaluation could the treating neurologist consider treating the subject with IVMP.

Evaluation of relapse cases by Independent Neurologic Evaluation Committee (INEC): INEC evaluated only objective relapses, i.e., those relapse cases that were preliminarily evaluated by the treating neurologist, subsequently assessed by the examining neurologist, and then, based on the examining neurologist's findings, determined to be a relapse by the treating neurologist. The INEC members' assessments were based on a review of subject records. These records included the subject's medical history, physical examination findings and vital signs, MS signs and symptoms, EDSS scores, information on the subject's neurological status, information from the treating neurologist's initial telephone conversation with the subject about the suspected relapse, and the most recent central laboratory results. INEC members had no knowledge of the subject's treatment assignment and were not provided with the subject's MRI scan data.

The INEC voting members did not meet to discuss their individual evaluations of whether an MS relapse had occurred. All evaluations were done independently. The majority vote of the 3 voting INEC members served as the INEC's final determination of a subject's MS relapse status. The conclusion of the INEC was to stand.

Disability Progression as measured by EDSS: In this study, disability progression was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS ≥1.0 that was sustained for 12 weeks or a 1.5 point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks.

EDSS scores were to be obtained at regular clinic visits (i.e., every 12 weeks) as well as at any unscheduled relapse assessment visits. However, sites were instructed to assess disability progression based on EDSS scores obtained at regular visits only. The treating nurse was to inform the treating neurologist if a subject experienced disability progression as defined above, and the subject was to be informed if he/she had experienced a worsening of physical disability and would be required to re-consent to continue participation in the study.

MRI Assessments

MRI assessments were performed in a subset of sites. All original digital data for all MRI images were transferred from these sites to a central MRI reading center for evaluation by physicians/technicians who were blinded to the subjects' treatment assignments. MRI visits were at baseline, weeks 24, 48 and 96. MRIs were not to be performed within 30 days of a course of steroids.

The following measurements were assessed:

- New or newly enlarging T2 weighted lesion count (relative to prior visit)
- T2 weighted lesion volume
- Baseline T2 weighted lesion count
- Gd enhancing lesion count
- Gd enhancing lesion volume
- Gd enhancing lesions at week 24, 48 that evolved into T1 non enhancing black holes at week 24
- T1 weighted lesion count, including non enhancing lesions and those that enhance with gadolinium at baseline
- New T1 weighted non enhancing hypointense lesion count (relative to prior visit)
- Total volume of non enhancing T1 weighted lesions
- Normalized brain volume at baseline
- Percent brain volume change, measured using the Structural Image Evaluation, using Normalization of Atrophy (SIENA) method (relative to baseline)
- Median magnetization transfer ratio (MTR) of whole brain at baseline
- Median MTR of normal appearing brain tissue (NABT) at baseline
- % change in MTR of whole brain (relative to baseline)
- % change in MTR of NABT
- Mean normalized MTR in Gd lesion volume (GdLV) at week 48 relative to baseline, and week 96 relative to week 48

Patient Reported Outcomes (PRO)

Subject's global impression of well being-VAS: This is an assessment of the subject's impression of his/her well being on study treatment, in which the subject draws a vertical line on a scale from 0-100 to indicate how they feel.

The SF-36 Health Survey is a 36 item questionnaire that is thought to measure the physical and psychological well being of a subject. Eight quality of life domains are used: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The recall period is over a 4 week period of time.

EQ-5D: This is a subject rated instrument that proposes to measure health outcome. This includes two components, the EQ-5D descriptive system and the EQ VAS. The descriptive system provides input about the subject's health state in 5 dimensions (mobility, self care, usual activities, pain/discomfort and anxiety/depression). For each dimension, the subject is to indicate whether he/she has no problems, some problems or severe problems. The EQ VAS is a tool that requires that the subject draw a line on a vertical scale describing his or her health on a scale from 0-100.

Safety Assessments

Clinical Safety assessments:

- Physical examination
- Vital signs
- 12 lead ECG
- AE monitoring

Laboratory Safety Assessments:

- Hematology, blood chemistry, lipid profile
- Plasma parathyroid hormone, Vitamin D
- Urinalysis including b2-microglobulin and microalbumin, urine cytology

Statistical Methods

Sample Size Justification

Subjects were randomized to BG-12, 240 mg bid daily, 240 mg tid and placebo in a 1:1:1 allocation. A sample size of 337 per treatment group was planned to have 90% power to detect a 30% reduction in the proportion of subjects relapsed at 2 years in each of the BG-12 groups compared with the placebo group, based on the Chi-square test. This calculation assumes that the estimates for proportion of subjects relapsed by 2 years are 48% for the placebo group and 33.6% for each of the BG-12 groups. It also assumes a drop out rate of 23% over the 2 years and a 5% type I error rate.

Analysis Populations

The ITT population was defined as all subjects who were randomized and received at least 1 dose of study treatment (BG-12 or placebo). Subjects were analyzed according to the treatment

group to which they were randomized. The ITT population is the primary population for the analysis of efficacy endpoints.

The per-protocol population was defined as subjects in the ITT population without any major protocol deviations, as described below.

- Violation of any of the following 3 inclusion criteria:
  - Must have had a confirmed diagnosis of RRMS according to McDonald criteria 1 to 4.
  - Must have had a baseline EDSS between 0.0 and 5.0, inclusive.
  - Must have experienced at least 1 relapse within the 12 months prior to randomization, with a prior brain MRI demonstrating lesion(s) consistent with MS, or have shown evidence of Gd-enhancing lesion(s) of the brain on an MRI performed within the 6 weeks prior to randomization.
- Poor study treatment compliance, defined as compliance up to the last dose of study treatment taken of <70%.
- Enrollment at any of the 3 sites closed due to issues with GCP compliance.

The MRI cohort was defined as subjects in the ITT population who consented to participate in the MRI portion of the study and had any MRI data.

The safety population was defined as all subjects who received at least 1 dose of study treatment. Subjects were analyzed in the treatment group to which they were randomized, provided they took the study treatment to which they were randomized for at least 50% of the time they were receiving study treatment.

The primary and secondary clinical efficacy endpoints were analyzed using the ITT population and per-protocol population; only the MRI endpoints were analyzed using the MRI cohort. All other efficacy endpoints were analyzed using the ITT population.

For the primary efficacy endpoint, statistical testing was based on a sequential (closed) testing procedure to control for the overall type 1 error. If the first comparison (BG-12 tid vs. placebo) was statistically significant ($p \leq 0.050$), then the second comparison (BG-12 bid vs. placebo) would be performed and considered statistically significant provided $p \leq 0.050$. However, if the first comparison was not statistically significant, then the second comparison would not be considered statistically significant.

With respect to the secondary efficacy endpoints, a closed testing procedure was used to control for the type 1 error due to multiplicity, which included both the ranking of the endpoints and the comparison of each dose group with placebo. Secondary endpoints were tested in the order in which they were ranked as follows:

1. Total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans in a subset of subjects at 2 years.
2. Total number of Gd-enhancing lesions on brain MRI scans in a subset of subjects at 2 years.
3. Annualized relapse rate at 2 years.
4. Progression of disability at 2 years.

For each secondary endpoint, the comparison of BG-12 tid vs. placebo was made, and, if significant ($p \leq 0.050$), the comparison of BG-12 bid vs. placebo was made and deemed statistically significant provided $p \leq 0.050$. However, if statistical significance was not achieved with the BG-12 tid group vs. placebo, the comparison of the BG-12 bid group vs. placebo was not considered statistically significant. If statistical significance was not achieved for an endpoint for a particular dose group, all endpoints of a lower rank for that dose group would not be considered statistically significant.

No closed testing procedures were performed for the analyses of tertiary efficacy endpoints. Treatment group comparisons were performed using a modeling approach. The covariates included in the models were pre-specified. All analyses included an adjustment for region. The definition of region was based not only on geography but also on the type of health care system and access to health care in each country. Regions were defined as follows:

Region 1: US

Region 2: Western European countries (including Austria, Belgium, France, Germany, Greece, Italy, Netherlands, Switzerland, UK), as well as Australia, Canada, New Zealand, Israel, and South Africa

Region 3: Eastern European countries (including Bosnia, Herzegovina, Croatia, Czech Republic, Poland, Moldova, Romania, Serbia, Slovakia, FYR Macedonia, and Ukraine), as well as India, Guatemala, and Mexico

In the primary analyses of all efficacy endpoints except for that of confirmed disability progression based on EDSS scores, observed data after alternative MS medications were initiated were excluded, or subjects were censored at the time the alternative MS medications were started if the subject had not experienced the event. For the primary analysis of MRI, MSFC, VFT, and PRO endpoints, post baseline data that were missing for any reason (e.g., early withdrawal, skipped visits, or the exclusion of data after alternative MS medications were started) were imputed.

Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of INEC confirmed subjects who relapsed at 2 years. The proportion of subjects relapsed was estimated as the probability of relapse from a Kaplan-Meier curve of the time to the first relapse during the study. Therefore, the primary efficacy endpoint was analyzed using the Cox proportional hazards model for the time to first relapse adjusted for the number of relapses in the 1 year prior to study entry, baseline age (<40 versus ≥40 years), EDSS score (≤2.0 versus >2.0), and region.

If a subject received alternative MS medication, data after the subject started on that therapy were excluded from the analyses. If a subject did not experience an INEC-confirmed relapse before starting the alternative MS medication, the subject's time on study was censored at the time the alternative MS medication was started. Likewise, if a subject did not experience an

INEC-confirmed relapse prior to prematurely withdrawing from the study, the subject was censored on the last date followed in the study. The start date for the calculation of time to censor or relapse was the date of the first dose or, if the date of the first dose is incomplete, the date of randomization.

Analysis of Secondary Efficacy Endpoints

Total number of new or newly enlarging T2 hyperintense lesions at 2 years
In this analysis, observed MRI data after a subject started alternative MS medication were excluded, and missing MRI data, regardless of reasons, were imputed. Missing post-baseline MRI data were imputed using the subject's observed post-baseline data, assuming new lesions developed at a constant rate. Missing data were not imputed for subjects with no post baseline data. If more than 1 MRI parameter value was available for a given visit, the value closest to the target visit was used in the analysis.

A negative binomial regression model was used for the analysis of the total number of new or newly emerging T2 hyperintense lesions at 1 year and 2 years. The model included treatment group and adjusted for region and baseline T2 hyperintense lesion volume. To reduce the influence of outliers, any imputed values greater than the biggest observed value were truncated at the biggest observed value in the analysis.

Total number of Gd enhancing lesions at 2 years
The ordinal logistic regression model was used for the analysis of the number of Gd-enhancing lesions at 1 year and 2 years. The model included treatment group and adjusted for region and baseline number of Gd-enhancing lesions. If a few subjects had an extremely large number of Gd-enhancing lesions at baseline, it was planned that the extreme values above 30 would be considered as 30 in the adjustment in the model.

Annualized relapse rate at 2 years
Only INEC-confirmed relapses were included in the analysis of this endpoint. Relapses that occurred after subjects received alternative MS medications were excluded from the analysis of relapse rate, and the subject's time on study was censored at the time the alternative MS medication was started.

The ARR in each treatment group was calculated as the total number of relapses experienced in a group divided by the total number of subject-years on study at 2 years (minus the time on alternative MS medication) for that group. This was the unadjusted relapse rate.

The endpoint was analyzed using a negative binomial regression model adjusted for baseline EDSS score (≤2.0 versus>2.0), baseline age (<40 versus ≥40 years), region, and the number of relapses in the year prior to study entry. The logarithmic transformation of the time on study was included in the model as the offset parameter.

Disability progression at 2 years

Progression was defined as confirmed when the minimum increase in the EDSS score was met at the next study visit occurring at least 74 days after the initial observation. The 74 day interval was based on the visit windows allowed in the protocol around the target visit day. Progression was not confirmed at a visit when a relapse was also occurring. A subject was considered to have a relapse for at least 29 days after the start of an INEC-confirmed relapse. If a subject met the above criteria for confirmed progression and was also experiencing a relapse, the subject had to meet the defined minimum criteria at the next visit in order for the progression to be confirmed. Progression could be confirmed at the premature study withdrawal visit according to the rules above.

If a subject experienced a tentative progression before starting alternative MS medication, the EDSS evaluation performed after the start of alternative MS medication were used to confirm whether the progression was sustained. If a subject experienced a tentative progression at week 96 and continued in the extension study (303), the first EDSS evaluation in that study (week 12) at the time of Study 303 database lock was used to confirm the tentative progression in the present study.

Death due to MS was counted as progression. If the subject was in the midst of a tentative progression at the time of death, the progression date was the date of the start of the progression. Otherwise, the progression date was the date of death.

Subjects who did not experience confirmed progression based on the above rules were censored. The censor date was the date of the subject's last EDSS assessment in the study or the last EDSS assessment before the start of alternative MS medication, unless the subject experienced tentative progression at that assessment. For subjects with a tentative progression at the last study visit, or at the last visit prior to the start of alternative MS medications that was not confirmed, the censor date was the date of the EDSS assessment prior to the last EDSS assessment.

Time to onset of disability progression was analyzed using a Cox proportional hazards model, adjusted by baseline EDSS value as a continuous variable, region, and age (<40 versus ≥40 years).

Protocol Amendments

5 protocol amendments occurred (10/24/06, 3/20/07, 5/22/07, 1/07/08 and 5/26/10) resulting in a total of six versions of the protocol. A high level summary of the changes made in the protocol amendments follow:

Global protocol amendment 1 (24 October 2006):

- Procedural oversights were corrected in the protocol (e.g., unnecessary efficacy tests and assessments were deleted from study visit 25).
- Changes were made to maintain consistency between BG-12 protocols 301 and 302.

Global protocol amendment 2 (20 March 2007):

- Revised and rank-ordered the secondary study objectives and endpoints and revised tertiary study objectives and endpoints.
- Revised medical history collection to include a review of cardiovascular risk factors. Instructed sites to promptly evaluate subjects who developed symptoms suggestive of underlying cardiac disease to determine whether further evaluation was required.
- Definitions for clinically relevant vital sign abnormalities were revised.
- Increased frequency of vital sign monitoring, urinalyses, and urine pregnancy tests. Addition of a lipid profile and urine cytology to the safety assessments. Required subjects with abnormal cytology results to discontinue study treatment.
- Added physical examination to and removed MSFC and VFT from unscheduled relapse assessment visit, and required that disability progression be assessed from EDSS scores performed at regular visits.
- The number of sites was increased from 140 to 160.
- Required that MRIs not be performed within 30 days of receiving a course of steroids, revised exclusion criterion #18 to increase the time prior to randomization that subjects had received corticosteroids or 4-aminopyridine or related treatment to ensure subjects were stable at enrollment.

Global protocol amendment 3 (22 May 2007):

- Increased the frequency of blood chemistry and urinalysis testing, and added calcium, magnesium, phosphate, uric acid, ß2-microglobulin, microalbumin, parathyroid hormone, and vitamin D as safety tests.
- Excluded subjects with abnormal urine tests, required additional testing for subjects who developed abnormal urine laboratory values and referral to a nephrologist if the abnormalities persisted on re-testing, and required subjects who developed renal dysfunction based on the nephrologist's evaluation to be discontinued from study treatment.
- Revised AE/SAE monitoring and recording (to occur through the last study visit, regardless of whether the subject discontinued the study treatment and remained in the study).

Global protocol amendment 4 (7 January 2008):

- Indicated that subjects who completed the study according to the protocol requirements had the option of entering an open-label extension that was to be conducted under a separate, independent protocol.

Global protocol amendment 5 (26 May 2010):

- The secondary objective of reduction of ARR at 1 year was revised to reduction of annualized relapse rate at 2 years, and the tertiary objective of reduction of ARR at 2 years was revised to reduction of ARR at 1 year.

5.3.2.1.1 Trial Population

Disposition

A total of 1237 subjects were randomized at 198 sites in 28 countries worldwide. The highest enrolling countries were the US (203), Germany (172), Poland (132) and India (114). Four-hundred and eight, 410, and 416 subjects received at least 1 dose of placebo, BG-12 bid and BG-12 tid, respectively. Of the subjects enrolled, 540 dosed subjects in 14 countries participated in the MRI cohort (180, 176, and 184 subjects in the placebo, BG-12 bid and BG-12 tid groups, respectively). Approximately 44% of patients were in the MRI cohort. A total of 838 subjects (68%) completed study treatment.

The percentage of subjects who discontinued study treatment was higher in the placebo group than the active treatment groups, with 35%, 31%, and 31% of subjects discontinuing treatment in the placebo, BG-12 bid, and BG-12 tid groups, respectively (refer to Table 11 below). The most common reasons for discontinuing the study treatment were consent withdrawn (8% placebo vs. 4% BG-12 bid and 4% BG-12 tid) and MS relapse (8% placebo vs. <1% BG-12 bid and 2% BG-12 tid. In the BG-12 bid and tid groups, the most common reason for discontinuing study treatment was experiencing an AE (placebo 5% versus 15% BG-12 bid and 13% BG-12 tid).

Overall, 101 subjects in the ITT population (8%) switched to alternative MS medications. The proportion of subjects who switched to alternative MS medication was higher in the placebo group (13%) than in the BG-12 bid (6%) and BG-12 tid (5%) groups. Among the 101 subjects who switched to alternative MS medications, the most common medication taken by subjects after switching was IFN ß-1a (76%), followed by GA (11%), and natalizumab (11%).

Reviewer's comment: Prior to 48 weeks the main reason for treatment discontinuation was due to adverse events whereas after 48 weeks, the main reason was due to the transition to alternate MS medication.

A total of 952 subjects (77%) completed the study. The percentage of subjects who withdrew from the study prematurely was similar across treatment groups, with 22%, 23%, and 23% of subjects withdrawing in the placebo, BG-12 bid, and BG-12 tid groups, respectively.

The per protocol population, included 1090 subjects divided into 381 placebo, 350 BG-12 bid and 359 BG-12 tid, respectively.

Table 11: Disposition of subjects in trial 301

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects randomized	410	411	416	1237
Number of subjects dosed	408 (100)	410 (100)	416 (100)	1234 (100)
Number of subjects who completed study drug	265 (65)	284 (69)	289 (69)	838 (68)
Number of subjects who discontinued study drug	143 (35)	126 (31)	127 (31)	396 (32)
MS relapse	31 (8)	4 (<1)	10 (2)	45 (4)
MS progression	14 (3)	7 (2)	7 (2)	28 (2)
Adverse event	22 (5)	61 (15)	56 (13)	139 (11)
Lost to follow-up	7 (2)	9 (2)	11 (3)	27 (2)
Consent withdrawn	34 (8)	18 (4)	18 (4)	70 (6)
Investigator decision	4 (<1)	4 (<1)	2 (<1)	10 (<1)
Subject non-compliance	3 (<1)	3 (<1)	9 (2)	15 (1)
Death	0	0	1 (<1)	1 (<1)
Other	28 (7)	20 (5)	13 (3)	61 (5)

Treatment discontinuation and withdrawal rates were examined by various subgroups defined by demographic and baseline MS disease characteristics, including, gender, age, weight, inclusion in the MRI cohort and region, number of relapses experienced by the subject in the previous year, prior treatment with medication for MS, baseline EDSS score and MRI lesions. Some differences between groups were noted. Treatment discontinuations were slightly more common among females (34%) than among males (27%). Treatment discontinuations were higher in Region 1 (43%) than in Region 2 (33%) and Region 3 (27%). Treatment discontinuations were also more common among subjects who had previously received MS treatment (36%) than MS treatment naïve subjects (27%).

Treatment Compliance

Compliance was assessed through capsule counts. Mean compliance (calculated based on the duration of exposure, from first to last dose taken) was 92.7% in the placebo group, 87.5% in the BG-12 bid group, and 88.0% in the BG-12 tid group.

Mean duration of study treatment exposure and mean compliance in the MRI cohort (approximately 76 weeks and 89%, respectively) were similar to that in the ITT population. Given the requirement for at least 70% compliance with the study treatment for inclusion in the per-protocol population, mean duration of exposure and study treatment compliance were higher in this population (approximately 83 weeks and 95%, respectively) than in the ITT population.

Protocol Deviations

Deviations spanned many areas and included eligibility criteria violations, dosing issues (missed doses, non compliance, incorrect medication), taking prohibited concomitant medications, evaluations performed outside the allowed visit window, efficacy or safety evaluations not performed or not valid, or a missed study visit. These deviations were captured on the subject's CRF. At different points in the study a core study management team reviewed these deviations to determine if sites needed retraining, to identify major protocol deviations and determine if they affected the planned statistical analysis. The sponsor reports that none of the protocol deviations

identified in this study had a significant effect on the study analyses or conclusions either individually or collectively.

Major protocol deviations were reported for 27 of 408 subjects in the placebo group, 60 of 410 subjects in the BG-12 bid group and 57 of 416 subjects in the BG-12 tid group. Low study treatment compliance was the most common major violation in all 3 groups (refer to Table 12 below).

Table 12: Summary of number of subjects and reasons for exclusion from the per-protocol population (trial 301)

Reasons for Exclusion	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects excluded from the Per-protocol population compared to the ITT population	27 (100)	60 (100)	57 (100)	144 (100)
Major inclusion/exclusion violation	6 (22)	4 (7)	3 (5)	13 (9)
Low study drug compliance (<70%)	14 (52)	49 (82)	51 (89)	114 (79)
From one of the three closed sites	8 (30)	9 (15)	6 (11)	23 (16)

Demographics, Baseline Characteristics and Treatment History

Demographics
The ITT population in the 3 treatment groups was well balanced in terms of most baseline demographic characteristics. Overall 74% were female, subjects ranged in age from 18-56 (mean age 38.5) with 52% under 40. The majority were White (79%), with 9% Asian, 5% other and 2% African American. The mean weight was 71 kg with a range from 35-142.5 kg.

Three regions were defined based on geography and access to health care. Overall 16% of subjects in the ITT population were from region 1, 42% were from region 2 and 42% were from region 3. The 3 regions were very well balanced between treatment groups.

The demographic characteristics of the MRI cohort were similar between groups except for the representation of regions. Region 1 was equally represented with approximately 16% in both groups, but in the MRI cohort 32% were from region 2 and 50% in region 2 while in the non MRI cohort 50% were from region 2 and 35% were from region 3.

Baseline disease characteristics
Patients were well matched between treatment groups in terms of baseline McDonald Criteria, EDSS scores, relapse history and time to diagnosis of MS in the ITT population. During the 12 months prior to the study, the mean number of relapses was 1.3, and the mean time since the MS diagnosis was 5.5 years (range 0-32).

The baseline disease characteristics between the MRI cohort and the non MRI cohort were similar with the following exceptions. For the MRI cohort 62% of subjects had been on approved treatment for RRMS as compared to 50% of subjects in the non MRI cohort. In addition, there were some notable differences in the MRI cohort in terms of baseline number of lesions on MRI. Patients in the MRI cohort receiving placebo were less likely to have 0 Gd enhancing lesions on their baseline MRI (57%) than that of the BG-12 bid (66%) or BG-12 tid (67%) groups. In addition patients in the placebo group had more Gd enhancing lesions than those in the active treatment group (see Table 13 below). The number of T2 lesions in the MRI cohort were well balanced by treatment group as was the number of T1 hypointense lesions.

Table 13: Baseline MRI evaluation- MRI cohort Trial 301

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects in the MRI cohort	180 (100)	176 (100)	184 (100)	540 (100)
Number of Gd lesions				
0	103 (57)	117 (66)	124 (67)	344 (64)
1-4	55 (31)	47 (27)	49 (27)	151 (28)
5-8	13 (7)	5 (3)	7 (4)	25 (5)
>=9	9 (5)	6 (3)	4 (2)	19 (4)
Unknown	0	1 (<1)	0	1 (<1)
n	180	175	184	539
Mean	1.6	1.2	1.2	1.4
SD	3.45	3.30	4.10	3.64
Median	0.0	0.0	0.0	0.0
Min, Max	0, 26	0, 23	0, 46	0, 46

5.3.2.1.2 Efficacy Analysis

Datasets analyzed

All clinical endpoints were evaluated by analyzing the ITT which included 1234 subjects. Sensitivity analyses were conducted on the per protocol population (1090 subjects) for the primary and secondary clinical efficacy endpoints. MRI efficacy endpoints were analyzed using the MRI cohort, which included 540 subjects in the ITT who had MRI data.

Primary Efficacy Analysis

The primary analysis was the proportion of subjects relapsed at 2 years based on INEC confirmed relapses and included data from all subjects in the ITT population (1234 subjects) until they completed the study, switched to alternative MS medication or withdrew from the study. This endpoint was analyzed using a Cox proportional hazards model, adjusted for the number or relapses in the 1 year before the study, baseline age (<40 vs. ≥ 40years), EDSS score (≤ 2 versus > 2.0) and region.

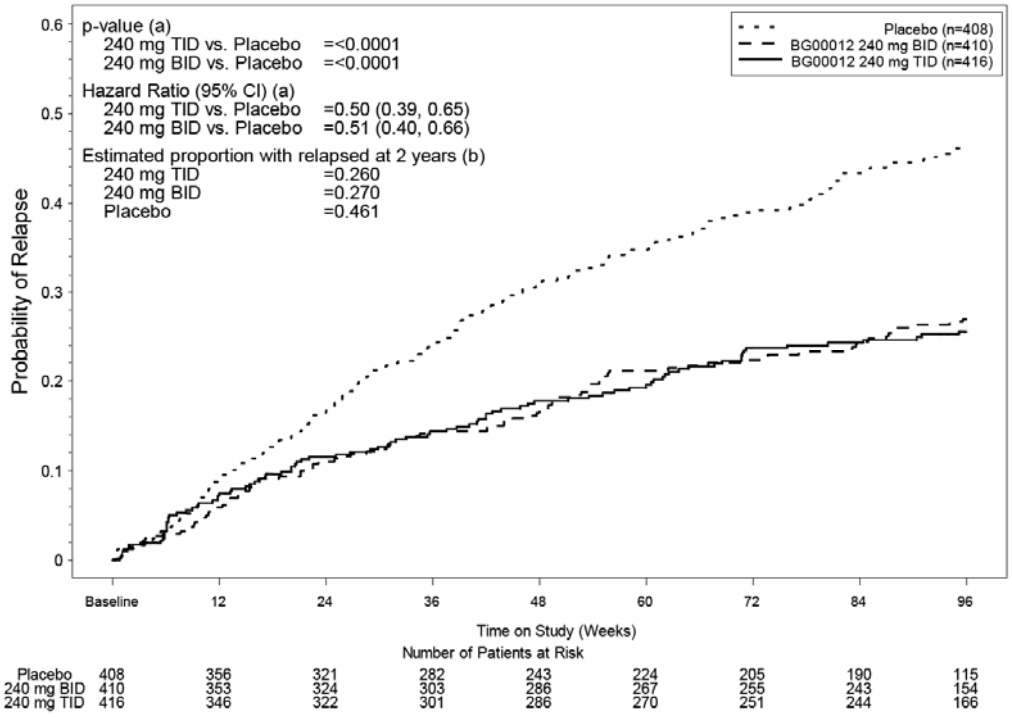
The hazard ratios obtained from the Cox proportional hazards model were 0.51 (95% CI, 0.40, 0.66) for BG-12 bid vs. placebo and 0.50 (95% CI, 0.39, 0.65) for BG-12 tid vs. placebo (see Table 14). The risk of relapse at 2 years was reduced by 49% (p <0.0001) and 50% (p <0.0001) following treatment with BG-12 bid and tid, respectively, compared with placebo.

Table 14: Summary of the proportion of subjects relapsed (INEC confirmed relapses) at 2 years -ITT

	Placebo	BG-12 BID	BG-12 TID
# of subjects (ITT)	408	410	416
# relapsed (%)	171 (42)	98 (24)	95 (23)
Proportion relapsed at 2 yrs	0.46	0.27	0.26
Hazard ratio (active/placebo)		0.51	0.50
95% CI		0.40, 0.66	0.39, 0.65
% reduction		49	50
p value (placebo comparison)		< 0.0001	<0.0001

The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 46.1% in the placebo group compared with 27.0% in the BG-12 bid group and 26.0% in the BG-12 tid group (Figure 3). Visual inspection of the Kaplan-Meier plot of the time to first relapse revealed a separation between placebo and the two active treatment groups, but nearly overlapping BG-12 bid and tid curves starting around week 12. The placebo and BG-12 curves appeared to continue to diverge from week 12 through the end of the 2 year treatment period.

Figure 3: Time to first relapse (INEC confirmed relapses) -ITT population



As can be seen in Table 15 below, a relatively high percentage of patients had unknown relapse status in each treatment group. The sponsor conducted a sensitivity analysis and assigned a relapse status of "yes" to all subjects with unknown relapse status that had withdrawn from the study or discontinued the study treatment for reasons indicative of MS relapse, lack or efficacy or a transition to alternative MS medication. After this reassignment was done, the proportion of subjects with a known assigned status of "relapsed" was 45% in the placebo group, compared with 26% and 25% in the BG-12 bid and BG-12 tid groups, respectively. The odds ratios obtained from the model were 0.42 for BG-12 bid vs. placebo and 0.41 for BG-12 tid vs. placebo. This sensitivity analysis supports the robust results obtained from the analysis of the primary endpoint.

Table 15: Summary of proportion of subjects relapsed (INEC confirmed) at 2 years - sensitivity analysis reassigning status of patients that reported an unknown relapse status- ITT population

		Placebo	**BG-12 BID**	**BG-12 TID**
# subjects in ITT		408 (100)	410 (100)	416 (100)
Relapse status at 2 years	No	173 (42)	227 (55)	236 (57)
	Yes	171 (42)	98 (24)	95 (23)
	Unknown	64 (16)	85 (21)	85 (20)
Relapse status at 2 years (unknown status assigned)	No	226 (55)	304 (74)	312 (75)
	Yes	182 (45)	106 (26)	104 (25)
Odds ratio (active/placebo			0.42	0.41
P value (compared to placebo			<0.0001	<0.0001

This reviewer will describe three additional sensitivity analyses conducted by the sponsor for the primary endpoint:

- The ITT including data from subjects both before and after subjects switched to alternative MS medications
- The per-protocol population
- The ITT population excluding the 23 subjects from the 3 sites with GCP violations

Results were consistent with those of the primary analysis, indicating that BG-12 treatment resulted in statistically significant ($p < 0.0001$) reductions of 46% to 51% in the risk of relapse at 2 years compared with placebo (refer to Table 16 below).

Table 16: Results of sensitivity analyses of the primary endpoint (trial 301)

	Placebo	**BG-12 BID**	**BG-12 TID**
ITT (n)	408	410	416
ITT with data after/before alt MS med transition			
# relapsed (%)	171, 42	98, 24	95, 23
HR (active/placebo)		0.52	0.51
95%		0.40, 0.67	0.39, 0.65
p value		<0.0001	<0.0001
# Per protocol (PP)	381	350	359
# relapsed in PP (%)	165 (43)	91 (26)	89 (25)
HR (active/placebo)		0.51	0.49
p value		< 0.0001	<0.0001
Number in analysis excluding subjects from 3 closed sites	400	401	410
# relapsed (%)	168 (42)	98 (24)	94 (23)
HR (active/placebo		0.53	0.50
95% CI		0.41, 0.68	0.39, 0.65
p value		< 0.0001	< 0.0001

Reviewer's comments: The three sensitivity analyses presented in the table above are supportive of the robust findings of the primary analysis.

Key Secondary endpoints

Total number of new or newly enlarging T2 Hyperintense lesions at 2 years
The number of new or newly enlarging T2 hyperintense lesions was analyzed using a negative binomial regression model, adjusted for region and baseline T2 hyperintense lesion volume. In the primary analysis, data obtained after subjects switched to alternative MS medication were excluded.

Over the 2 years of the study, the adjusted mean of new or newly enlarging T2 hyperintense lesions that developed in subjects receiving placebo was 17, compared with the adjusted mean of 2.6 and 4.4 in subjects receiving BG-12 bid or tid, respectively. The adjusted lesion mean ratios obtained from the model were 0.15 (p <0.0001) for BG-12 bid vs. placebo and 0.26 (p <0.0001) for BG-12 tid vs. placebo. This indicates that BG-12 bid and tid reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years by 85% and 74%, respectively, compared with placebo (p <0.0001 for both comparisons). Refer to Table 17 below.

Table 17: Number of new or newly enlarging T2 lesions at 2 years compared to baseline-MRI cohort (trial 301)

	Placebo	BG-12 BID	BG-12 TID
MRI cohort (n)	180	176	184
n for analysis[7]	165	152	152
Mean	16.5	3.2	4.9
Adjusted mean	17	2.6	4.4
Lesion mean ratio		0.15	0.26
95% CI		0.10, 0.23	0.17, 0.38
p value		<0.0001	<0.0001

7 observed data after subjects switched to alternative MS medication are excluded.

Number of Gd-Enhancing Lesions at 2 Years

This endpoint was analyzed using an ordinal logistic regression model, adjusted for region and the number of Gd enhancing lesions at baseline. In this analysis, data after subjects switched to alternative MS medication were excluded.

At 2 years, the mean number of Gd-enhancing lesions in the placebo group was 1.8, compared with 0.1 and 0.5 in the BG-12 bid and tid groups, respectively. The odds ratios obtained from the model were 0.10 (95% CI, 0.05, 0.22; p <0.0001) for BG-12 bid vs. placebo and 0.27 (95% CI, 0.15, 0.46; p <0.0001) for BG-12 tid vs. placebo. This indicated that treatment with BG-12 bid and tid resulted in statistically significant reductions over placebo of 90% and 73%, respectively, in the odds of having greater Gd-enhancing lesion activity at 2 years (refer to Table 18).

Table 18: Number of Gd enhancing lesions at 2 years-MRI cohort (trial 301)

	Placebo	BG-12 BID	BG-12 TID
MRI cohort (n)	180	176	184
n	165	152	152
Mean, median	1.8 (0)	0.1 (0)	0.5 (0)
Odds ratio (active/placebo)		0.10	0.27
95% CI		0.05, 0.22	0.15, 0.46
p value		< 0.0001	<0.0001

Annualized Relapse Rate at 2 Years

The primary analysis of the annualized relapse rate over 2 years was based on INEC-confirmed relapses. Data after subjects switched to alternative MS medication were excluded. The total number of subject-years followed was approximately 612, 629, and 633 in the placebo, BG-12 bid, and BG-12 tid groups, respectively. The endpoint was analyzed using negative binomial regression, adjusted for EDSS score (≤ 2.0 vs. >2.0), baseline age (<40 vs. ≥40 years), region, and number of relapses in the year prior to study entry.

The adjusted annualized relapse rate over 2 years was 0.364 (95% CI, 0.303, 0.436) in the placebo group, compared with 0.172 (95% CI, 0.138, 0.214) in the BG-12 bid group and 0.189 (95% CI, 0.153, 0.234) in the BG-12 tid group. The rate ratios obtained from the model were 0.473 (p <0.0001) for BG-12 bid vs. placebo and 0.521 (p <0.0001) for BG-12 tid vs. placebo (refer to Table 19). This indicated that the annualized relapse rate over 2 years was significantly reduced by 53% and 48% following treatment with BG-12 bid and tid, respectively, compared with placebo.

Table 19: Summary of ARR (INEC confirmed) at 2 years- ITT population

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408 (100)	410 (100)	416 (100)
Number of subjects with relapses of			
0	237 (58)	312 (76)	321 (77)
1	115 (28)	75 (18)	64 (15)
2	44 (11)	19 (5)	20 (5)
3	8 (2)	1 (<1)	9 (2)
>= 4	4 (<1)	3 (<1)	2 (<1)
Total number of relapses	246	128	140
Total number of subject-years followed	612.35	628.61	633.48
Unadjusted annualized relapse rate (a)	0.402	0.204	0.221
Adjusted annualized relapse rate (95% CI) (b)	0.364 (0.303,0.436)	0.172 (0.138,0.214)	0.189 (0.153,0.234)
Rate ratio (active/placebo) (95% CI) (b)		0.473 (0.365,0.613)	0.521 (0.404,0.670)
p-value (compared to placebo)		<0.0001	<0.0001

Disability progression

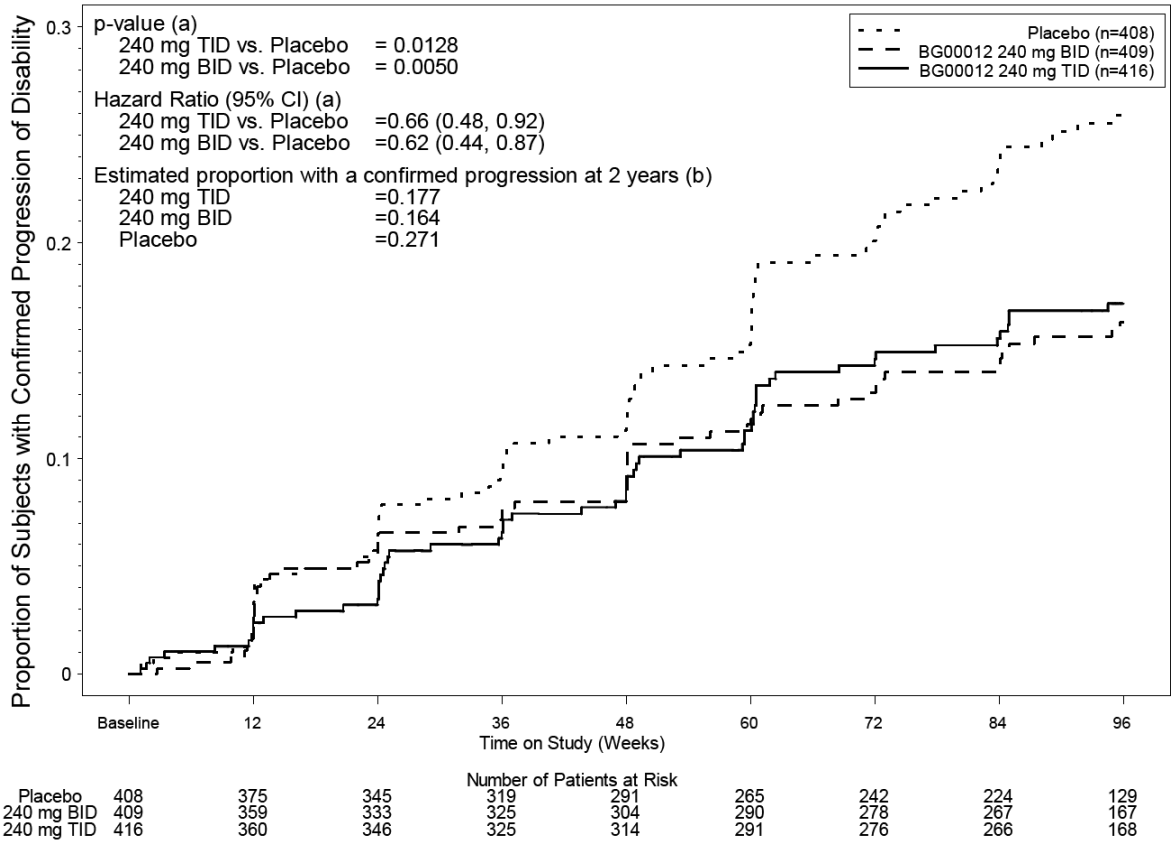
Time to disability progression was analyzed by a Cox proportional hazards model, adjusted by baseline EDSS values as a continuous variable, region and age (<40 or ≥40). The hazard ratios obtained from the model were 0.62 (95% CI, 0.44, 0.87; p = 0.0050) for BG-12 bid vs. placebo and 0.66 (95% CI, 0.48, 0.92; p = 0.0128) for BG-12 tid vs. placebo, representing statistically significant reductions over placebo of 38% and 34%, respectively (refer to Table 20).

Table 20: Summary of time to confirmed progression of disability as measured by an increase in EDSS (12 week confirmation)-ITT (trial 301)

	Placebo	BG-12 BID	BG-12 TID
# ITT	408	410	416
# progressed (%)	89 (22)	57 (14)	62 (15)
Estimated proportion of subjects with progression at 2 year	0.271	0.164	0.177
HR (active/placebo)		0.62	0.66
95% CI		0.44, 0.87	0.48, 0.92
p value		0.005	0.0128

The Kaplan-Meier estimate of the proportion of subjects who progressed by 2 years was 27.1% in the placebo group, compared with 16.4% and 17.7% in the BG-12 bid and tid groups, respectively (refer to Figure 4) .

Figure 4: Time to confirmed progression of disability as measured by increase in EDSS (12 week confirmation)-ITT (trial 301)



Three of the sensitivity analyses performed by the sponsor will be presented in this review as follows: One on the per-protocol population, a second on the ITT population excluding the 23 subjects from 3 sites with GCP violations and the third on subjects that had confirmed disability progression after 24 weeks. The risk of confirmed (12-week) disability progression at 2 years was achieved with BG-12 bid (p =0.0101) and BG-12 tid (p =0.0472) when the per protocol population was analyzed. When the ITT population excluding the 23 subjects from 3 sites with GCP violations was analyzed, there also was a nominally significant reduction in time to confirmed disability progression at 2 years with BG-12 bid (p=0.006) and BG-12 tid (p=0.0217) when compared with placebo.

The analysis performed on subjects that had confirmed disability progression after 24 weeks was not supportive of efficacy. The Kaplan-Meier estimate of the percentage of subjects who progressed according to this definition by 2 years was 16.9% in the placebo group, compared with 12.8% and 11.9% in the BG-12 bid and tid groups, respectively. The hazard ratios obtained from the model were 0.77 (95% CI, 0.52, 1.14; p = 0.1893) for BG-12 bid vs. placebo and 0.69 (95% CI, 0.46, 1.04; p = 0.0760) for BG-12 tid vs. placebo. These results are not associated with significant changes for BG-12 bid (p=0.183) or BG-12 tid (p=0.076) as compared to placebo to reduce the risk of confirmed (24-week) disability progression at 2 years and therefore are not supportive of the 12 week disability progression results.

The data were further inspected to understand the reasons why a statistically significant effect was not maintained after 24 weeks. It was noted that among the subjects who progressed after 12 weeks (89, placebo; 57, BG-12 bid; 62, BG-12 tid), the proportion without a confirmed progression after 24 weeks was greater in the placebo group (36%) than the BG-12 bid (23%) and BG-12 tid (34%) groups. Yet, a greater proportion of subjects in the placebo group (16%) than the BG-12 bid (14%) and BG-12 tid (11%) groups did not have EDSS data at least 24 weeks after the start of the progression. Six percent of the placebo subjects without a confirmed (24-week) progression started on alternative MS medication within 24 weeks after the start of their progression and there were no such subjects in the BG-12 groups. Alternative MS medication use by the placebo subjects could have changed the course of their progression and reduced the number of subjects with a confirmed progression after 24 weeks.

Other Tertiary Endpoints

The Multiple Sclerosis Functional Composite (MSFC) scale

The MSFC is an exploratory scale that was developed to evaluate disability. This scale is composed of three components, the timed 25 foot walk (T25FW: walking ability measure), the 9 hole peg test (9HPT: arm function measure) and the paced auditory serial addition test 3 (PASAT 3: cognitive measure). From these 3 component scores, a z-score is computed based on a comparison of the patient's score with that of a reference population. Z-scores represent the number of standard deviations between scores for the individual and the reference population. A positive change in the composite z-score indicates an improvement while a negative change indicates worsening. This scale was developed to provide a more sensitive measure of change than the EDSS, yet there is not a consensus in the MS community that the changes this scale

measures are representative of clinically meaningful and reliable changes related to disability progression.

Changes from baseline in z-scores were compared between treatment groups, adjusted for region and MSFC z-score at baseline. BG-12 bid and tid improved MSFC composite z-scores at 2 years (p = 0.0006 and p = 0.0004, respectively) compared with placebo. The subset test scores that contributed to this nominally significant overall score are the following. Nominally significant improvement in PASAT 3 and 9HPT z-scores were observed at 2 years with both BG-12 doses, and a positive trend was observed on the T25FW (See Table 21).

Table 21: Change of MSFC z score from baseline to 2 years- ITT (trial 301)

	Placebo	**BG-12 BID**	**BG-12 TID**
#ITT	408	410	416
n	396	394	402
T25FW (z score)			
mean, SD	-0.328, 2.105	-0.047, 1.132	-0.149, 1.316
min, max	-23.75, 5.52	-13.91, 10.02	-13.71, 7.71
p value (active vs. placebo)		0.118	0.69
9HPT (z score)			
mean, SD	-0.034, 0.694	0.042, 0.661	0.089, .558
min, max	-4.61, 4.96	-5.20, 3.84	-2.36, 4.91
p value		0.0031	0.001
PASAT 3 (z score)			
mean, SD	0.150, 0.695	0.220, 0.5796	0.240, 0.656
min, max	-3.86, 3.32	-1.97, 3.59	-1.79, 3.77
p value		0.0041	0.0114
MSFC Composite score			
mean, SD	-0.071, 0.8447	0.087, 0.483	0.06, 0.583
min, max	-7.69, 3.25	-3.53, 4.49	-5.03, 4.33
p value		0.0006	0.0004

Since the composite z-score is difficult to interpret, this reviewer is also presenting the data for the MSFC as actual change from baseline over 2 years in raw scores (refer to Table 22). Please note that the p values for the comparisons between the active and placebo groups were based on analysis of covariance on rank data, adjusted for region and the component at baseline. This analysis does not test the equality of the raw means in the analysis of covariance model and therefore the p values provided in the table are not based on testing of the differences in mean changes between treatment groups.

Table 22: MSFC: Change of actual scores from baseline to 2 years- ITT population (trial 301)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in ITT population	408	410	416
Change from baseline to 2 years (Week 96)			
25-Foot Walk (sec.)			
n	396	395	402
Mean	3.71	0.53	1.69
SD	23.809	12.809	14.885
Median	0.15	0.10	0.15
Min, Max	-62.4, 268.7	-113.4, 157.3	-87.3, 155.0
p-value (a)		0.1137	0.6891
9 HPT (sec.)			
n	396	395	402
Mean	5.20	5.25	-0.37
SD	60.549	56.132	14.079
Median	0.06	-0.30	-0.34
Min, Max	-158.8, 755.8	-193.7, 757.2	-179.9, 184.5
p-value (a)		0.0146	0.0009
PASAT 3 (# items)			
n	395	393	402
Mean	1.7	2.5	2.7
SD	7.75	6.46	7.31
Median	1.0	2.0	2.0
Min, Max	-43, 37	-22, 40	-20, 42
p-value (a)		0.0048	0.0122

Reviewer's comment: The data provided suggests that a positive p value for the composite z-score on the MSFC has limited interpretability in terms of understanding whether clinically significant changes in disability have occurred with active product as compared to control. In fact, it seems based on the data provided in this submission that nominally significant p values are associated with raw actual scores changes that do not appear to be clinically significant. As can be seen in Table 21, nominally significant p values for the comparisons on placebo and BG-12 active treatment on the 9HPT and the PASAT-3 were identified which then yielded nominally significant values of the composite z-score. These changes were associated with very small numerical changes in the actual raw score as can be seen in Table 22. The magnitude of the change varies depending on whether one focuses on the changes seen in the mean or median values, but either way, these changes are numerically very small and have an uncertain clinical significance. In addition, there is a high degree of variability in these values. The fact that the composite z-score is nominally significant suggests that this analysis is overestimating an effect on disability as the data from the actual scores do not look highly supportive of efficacy.

Brain Atrophy

Brain atrophy, was measured as the percentage change in whole brain volume (PBVC) using the SIENA method. Percentage changes were compared between treatment groups using an ANCOVA on ranked data, and adjusting for region and normalized brain volume at the reference time point. Data obtained after subjects switched to alternative MS medication were excluded.

The pre-specified analysis of interest was the PBVC from 6 months to 2 years. Six months was chosen as the baseline reference time point because in RRMS studies of therapies with anti-inflammatory properties a greater relative decrease in brain volume has been observed in the therapeutic agent arm within the first several months of treatment, presumably due to a greater reduction in inflammation and edema.

At 2 years, the median percentage change in brain volume from 6 months was -0.660% in the placebo group compared with -0.460% and -0.550% in the BG-12 bid and tid groups, respectively. The percentage change seen with BG-12 bid and tid represented 30% ($p = 0.0214$) and 17% ($p = 0.2478$) smaller reductions in brain volume relative to placebo, with the difference between BG-12 bid and placebo reaching nominal significance.

Reviewer's comments: Changes in whole brain atrophy is an exploratory endpoint that is proposed to be informative in terms of MS disease progression and disability. In this trial the results are not clearly interpretable. Although there was a nominally significant effect of this endpoint in the BG-12 bid vs. placebo comparison, the lack of a dose response (i.e. further improvement on the BG-12 tid dose) detracts from the interpretability of the findings for the BG-12 dose.

Number of relapses requiring IV steroid therapy
The analysis of relapses requiring IV steroids at 2 years was based on those confirmed by INEC. Data after subjects switched to alternative MS medications were excluded. The total number of subject-years of data included was approximately 612, 629, and 633 for the placebo, BG-12 bid, and BG-12 tid groups, respectively. The endpoint was analyzed using negative binomial regression, adjusted for region.

A total of 211 INEC-confirmed relapses required IV steroids in the placebo group over 2 years, compared with 111 and 114 in the BG-12 bid and tid groups, respectively. The percentage of subjects experiencing 1 or more relapses that required IV steroids in the placebo, BG-12 bid, and BG-12 tid groups was 38%, 21%, and 20%, respectively. The adjusted ARR requiring IV steroids at 2 years was 0.310 (95% CI, 0.253, 0.379) in the placebo group, compared with 0.149 (95% CI, 0.117, 0.189) and 0.150 (95% CI, 0.118, 0.191) in the BG-12 bid and tid groups, respectively. These results suggest that there were nominally significant fewer relapses in the BG-12 groups requiring treatment with steroids compared with placebo.

Patient Reported Outcomes

Patient-reported outcomes were assessed through the use of 3 instruments: the Global Impression of Well Being as measured by VAS, the SF-36 Health Survey, and the EQ-5D (EQ-VAS and EQ-5D).

Global Impression of Well Being as Measured by VAS
The VAS was used to measure subjects' self-assessment of their overall well being; scores ranged from 0 to 100, with higher scores indicating better well being. While individual subject VAS scores in all treatment groups were highly variable, mean baseline scores were generally

similar in the placebo (64.3), BG-12 bid (65.1), and BG-12 tid (65.3) group. However, at 2 years, mean VAS scores were lower in the placebo group (60.3) than in the BG-12 bid (64.3) and BG-12 tid (65.7) groups. Thus, subjects in the BG-12 groups reported better impression of well being compared with subjects in the placebo group.

SF-36

The SF-36 Health Survey is a 36-item subject completed questionnaire that measures the following 8 domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The 8 domains are grouped into 2 summary scores: the physical and mental component scale (PCS and MCS) scores. Higher scores indicate better physical and mental function.

On the PCS, mean baseline scores were 43.3, 42.9, and 43.7 in the placebo, BG-12 bid, and BG-12 tid groups, respectively. The mean change from baseline to 2 years was a decrease of 1.36 in the placebo group, compared with increases of 0.45 ($p = 0.0003$) in the BG-12 bid group and 0.51 ($p < 0.0001$) in the BG-12 tid group.

At baseline, mean MCS scores were 45.7, 45.3, and 45.1 in the placebo, BG-12 bid, and BG-12 tid groups, respectively. At 2 years, the mean change from baseline in the MCS was a reduction of 1.06 in the placebo group compared with increases of 0.20 ($p = 0.0651$) in the BG-12 bid group and 1.05 ($p = 0.0017$) in the BG-12 tid group.

EQ-5D

The EQ-5D is a subject rated instrument that includes the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Mean EQ-5D index and EQ VAS scores at baseline were similar across treatment groups. At 2 years, the distribution of scores for the EQ-5D dimensions of mobility and usual activities in the BG-12 groups demonstrated that a greater proportion of subjects (approximately 60% and 58%, respectively) in the BG-12 groups reported no problems compared with 50% and 52%, respectively, in the placebo group. Responses for the dimensions of self-care, pain/discomfort, and anxiety/depression were generally similar across all groups.

The mean changes from baseline to 2 years in the EQ-5D index ($p = 0.0053$) and EQ VAS ($p = 0.0002$) scores indicated significantly better health state in the BG-12 tid group compared with placebo. In the BG-12 bid group, the mean change from baseline in the EQ VAS score at 2 years also demonstrated a significantly better subject-reported state of health compared with placebo ($p = 0.0008$). The mean change from baseline in the EQ- 5D index score at 2 years in the BG-12 bid group indicated better state of health as compared with placebo, although the difference between groups was not nominally significant ($p = 0.0910$).

Subpopulations

Demographic subgroups were defined for gender (male vs. female), baseline age (<40 vs. ≥40 years), baseline weight quartiles (≤58 kg, >58 to 68 kg, >68 to 81 kg, >81 kg), whether or not the subject was included in the MRI cohort (yes vs. no), and region (1, 2, and 3). Subgroups based on baseline disease characteristics were defined for the number of relapses experienced by the subject in the year prior to study entry (≤1 vs. ≥2 relapses), baseline McDonald criteria (1 and 2-4), prior treatment with a medication for MS (no vs. yes), baseline EDSS score (≤2.0 vs. >2.0), baseline T2 hyperintense lesion volume (≤median or >median), and baseline Gd-enhancing lesion number (absent vs. present).

For the three clinical endpoints, ARR, proportion relapsing at 2 years and disability progression the effect of BG -12 240 mg bid and 240 mg tid was generally consistent across all subgroups, although the treatment effect appeared greater among subjects younger than 40 years of age, naïve to MS treatment and subjects with a baseline EDSS score of ≤ 2. For the MRI endpoints listed as the key secondary endpoints, the effect of BG-12 240 mg bid and 240 mg tid treatment was generally consistent across subgroups.

Please refer to Table 23 for the most marked differences found in the subgroup analyses for either a primary or key secondary endpoint. For the endpoint proportion relapsing at 2 years, patients < 40 at baseline and/or patients with an EDSS ≤2 at baseline had a more robust treatment effect. For the endpoint ARR, patients < 40 at baseline and/or those with an EDSS ≤2 at baseline had a more robust treatment effect. For the endpoint disability progression, a more robust treatment effect was observed in patients < 40 at baseline, with ≤2 EDSS at baseline, who had no prior treatment and/or were not in the MRI cohort.

Table 23: Subgroup analyses (trial 301)

	Placebo	**BG-12 240 mg BID**	**BG-12 240 mg TID**
Proportion relapsed	0.533	0.265	0.270
<40 (HR[1]-active/placebo)	0.533	0.265 (0.41)	0.270 (0.44)
≥40 (HR-active/placebo)	0.388	0.276 (0.74)	0.251 (0.63)
≤2 EDSS Rate ratio (active/placebo)	0.457	0.188 (0.35)	0.188 (0.34)
>2 EDSS (rate ratio)	0.465	0.362 (0.71)	0.338 (0.68)
MRI cohort (HR-active/placebo)	0.539	0.252 (0.41)	0.328 (0.56)
Not in MRI cohort (HR-active/placebo)	0.393	0.284 (0.63)	0.208 (0.45)
ARR			
≤2 EDSS (Rate ratio-active/placebo)	0.340	0.099 (0.292)	0.113 (0.331)
>2 EDSS (rate ratio-active/placebo)	0.381	0.266 (0.698)	0.282 (0.740)
<40 (rate ratio-	0.518	0.194 (0.374)	0.214 (0.414)

active/placebo)			
≥40 (rate ratio-active/placebo)	0.239	0.159 (0.655)	0.170 (0.710)
Disability progression			
Prior MS treatment (HR-active/placebo)	0.26	0.20 (0.83)	0.21 (0.86)
No prior treatment (HR-active/placebo)	0.28	0.12 (0.38)	0.14 (0.46)
≤2 EDSS (rate ratio-active/placebo)	0.29	0.15 (0.52)	0.15 (0.50)
>2 EDSS (rate ratio-active/placebo)	0.25	0.18 (0.73)	0.21 (0.85)
<40 (HR-active/placebo)	0.26	0.11 (0.38)	0.17 (0.62)
≥40 (HR-active/placebo)	0.27	0.23 (0.92)	0.18 (0.68)
MRI cohort (HR-active/placebo)	0.28	0.21 (0.80)	0.21 (0.76)
Not in MRI cohort (HR-active/placebo)	0.27	0.13 (0.48)	0.13 (0.57)

[1] ***Hazard Ratio***

5.3.3 Protocol 109MS302

Study Title: A Randomized, Multicenter, Placebo-Controlled and Active Reference (Glatiramer Acetate) Comparison Study to Evaluate the Efficacy and Safety of BG-12 in Subjects with Relapsing-Remitting Multiple Sclerosis

Trial 302 is of similar design to trial 301 in that both trials were randomized, multicenter, placebo controlled trials with 3 similar arms (placebo, BG-12 bid and BG-12 tid) to evaluate the efficacy and safety of BG-12 in subjects with RRMS, but trial 302 also had a fourth arm, an open label active reference comparator, Glatiramer Acetate.

There were other notable differences as follows:

- The primary endpoint in study 302 was the comparison vs. placebo in the "ARR over 2 years", rather than as in 301, "the proportion of relapsing subjects at 2 years".
- The key secondary outcome " total number of Gd enhancing lesions at 2 years" that was included in trial 301, was not listed as a key secondary outcome in trial 302, instead "total number of new T1 hypointense lesions at 2 years" was included as a key secondary outcome.
- The designs for both trials included defined treatment options for subjects who relapsed or experienced disability progression. In study 302, subjects who completed 48 weeks of blinded study treatment and experienced 2 INEC confirmed relapses could choose to receive open label treatment with an approved alternative MS medication, but in trial 301, patients could choose to receive open label treatment if they had completed 48

weeks of blinded study treatment and experienced at least 1 INEC confirmed relapse that occurred on or after week 24.

The description of protocol 302 below will focus on differences in this trial as compared to 302.

Objectives
The primary objective of this study was to determine whether BG-12 is effective in reducing the rate of clinical relapses at 2 years.

The secondary objectives of this study were identical to trial 301 with the exception of the following. Trial 302 planned to determine whether BG-12 when compared with placebo was effective in reducing the proportion of subjects relapsing at 2 years and in reducing the total number of new hypointense T1 lesions at 2 years.

Study Design: This was a randomized, multicenter, double blind, placebo-controlled, active reference comparison study. Subjects were randomized into 1 of 4 groups in a 1:1:1:1 ratio. Subjects in groups 1, 2, and 3 received 2 capsules orally 3 times a day. Subjects randomized to the GA arm were treated with open label GA. There was no matched injectable placebo for GA.

- Group 1: 308 subjects received BG-12, 240 mg bid
- Group 2: 308 subjects received BG-12, 240 mg tid
- Group 3: 308 subjects received placebo
- Group 4: 308 subjects received GA: 20 mg SC injection, once daily.

All study management personnel, site personnel, investigators, and subjects directly involved in the study were blinded to subject treatment in groups 1, 2, and 3. Only the examining neurologist was blinded to all 4 groups, including group 4 (GA).

Subjects in groups 1, 2, 3, and 4 had the option of switching to an approved, open label MS therapy in accordance with local practices managed by the Investigator if:

- the subject has completed 48 weeks of blinded treatment and experiences 2 confirmed relapses, or
- the subject experienced significant disability progression as defined by the protocol

Reference Comparator
This study included an active control (GA), in addition to a placebo control. The sponsor states in their submission, that although an active control is included in this trial in addition to a placebo control, this study was not designed, nor was it powered for a statistical comparison of the safety and efficacy of GA with BG-12. As a widely prescribed, first-line treatment for the indication is being sought for BG-12, GA was considered to be an appropriate comparator in this study population based on input from other regulatory agencies such as the EMA. GA administration was single blind, with evaluations by a blinded examining neurologist, and confirmation of relapses by a blinded INEC.

Study Population
The inclusion and exclusion criteria are identical to trial 301.

Treatments
Subjects were randomly assigned to treatment with BG-12 240 mg bid (group 1), BG-12 240 mg tid (group 2), placebo (group 3), or GA 20 mg qd (group 4) for a total of 96 weeks. Subjects in groups 1, 2, and 3 were to take 2 capsules of blinded study treatment orally tid, except during the first week, when they were to take 1 capsule orally tid. Subjects in group 4 received GA SC.

Glatiramer Acetate Description
Subjects randomized to treatment with GA were to receive it open label. GA was packaged as a single use prefilled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile solution containing 20 mg of GA and 40 mg of mannitol.

GA prefilled syringes were supplied in administration packs. Each pre-filled syringe was for single use only. Each administration pack contained at least a 4 week supply of GA

Dose Reductions
Dose reduction was allowed only for subjects in groups 1, 2, or 3 who were unable to tolerate blinded study treatment due to flushing and/or GI disturbances. Subjects who could not tolerate blinded study treatment were to reduce their dose by taking 1 capsule tid for 1 month. After 1 month at the reduced dose, subjects were to resume taking 2 capsules tid. If the subject was still unable to tolerate the study treatment, the subject was required to discontinue study treatment. Dose reductions were not allowed for abnormal laboratory values. All subjects who prematurely discontinued dosing with study treatment were to remain in the study and continue on a modified schedule of tests and assessments. For subjects in groups 1, 2, and 3, treatment assignment was to remain blinded throughout the study.

Prohibited Concomitant medication
Identical to those described for trial 301

Study Schedule
Identical to the schedule in trial 301

Efficacy and Safety assessments
Identical to those described for trial 301

Statistical Methods

Analysis Populations
ITT, MRI cohort and the safety population are defined in the same way as in trial 301

The per protocol population is identical to that in trial 301 except that this population must not have been exposed to previous treatment with GA, Fumaderm or BG-12.

For the primary efficacy endpoint, statistical testing was based on a sequential (closed) testing procedure to control for the overall type I error for BG-12 and placebo only: if the first

comparison (BG-12 tid vs. placebo) was statistically significant ($p \leq 0.05$), then the second comparison (BG-12 bid vs. placebo) would be performed and considered statistically significant provided the p value was ≤ 0.05. However, if the first comparison was not statistically significant, then the second comparison would not be considered statistically significant.

With respect to the secondary efficacy endpoints, a closed testing procedure was used to control for the type I error due to multiplicity, which included both the ranking of the endpoints and the comparison of each BG-12 dose group with placebo, as follows. Secondary endpoints were tested in the order in which they were ranked:

1. Total number of new or newly enlarging T2 hyperintense lesions on brain MRI scans in a subset of subjects at 2 years.
2. Total number of new T1 hypointense lesions on brain MRI scans in a subset of subjects at 2 years.
3. Proportion of subjects with clinical relapse at 2 years.
4. Progression of disability at 2 years

A similar closed testing procedure was performed separately for GA versus placebo.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint was the ARR at 2 years. The primary analysis of the primary efficacy endpoint included only INEC confirmed relapses. Relapses that occurred after subjects received alternative MS medications were excluded from the primary analysis of relapse rate, and the subject's time on study was censored at the time the alternative MS medication was started.

The ARR in each treatment group was calculated as the total number of relapses experienced in a group divided by the total number of subject-years on study at 2 years (minus the time on alternative MS medication) for that group. This was the unadjusted relapse rate. The endpoint was analyzed using a negative binomial regression model adjusted for baseline EDSS score (≤ 2.0 versus >2.0), baseline age (<40 versus ≥ 40 years), region, and the number of relapses in the year prior to study entry. The logarithmic transformation of the time on study was included in the model as the "offset" parameter.

Analysis of Secondary Efficacy Endpoints

Total number of new or newly enlarging T2 hyperintense lesions at 2 years
The method used to analyze this endpoint was identical to that used to analyze this endpoint in trial 301.

Number of new T1 hypointense lesions at 2 years
The rules for data inclusion in the analysis of this endpoint were the same as those used for the analysis of the number of new or newly enlarging T2 hyperintense lesions at 2 years. The number of lesions was analyzed using negative binomial regression, adjusted for the baseline

volume of T1 hypointense lesions and region. To reduce the influence of outliers, imputed values greater than the biggest observed value were truncated at the biggest value in the analysis.

The proportion of subjects with clinical relapse at 2 years
The method used to analyze this endpoint was identical to that used to analyze the primary endpoint in trial 301.

Disability progression as measured by the EDSS at 2 years
The method used to analyze this endpoint was identical to that used to analyze this endpoint in trial 301.

Sample Size Estimation

Subjects were randomized to placebo, BG-12 bid, BG-12 tid, or GA in a 1:1:1:1 allocation. It was anticipated that the ARR in the placebo group would be approximately 0.61, while the rate on the BG-12 group would be approximately 0.456. A sample size of 308 subjects per group (BG-12 or placebo) would provide approximately 84% power to detect a 25% reduction in the annualized relapse rate at 2 years in the BG-12 group compared with the placebo group (difference between 0.61 and 0.456). A dropout rate of 23% over 2 years was assumed. Due to the 1:1:1:1 randomization ratio, the GA group also had 308 subjects. The total planned sample size for the study was 1232.

Reviewer's comment: Although the two trials had similar overall numbers of patients enrolled in the trial, since trial 302 had an additional arm, the two trials had a different number of patients per treatment arm. Therefore in trial 301 there were approximately 400 patients per treatment arm and in trial 302 there were approximately 350 patients per treatment arm.

Protocol Amendments

At the time ***Protocol Amendment 1*** was implemented, 4 subjects had been enrolled in the study. Two subjects were enrolled under protocol amendment 1. The following major changes were made:

- Medical history was revised to emphasize a review of cardiovascular risk factors.
- Abbreviated clinical visits were revised to include vital signs and urine pregnancy tests.
- A physical examination was added to the unscheduled relapse assessment visit; the MSFC and VFT were removed.
- A specific lipid profile was added (including blood cholesterol, HDL, LDL, and triglyceride levels), separate from the blood chemistry panel in laboratory safety assessments.
- MRI was prohibited within 30 days of receipt of a course of steroids.
- Urine cytology was added as a laboratory safety assessment.
- Exclusion criterion number 18 was revised to increase the time restriction of IV/oral corticosteroids or 4-aminopyridine or related products prior to randomization.
- Text was added to clarify the EDSS scores that qualify for disease progression.

- The primary objective was revised.
- Changes were made to the statistical analysis procedures (e.g., the primary analysis method was changed to Cox proportional hazards model).
- Secondary objectives were revised.
- Secondary endpoints were rank-ordered based on regulatory authority comments.
- Tertiary study objectives were revised. Additional revisions were made to MRI text, including adding text regarding MTR.
- Text regarding recording cardiac AE or SAE events was added.

Protocol Amendment 2, dated 22 May 2007
At the time protocol amendment 2 was implemented, 6 subjects had been enrolled. An additional 414 subjects were enrolled under protocol amendment 2, which was modified as described below:

- Blood chemistry and urinalysis were added to abbreviated clinical visits.
- The procedure for urine cytology testing was revised.
- An exclusion criterion was added for abnormal urine tests.
- Additional testing for subjects who develop abnormal urine laboratory values was added.
- A bullet point was added for discontinuation of study treatment based on renal dysfunction.
- The blood chemistry panel was revised to include calcium, magnesium, phosphate, uric acid, and glucose. Urinalysis was revised to include 2-microglobulin and microalbumin.
- Parathyroid hormone and vitamin D levels were added to safety assessments.
- Changes were made to the protocol to increase safety monitoring for renal function: blood chemistry and urinalysis was previously performed monthly for 6 months then every 3 months thereafter and was revised to be performed monthly for the entire study.

Protocol Amendment 3, dated 09 January 2008
At the time protocol amendment 3 was implemented, 420 subjects had been enrolled. An additional 1009 subjects were enrolled under protocol amendment 3. The major changes in the amendment are outlined below:

- Testing for hepatitis C and HBsAg was added to the study activities chart.
- Text was clarified regarding subjects who choose to use Avonex as rescue therapy and Biogen Idec providing it free of charge.
- Text was added to specify that all subjects who complete this trial according to the protocol requirements could choose to be enrolled into an open-label extension study, not less than 1 year in duration, in which all subjects would receive BG-12. The text also stated that this extension study would be conducted under a separate, independent protocol.

Changes in the Planned Analyses
The protocol and SAP pre-specified that the benefit risk assessment of BG-12 relative to GA would be performed via an indirect comparison of the relative effect of each active treatment versus placebo on efficacy parameters and via comparison across treatment groups on safety parameters. The sponsor also performed the direct estimation of effect of BG-12 versus GA. The

treatment effect of BG-12 versus GA for the primary and secondary efficacy endpoints was measured in terms of point estimates and 95% CIs to describe the variability about the estimated effects.

5.3.3.1 Efficacy Results Trial 302

5.3.3.1.1 Trial Population

Disposition

A total of 1430 subjects were enrolled and randomized at 200 sites in 28 countries worldwide. The highest enrolling countries were Poland (282), US (267), India (107) and Ukraine (104). Of the 1430 subjects randomized, 1417 subjects made up the ITT and safety population (365 placebo, 359 BG-12 bid, 345 BG-12 tid, 350 GA). Thirteen subjects that were randomized were not dosed, 3 in the BG-12 bid group and 10 in the GA group. Among the 10 randomized to GA, 8 withdrew consent because they had been randomized to open label GA treatment and 2 others withdrew consent for other unstated reasons.

The per protocol population included 1323 subjects overall divided as 351, 332, 303, 337 in placebo, BG-12 bid, BG-12 tid, GA, respectively. The MRI cohort included 681 subjects (167, 169, 170 and 175, placebo, BG-12 bid, BG-12 tid, GA, respectively).

Overall, 1000 subjects (71%) completed study treatment, 64% in placebo, 70% in BG-12 bid, 72% in BG-12 tid and 75% in GA. Treatment discontinuations were more common with placebo than active treatment groups. In the first 3 months treatment discontinuations were more common in the active treatment group, then following 1 year the curves crossed and treatment discontinuations were more common in placebo (refer to Figure 5). This is the time point when subjects with confirmed relapses could cross over to alternative MS treatment.

Please refer to Figure 6 for a comprehensive listing of the reported reasons for study treatment discontinuation. The most common reason for discontinuation of study treatment was other (9%) and AEs (9%). AEs resulted in study treatment discontinuation by treatment group as follows: placebo 6%, BG-12 bid 10%, BG-12 tid 11% and GA 8%. A total of 33 subjects discontinued study drug because of MS relapse (5% placebo, 2% BG-12 bid, <1% BG-12 tid and 2% GA). Of the patients that listed other as the reason for study treatment withdrawal, 11 patients had reasons listed related to MS relapse or progression, yet most of these patients were in the placebo group. Overall, 115 (8%) subjects in the ITT population switched to alternative MS medications. The proportion of subjects who switched to alternative MS medication was higher in the placebo group (11%) than in the BG-12 bid (7%), BG-12 tid (8%), and GA (6%) groups.

The rate of treatment discontinuations was higher for females (32%) than males (24%) and for subjects with > median T2 lesion volume (33% vs. 24%) and the presence of Gd enhancing lesions (33% vs. 26%). The rate of treatment discontinuation was also slightly higher for region 1 (36%) as compared to region 2 (31%) and region 3 (27%).

Figure 5: Time to discontinuation of study drug- ITT population (trial 302)

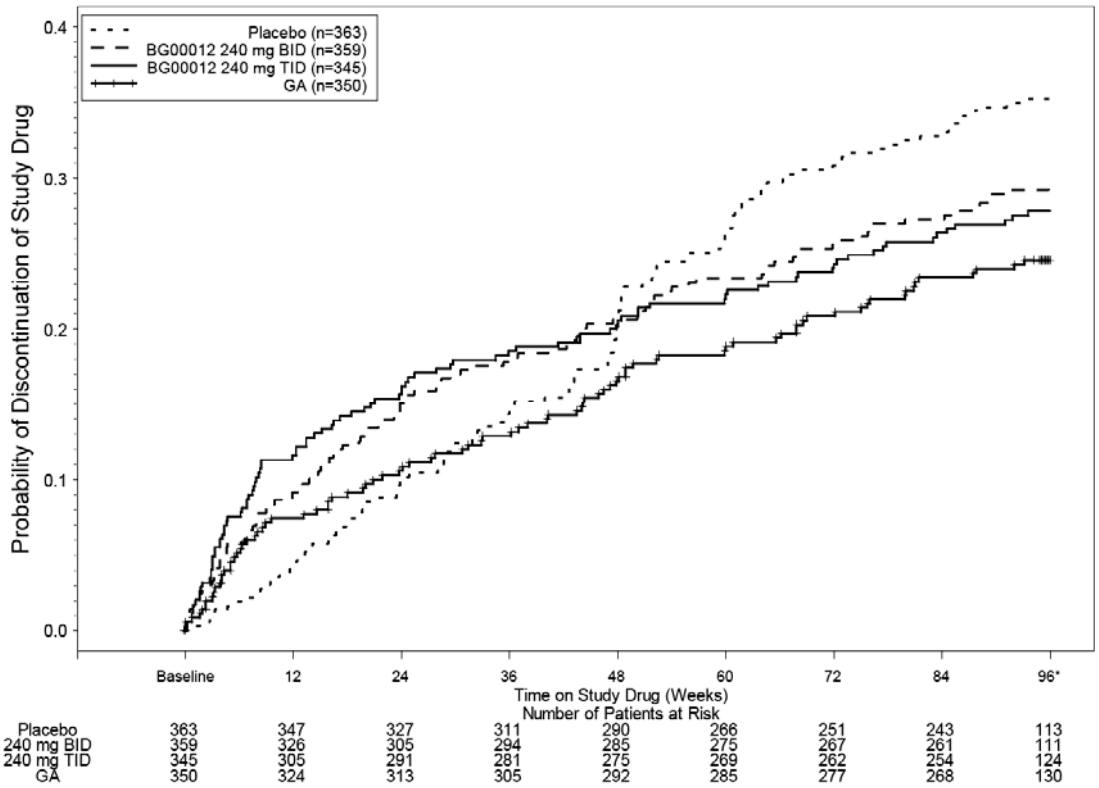
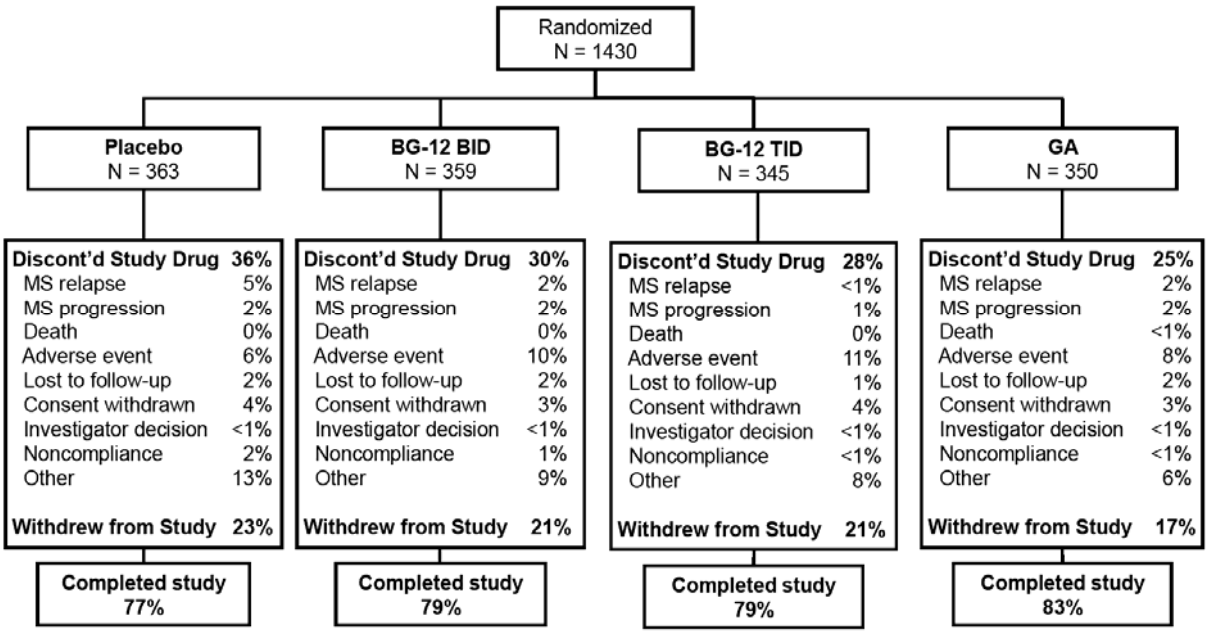


Figure 6: Patient disposition trial 302



Since patients could terminate study treatment and continue in the study, there were fewer patients that completed study treatment than those that completed the study. Overall, 1127 subjects (80%) completed the study and the percentage per treatment group was well balanced as follows: placebo 77%, BG-12 bid and tid 79% and GA 83%.

Treatment Compliance

Compliance was assessed through capsule or syringe counts. In the ITT population, mean compliance (calculated based on the duration of exposure, from first to last dose taken) was approximately 94% in the placebo group, 91% in the BG-12 bid group, 89% in the BG-12 tid group, and 97% in the GA group (Table 95).

The mean duration of study treatment exposure and mean compliance in the MRI cohort were approximately 79 weeks and 93%, respectively, and were similar to that of the ITT population. The mean duration of exposure and study treatment compliance were higher in the per-protocol population (approximately 83 weeks and 96%, respectively) than in the ITT population.

Protocol Violations

Patients with major protocol deviations defined in the statistical analysis plan as major violations of inclusion/exclusion criteria and low study treatment compliance were excluded from the per-protocol population. The sponsor's review of the clinical database identified major protocol deviations for 12 (3%) subjects in the placebo group, 27 (7%) subjects in the BG-12 bid group, 42 (12%) subjects in the BG-12 tid group, and 13 (4%) subjects in the GA group. Low study treatment compliance (subjects who took <70% of the assigned doses) was the most common major deviation in all 4 groups (85%); 18% of subjects had a major deviation for inclusion/exclusion criteria.

Deviations related to incorrect study treatment were also identified for 10 subjects. One subject randomized to BG-12 tid actually received GA throughout the entire study. This subject was included in the BG-12 tid group for ITT analyses and in the GA group for safety analyses. An additional 9 subjects received the incorrect study treatment kit at a single clinic visit. Each kit contained sufficient study treatment to cover 4 weeks. The 9 subjects who received the incorrect study treatment kit at a single visit included 1 subject randomized to placebo who received BG-12 bid, 3 subjects randomized to BG-12 bid who received placebo, 1 subject randomized to BG-12 tid who received placebo, 2 subjects randomized to BG-12 bid who received BG-12 tid, and 2 subjects randomized to BG-12 tid who received BG-12 bid. As all of these subjects received more than 70% of the correct study treatment, they were not excluded from the per-protocol population and were analyzed according to randomized treatment for the ITT and safety analyses.

Additionally, a number of subjects did not undergo a protocol specified referral to a Nephrologist based on abnormal urinalysis value. The sponsor states that these subjects were continuously monitored and received appropriate medical management throughout the study, and so this procedural deviation did not present an undue risk to subject safety or have a significant effect on the safety analyses or conclusions.

Concomitant medications
The majority of subjects (88%) in the ITT group used at least 1 other medication while receiving study treatment. The most frequently used concomitant medications (≥10% of subjects) were methylprednisolone (31%), paracetamol (21%), ibuprofen (17%), omeprazole (13%), and amoxicillin (10%). The use of concomitant medications was similar across treatment groups, with the exception of methylprednisolone, which was administered to 40% of subjects in the placebo group, compared with 28% of subjects in the BG-12 bid group, 24% of subjects in the BG-12 tid group, and 33% of the subjects in the GA group.

Reviewer's comment: A much higher percentage of subjects used methylprednisolone in the placebo group than in the BG treatment groups consistent with what would be expected if the placebo group had increased MS activity and relapses.

Demographics, Baseline Characteristics and Treatment History

Demographics
In the ITT population the 4 treatment groups were generally well balanced with respect to baseline demographic characteristics. Overall, 70% of subjects were women. Subjects ranged in age from 18 to 56 years (mean 37 years); 59% of subjects were younger than 40 years of age. The majority of subjects (84%) were White. Mean weight was 72 kg, and mean body mass index was 25.4 kg/m2.

Three regions were defined, based on geography, type of health care system, and access to health care in each country. Region 1 represented 19% of subjects; 15% of study subjects were enrolled from region 2 and 66% from region 3. The demographic characteristics were generally similar across the 3 regions, however, slight trends were observed for gender distribution and subject age. The proportion of males was lower in region 1 (22%) as compared to region 2 (28%) or region 3 (32%). The BG-12 tid group included more females (72%) than the BG-12 bid (68%) or placebo (69%) group.

The MRI cohort and non MRI cohort were similar with respect to key demographic characteristics with the exception that a greater percentage of patients in the MRI cohort were from region 3 (69%) than in the non MRI cohort (64%), and a greater percentage of patients in the non MRI cohort were from region 2 (18%) than in the MRI cohort (12%).

Baseline disease characteristics
During the 12 months prior to the start of the study, the mean number of relapses was 1.4. The mean time since MS diagnosis was 4.7 years (range 0-33). EDSS scores were well balanced between groups, with mean scores approximately 2.6. Similar to the results seen for the ITT population, the treatment groups within the per protocol group and MRI cohort were well balanced with respect to baseline disease characteristics.

In addition, the MRI cohort and non MRI cohort were similar with respect to baseline disease characteristics with a few exceptions. A higher percentage of subjects were White in the MRI

cohort (91%, as compared to the non MRI cohort 77%) and a lower percentage of subjects were Asian in the MRI cohort (4%) than in the non MRI cohort (11%) as displayed in Table 24 below.

Table 24: Key demographic and baseline characteristics- MRI cohort and non-MRI cohort (trial 302)

	MRI cohort	
Number of subjects	Yes	No
Age (mean)	37.5	37.1
Female gender (%)	478 (70)	515 (70)
White	91%	77%
Asian	4%	11%
Region 1	134 (20)	134 (18)
Region 2	79 (12)	133 (18)
Region 3	468 (69)	469 (64)
EDSS score (mean)	2.5	2.6
Prior MS tx (yes)	263 (39)	309 (42)
# relapses past yr. (mean)	1.3	1.4
Mean time since first MS symptoms in years (mean)	7.9	7.4

The treatment groups within the MRI cohort were well balanced in terms of demographic characteristics and baseline MS characteristics. In all treatment groups 40% of the subjects had been on prior MS medication. Within the MRI cohort, baseline MRI parameters were representative of a population of subjects with RRMS and were generally well balanced across the 4 treatment groups. Minor differences were noted between treatment groups, for example for Gd-enhanced lesions the BG-12 tid group had a numerically smaller mean # of Gd-enhancing lesions at baseline (1.9) than were noted in the placebo and BG-12 bid groups (2.7). More than half of all subjects (54%) had no Gd-enhancing lesions, 34% had 1 to 4 lesions, 5% had 5 to 8 lesions, and 7% had 9 or more lesions. Overall, the BG-12 tid group had numerically greater number of subjects with no lesions at baseline (56%) than the placebo and BG-12 bid groups (51-52%), and the placebo and BG-12 bid groups had more patients with ≥ 9 Gd-enhanced lesions 8% compared to patients in the BG-12 tid group (5%). The volume of T2 lesions was comparable between treatment groups.

In conclusion, the demographics and baseline characteristics of the MRI cohort appear to be representative of the overall ITT population.

5.3.3.1.2 Efficacy Analysis

Data sets analyzed

All clinical endpoints were evaluated by analyzing the ITT which included 1417 subjects. In addition sensitivity analyses were conducted for the primary and secondary clinical efficacy

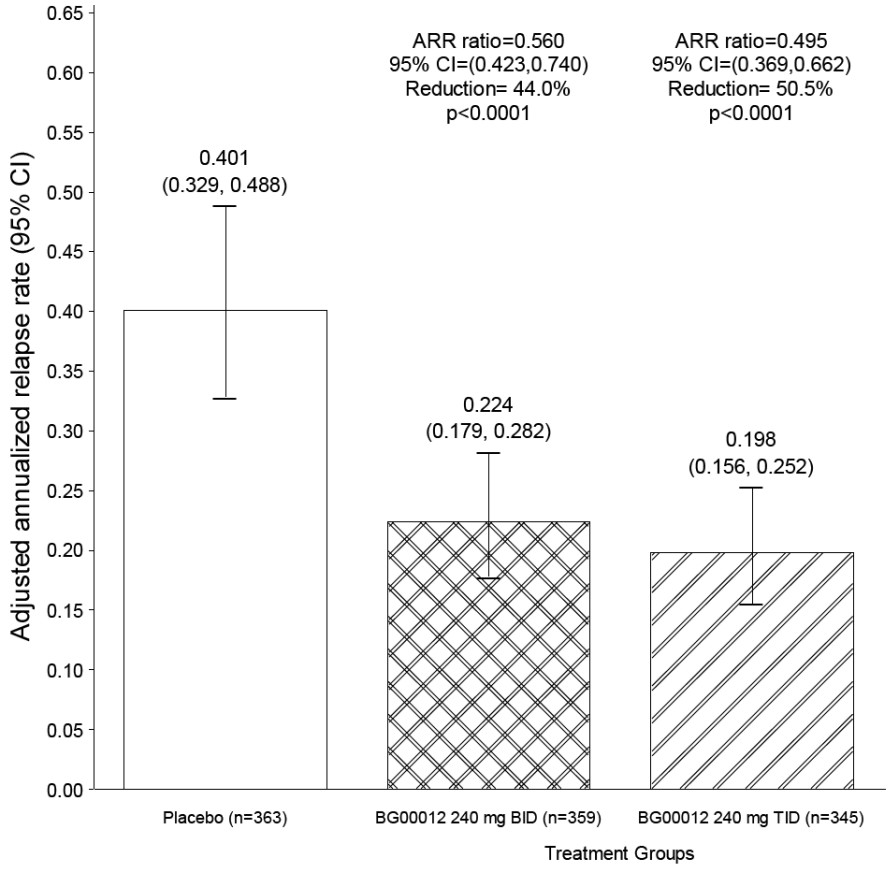
endpoints using the per protocol population (1323 subjects). MRI efficacy endpoints were analyzed using the MRI cohort, which included 681 subjects in the ITT who had MRI data.

Primary Efficacy Analysis

The primary analysis was the ARR at 2 years based on INEC-confirmed relapses. This analysis was conducted on the ITT population excluding data from patients after they switched to alternative MS therapy. Data were analyzed using negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs. >2.0), baseline age (<40 vs. ≥40 years), region, and number of relapses in the year prior to study entry.

The adjusted ARR at 2 years was 0.401 (95% CI, 0.329, 0.488) in the placebo group, compared with 0.224 (95% CI, 0.179, 0.282) in the BG-12 bid group and 0.198 (95% CI, 0.156, 0.252) in the BG-12 tid group (Figure 7). Compared to placebo, BG-12 240 mg administered bid and tid reduced the adjusted ARR over 2 years by 44.0% and 50.5%, respectively (p< 0.0001 for both comparisons).

Figure 7: Summary of ARR (INEC confirmed) at 2 years-ITT population



Although the primary analysis of the ARR was evaluated based on the adjusted ARR, described above in Figure 7, the results calculated for the unadjusted ARR and the rate ratio

(active/placebo) and percentage reduction (active/placebo) also provided nominally significant values for the active treatment vs. placebo comparisons (refer to Table 25 below).

Table 25: Summary of ARR (INEC confirmed) at 2 years-ITT (trial 302)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Unadjusted annualized relapse rate (a)	0.378	0.224	0.200
Adjusted annualized relapse rate (95% CI) (b)	0.401 (0.329,0.488)	0.224 (0.179,0.282)	0.198 (0.156,0.252)
Rate ratio (active/placebo) (95% CI) (b)		0.560 (0.423,0.740)	0.495 (0.369,0.662)
Percentage reduction (active vs. placebo) (95% CI) (b)		44.0 (26.0, 57.7)	50.5 (33.8, 63.1)
p-value (compared to placebo)		<0.0001	<0.0001

A sensitivity analysis looking at the per protocol population was consistent with the primary analysis and showed reductions over placebo in the ARR at 2 yrs in both BG-12 treatment groups (p<0.0001). In addition, the sensitivity analysis of the adjusted ARR including all INEC confirmed relapses occurring before and after the transition to alternative MS medications resulted in an ARR of 0.381 in the placebo group (95% CI, 0.316, 0.460) compared with 0.217 (95% CI, 0.174, 0.271) in the BG-12 bid group and 0.205 (95% CI, 0.163, 0.257) in the BG-12 tid group. This analysis was also supportive of efficacy of the ARR of BG-12 groups over placebo.

Secondary efficacy endpoints

Number of New or Newly Enlarging T2 Hyperintense lesions at 2 years

The number of new or newly enlarging T2 hyperintense lesions was analyzed using a negative binomial regression model, adjusted for region and baseline T2 hyperintense lesion volume. In this analysis, data obtained after subjects switched to alternative MS medication were excluded.

Over the 2 years of the study, the adjusted mean of 17.4 new or newly enlarging T2 hyperintense lesions developed in subjects receiving placebo, compared with 5.1 in subjects who received BG-12 bid and 4.7 in subjects who received BG-12 tid (refer to Table 26). The adjusted lesion mean ratios obtained from the model were 0.29 for BG-12 bid and 0.27 for BG-12 tid, which corresponds to reductions of 71% and 73%, respectively, in the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years compared with placebo (p <0.0001 for both comparisons).

Table 26: MRI: Number of new or newly enlarging T2 lesions at 2 years compared to baseline- MRI cohort (trial 302)

Number of subjects in MRI cohort	167	169	170
Number of lesions			
0	17 (12)	38 (27)	43 (31)
1	7 (5)	24 (17)	21 (15)
2	4 (3)	16 (11)	13 (9)
3	5 (4)	11 (8)	12 (9)
>=4	106 (76)	51 (36)	51 (36)
n	139	140	140
Mean	19.9	5.7	5.1
SD	25.27	11.07	8.73
Median	11.0	2.0	2.0
25th, 75th percentile	4.0, 26.0	0.0, 5.5	0.0, 6.0
Min, Max	0, 119	0, 84	0, 63
Adjusted mean (95% CI) (a)	17.4(13.5,22.4)	5.1 (3.9, 6.6)	4.7 (3.6, 6.2)
Lesion mean ratio (95% CI) (a)		0.29(0.21,0.41)	0.27(0.20,0.38)
% reduction (vs placebo) and (95% CI)(a)		71(59, 79)	73(62, 80)
p-value (a)		<0.0001	<0.0001

Number of New T1 Hypointense Lesions at 2 Years

The number of new T1 hypointense lesions was analyzed using a negative binomial regression model, adjusted for region and baseline T1 hypointense lesion volume. This analysis included only new non-enhancing T1 hypointense lesions (i.e., black holes that developed after the baseline scan). Data obtained after subjects switched to alternative MS medication were excluded.

Over 2 years, an adjusted mean of 7.0 new non-enhancing T1 hypointense lesions developed in the placebo group, compared with a mean of 3.0 new lesions in the BG-12 bid group and 2.4 in the tid group (refer to Table 27). Compared to placebo, the number of new T1 hypointense non-enhancing lesions that developed over 2 years was reduced by 57% and 65%, respectively, in the BG-12 bid and tid groups ($p<0.0001$ for both comparisons).

Table 27: Number of new T1 hypointense lesions at 2 years compared to baseline- MRI cohort (trial 302)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Number of subjects in MRI cohort	167	169	170
Number of lesions			
0	29 (21)	55 (39)	61 (44)
1	8 (6)	21 (15)	21 (15)
2	10 (7)	15 (11)	19 (14)
3-4	29 (21)	12 (9)	9 (6)
>=5	63 (45)	37 (26)	30 (21)
n	139	140	140
Mean	8.1	3.8	2.7
SD	10.43	6.91	5.09
Median	4.0	1.0	1.0
25th, 75th percentile	1.0, 11.0	0.0, 5.0	0.0, 3.0
Min, Max	0, 47	0, 47	0, 45
Adjusted mean (95% CI) (a)	7.0(5.3,9.2)	3.0 (2.3, 4.0)	2.4 (1.8, 3.2)
Lesion mean ratio (95% CI) (a)		0.43(0.30, 0.61)	0.35(0.24, 0.49)
% reduction (vs placebo) and (95% CI)(a)		57(39, 70)	65(51, 76)
p-value (a)		<0.0001	<0.0001

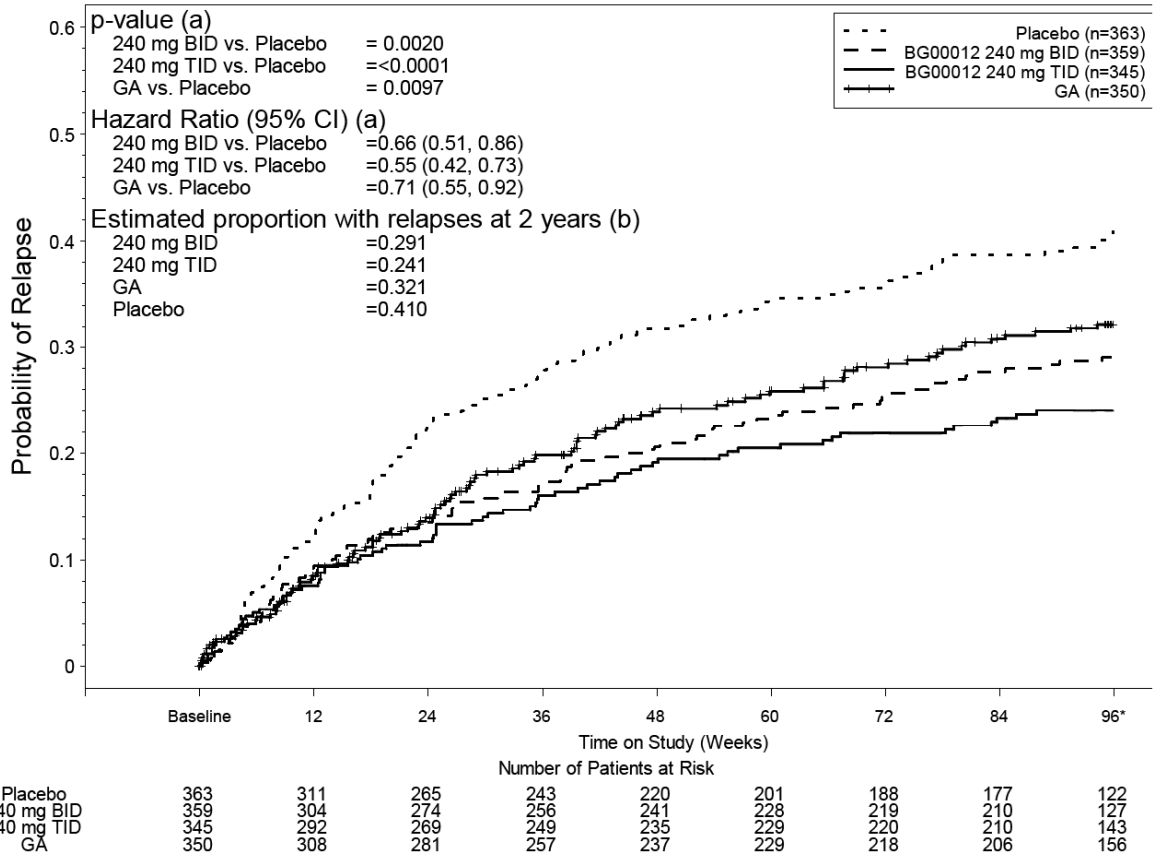
Proportion of Subjects Relapsed at 2 years

The analysis of the proportion of subjects who relapsed was based on INEC-confirmed relapses and included data from all subjects in the ITT population until they completed the study, switched to alternative MS medication, or withdrew from the study. The endpoint was analyzed using a Cox proportional hazards model, adjusted for the number of relapses in the 1 year before study entry, baseline age (<40 vs. ≥40 years), EDSS score (≤2.0 vs. >2.0), and region.

The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 41% in the placebo group compared with 29% in the BG-12 bid group and 24% in the BG-12 tid group. The hazard ratios (95% CI) obtained from the model were 0.66 (0.51, 0.86) for BG-12 bid and 0.55 (0.42, 0.73) for BG-12 tid, corresponding to reductions of 34% (p=0.0020) and 45% (p <0.0001), respectively, in the risk of relapse following treatment with BG-12 bid and tid compared with placebo.

Visual inspection of the Kaplan-Meier plot of the time to first relapse revealed a separation between placebo and BG-12 bid and tid curves starting around week 12 (Figure 8). The placebo and BG-12 curves appeared to continue to diverge from week 12 through the end of the 2 year treatment period.

Figure 8: Time to first relapse (INEC confirmed relapses) - ITT population (trial 302)



Disability Progression at 2 years

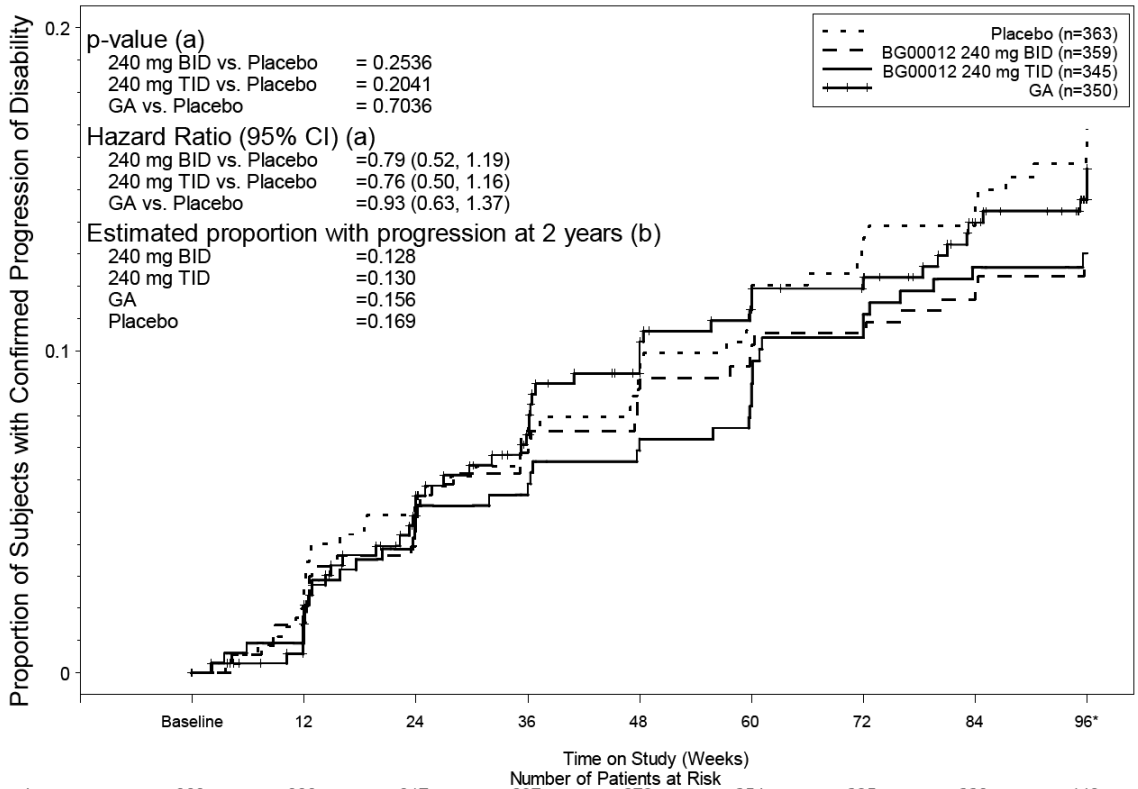
For the analysis of disability progression, a progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. Data after subjects switched to alternative MS medication could be used to confirm a progression that began before alternative MS medication was initiated. Time to onset of confirmed disability progression was assessed using a Cox proportional hazards model, adjusting for the baseline EDSS score as a continuous variable, region, and age (<40 versus ≥40 years).

The Kaplan-Meier estimate of the proportion of subjects who progressed by 2 years was 16.9% in the placebo group, compared with 12.8% and 13.0% in the BG-12 bid and BG-12 tid, groups, respectively. The hazard ratios obtained from the model were 0.79 (95% CI 0.52, 1.19; p=0.2536) for the BG-12 bid group and 0.76 (95% CI 0.50, 1.16; p=0.2041) for the BG-12 tid group, over placebo in the risk of confirmed (12-week) disability progression at 2 years (Figure 9). This difference was not statistically significant and thus not was supportive of efficacy.

The sponsor proposed that one contributing factor to the lack of efficacy demonstrated on time to disability progression in trial 302 was the fact that the placebo disability progression rate was very low in this study compared to the placebo rate in trial 301.

Reviewer's comment: It is true that the placebo disability progression rate as measured in trial 302 is lower than that seen in trial 301, and is more comparable numerically to the values obtained for the active treatment arms in trial 301. Yet this does not reduce the validity of the analysis of disability progression in trial 302 or allow for different conclusions to be drawn with the current data presented. In general, each trial should stand alone on individual endpoints and the control arms from one trial cannot be generalized to another trial without significantly affecting the integrity of the study.

Figure 9: Time to confirmed progression of disability (12 week confirmation) as measured by increase in EDSS- ITT population (trial 302)



Number of Patients at Risk

Placebo	363	339	317	297	273	254	235	228	149
240 mg BID	359	323	302	283	270	263	257	249	146
240 mg TID	345	309	287	277	269	262	249	238	159
GA	350	326	307	291	279	269	262	249	178

The sponsor performed an additional sensitivity analysis to look at disability progression based on 24 week confirmation. The Kaplan-Meier estimate of the percentage of subjects with 24 week confirmed progression at 2 years was 12.5% in the placebo group, compared with 7.8% and 8.6% in the BG-12 bid and tid groups, respectively. The hazard ratios (95% CI) from the model were 0.62 (0.37, 1.03) for the BG-12 bid group (p=0.0630) and 0.67 (0.40, 1.11) for the BG-12 tid group (p=0.1172). Among the subjects with 12 week confirmed progression, 75% of placebo subjects, as compared to 60% and 66% of subjects in the BG-12 bid and tid groups, respectively, had 24-week sustained progression.

Reviewer's comment: This post hoc analysis looking at 24 week confirmed disability progression at 2 years suggests that there may be a positive trend in the BG-12 active treatment groups as compared to placebo for this endpoint with the BG-12 bid vs. placebo comparison approaching nominal significance. If there was a positive trend in the low dose group, one would expect to see a larger treatment effect in the higher dose group if there was a dose response relationship.

To further explore the strength of the evidence in this trial for 12 week confirmed disability progression, the sponsor performed a sensitivity analysis of this endpoint on the per protocol population. This analysis was also not supportive of efficacy (see Table 28).

Table 28: Summary of time to confirmed disability progression at 2 years- per protocol population (trial 302)

	Placebo	BG-12 BID	BG-12 TID
N (per protocol pop.)	351	332	303
Subjects progressed	52 (15%)	38 (11%)	35 (12%)
% subjects progressed at 2 years	17.1	12.4	12.5
HR(95% CI) active/placebo		0.75 (0.49, 1.13)	0.71 (0.46, 1.09)
p value		0.1682	0.1198

Reviewer's comment: Overall, the data from trial 302 is not supportive of a treatment effect for BG-12 for the 12 week confirmed disability progression endpoint in the pre-specified primary analysis and in the per protocol population, although there is a positive trend for both active treatment groups over placebo.

Other Tertiary endpoints

Multiple Sclerosis Functional Composite scale

The MSFC was a tertiary endpoint in this trial. Please refer to section 5.3.2.1.2 of this review for a description of the components of the MSFC and the background of this scale. The results of the MSFC and individual PASAT 3, 9HPT and T25FW subtests, according to the sponsor, indicated a trend towards improved functioning in the BG-12 groups as compared to placebo.

Changes from baseline in z-scores were compared between treatment groups using analysis of covariance (ANCOVA) based on rank data, adjusted for region and MSFC z-score at baseline. In the primary analysis, data obtained after subjects switched to alternative MS medication were excluded. A positive change in the composite z-score indicates improvement, and a negative change indicates worsening. The mean (median) change from baseline to 2 years in the MSFC composite z-score was -0.034 (0.024) in the placebo group, compared with 0.017 (0.053) (p=0.0576) in the BG-12 bid group and 0.018 (0.043) (p=0.1986) in the BG-12 tid group.

Due to the difficulty in determining the clinical meaning of the changes in the z-scores, this reviewer will present the MSFC subscores as the change of the actual score from baseline to 2 years in the ITT population. As can be seen in Table 29 it is apparent that even nominally significant changes are associated with very small changes in the actual scores between placebo and the BG-12 group. For the T25FW there was a nominally significant difference (p=0.038) in the comparison of BG-12 tid to placebo based on a 0.86 sec change (BG-12 tid) as compared to a 0.95 sec change (BG-12 tid) and a 1.70 sec change in the placebo group.

Reviewer's comment: Overall, the subtests that revealed a nominally significant change in the MSFC represented a very small amount of change that has uncertain clinical relevance.

Table 29: MSFC: Change of raw scores from baseline to 2 years- ITT (trial 302)

	Placebo	**BG-12 BID**	**BG-12 TID**
# in ITT	363	359	345
Change from baseline to 2 years T25FW (sec)			
# for subtests	358	351	332
Mean, SD	1.70, 9.584	0.95, 5.774	0.86, 10.616
Median	0.25	0.15	0.20
Min, max	-44.7, 99.4	-14.5, 64.2	-99.7, 101.1
p value		0.1954	0.0380
Change from baseline to 2 years 9HPT (sec)			
Mean, SD	0.80, 31.95	-1.06, 21.01	1.68, 42.34
Median	-0.17	-0.23	-0.02
Min, max	-371.8, 366.7	-378.4, 51	-193.5, 743
p value		0.5272	0.6819
Change from baseline to 2 years PASAT 3 (# items)			
Mean, SD	1.1, 6.68	1.5, 7.41	1.7, 6.48
Median	1.0	1.0	1.0
Min, max	-25, 25	-47, 27	-35, 24
p value		0.1093	0.224

Number of relapses requiring IV steroid therapy

The analysis of relapses requiring IV steroids at 2 years was based on relapses confirmed by INEC. Data after subjects switched to alternative MS medications were excluded. The total number of subject-years of data included in this analysis was approximately 561, 553, and 530

for the placebo, BG-12 bid, and BG-12 tid groups, respectively. This endpoint was analyzed using negative binomial regression and was adjusted for region.

Over 2 years, 191 relapses in 130 subjects in the placebo group required IV steroid therapy, compared with 110 relapses in 82 subjects in the BG-12 bid group and 95 relapses in 69 subjects in the BG-12 tid group. The percentage of subjects in the placebo, BG-12 bid, and BG-12 tid groups who experienced 1 or more relapses that required IV steroids was 36%, 23%, and 20%, respectively. The adjusted ARR requiring IV steroids at 2 years was 0.344 in the placebo group, compared with 0.194 and 0.176 in the BG-12 bid and tid groups, respectively. The rate ratios obtained from the model were 0.564 (p=0.0002) for BG-12 bid vs. placebo and 0.514 (p <0.0001) for BG-12 tid vs. placebo, representing reductions over placebo of 43.6% and 48.6%, respectively, in the annualized rate of relapse requiring IV steroids (refer to Figure 10).

Figure 10: Summary of number of relapses requiring IV steroid therapy at 2 years- ITT (trial 302)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Unadjusted annualized rate of relapses requiring IV steroid use(a)	0.340	0.199	0.179
Adjusted annualized rate of relapse requiring IV steroid use (95% CI) (b)	0.344 (0.278,0.424)	0.194 (0.152,0.247)	0.176 (0.136,0.228)
Rate ratio (active/placebo) (95% CI) (b)		0.564 (0.418,0.759)	0.514 (0.377,0.699)
Percentage reduction (active vs. placebo) (95% CI) (b)		43.6 (24.1, 58.2)	48.6 (30.1, 62.3)
p-value (compared to placebo)		0.0002	<0.0001

Brain Atrophy

Brain atrophy was measured as the PBVC using the SIENA method. In this study, the percentage changes were compared between treatment groups using an ANCOVA on ranked data, and adjusting for region and normalized brain volume at the reference time point. Data obtained after subjects switched to alternative MS medication were excluded.

The pre-specified analysis of interest was the PBVC from 6 months to 2 years because previous studies of RRMS therapies with anti-inflammatory properties have shown a greater relative decrease in brain volume in the therapeutic agent arm within the first several months of treatment that are presumably due to a greater reduction in inflammation and edema. However, as this effect, which is sometimes referred to as “pseudo atrophy” was not discernable in any of the treatment groups in this study; the change from baseline to 2 years was also analyzed to evaluate the change over a longer period of time.

From baseline to 2 years, the median PBVC in the placebo group was -0.945% as compared to

-0.660% in the BG-12 bid group (p=0.0646) and -0.750% in the BG-12 tid group (p=0.2636). Between 6 months and 2 years, a median change of -0.765% was seen in the placebo group compared with -0.720% (p=0.8306) in the BG-12 bid group and -0.745% (p=0.5621) in the BG-12 tid group. There were no significant changes identified in brain atrophy as measured by the SIENA method between treatment groups.

Other Analyses

Comparison of Efficacy: BG-12 and GA

The sponsor states that the efficacy of GA seen in this trial was consistent with that described in the product labeling, therefore, providing assay sensitivity and support for the validity of this trial. The estimated treatment effect of BG-12 bid and tid vs. placebo was larger than the effect of GA vs. placebo for the primary and all the secondary efficacy endpoints. It is notable that this trial was not designed or powered to analyze the superiority or non-inferiority of BG-12 to the reference comparator, GA. The sponsor calculated in a direct comparison, the treatment effect of BG-12 on the primary and secondary endpoints and compared them to that of GA with the following results:

- Adjusted ARR reductions at 2 years of 21.6% (-4.7, 41.3%) in the BG-12 bid group and 30.7% (6.5, 48.7%) in the BG-12 tid group over GA.
- Adjusted mean reductions of the number of new or newly enlarging T2 hyperintense lesions at 2 years of 36.4% (11.7, 54.1%) in the BG-12 bid group and 40.9% (17.9, 57.5%) in the BG-12 tid group over GA.
- Adjusted mean reductions in the number of new T1 hypointense lesions of 26.4% (-4.3, 48.1%) in the BG-12 bid group and 41.0% (16.1, 58.5%) in the BG-12 bid group over GA.
- Hazard rate reductions of the proportion of subjects relapsed at 2 years of 7.7% (-22.2, 30.2%) in the BG-12 bid group and 22.4% (-4.3, 42.3%) in the BG-12 tid group over GA
- Hazard rate reductions of 12-week confirmed progression of disability at 2 years of 15.1% (-29.1, 44.2%) in the BG-12 bid group and 17.7% (-26.0, 46.3%) in the BG-12 tid group.

Reviewer's comment: As this was an open label arm in an otherwise randomized double blind trial, it is difficult to determine the bias incorporated in the GA treatment effect described above. Therefore since the analyses above were generated from data from an arm in this trial that was not well controlled, the data would not qualify as sufficient evidence to support any comparative claims in the label.

Patient Reported Outcomes

Global Impression of Well Being as Measured by VAS

The VAS was used to measure subjects' self assessment of their overall well being; scores ranged from 0 to 100, with higher scores indicating better well being. While individual subject VAS scores in all active treatment and placebo groups were highly variable, mean baseline scores were generally similar in the placebo (63.1), BG-12 bid (64.2), and BG-12 tid (63.8) groups. However, at 2 years, mean VAS scores were lower in the placebo group (59.2) than in

the BG-12 bid (64.5) and BG-12 tid (63.6) groups. Thus, subjects in the BG-12 groups reported better impressions of well being compared with subjects in the placebo group. The mean change from baseline to 2 years in the VAS score in the placebo group was -3.9, compared with 0.3 (p=0.0003) in the BG-12 bid group and -0.3 (p=0.0025) in the BG-12 tid group.

SF-36,
The SF-36 Health Survey is a 36 item subject completed questionnaire that measures 8 domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. The 8 domains are grouped into 2 summary scores for the physical (PCS) and mental (MCS) component scale scores. Higher scores indicate better physical and mental functioning. Mean changes in scores for the physical and mental component scales declined in placebo and increased in BG-12 groups indicating improvement of physical and mental aspects of health status.

EQ-50.
This scale is a subject rated instrument that provides a profile of the subject's health state in 5 dimensions. Although changes trended in favor of the active treatment group, these changes were associated with p values > 0.05.

Examination of Subgroups

Subgroup analyses showed that BG-12 treatment was effective across all demographic and baseline disease characteristic subgroups on the clinical efficacy endpoints of ARR, the proportion of subjects relapsed, and the proportion of subjects with 12-week confirmed disability progression at 2 years, but there were some notable differences worth mentioning (refer to Figure 11 and Figure 12).

Subgroups of Interest
Treatment with BG-12 bid and tid reduced the ARR at 2 years by 47% and 67%, respectively, over placebo among subjects <40 years of age at baseline, and by 36% and 13%, respectively, over placebo among subjects aged ≥40 years.

Among subjects with baseline EDSS score ≤2.0, treatment with BG-12 bid and tid reduced the ARR at 2 years by 52% and 66%, respectively, over placebo. Reductions of 37% over placebo were observed among subjects with baseline EDSS scores >2.0 in both the BG-12 bid and tid groups. The efficacy of BG-12 was also consistent with respect to prior MS treatment. Treatment with BG-12 bid and tid reduced the ARR by 53% and 55% over placebo among subjects who had received prior MS treatment and by 36% and 46%, respectively, among subjects who had not previously received MS treatment.

The treatment effect of BG-12 on the MRI efficacy endpoints (number of new or newly enlarging T2 hyperintense lesions, the number of new T1 hypointense lesions, and the number of Gd-enhancing lesions) was also generally consistent across the subgroups defined by demographic and baseline disease characteristics.

In addition the ARR for the MRI cohort had a numerically lower effect size than that of the non MRI cohort for the comparison of the tid dose and placebo, whereas with the comparison of the bid dose and placebo showed the opposite effect (the MRI cohort had a larger treatment effect).

Figure 11: ARR (INEC confirmed) at 2 years- rate ratio for the BG-12 240 mg bid vs. placebo comparison and 95% CI by demographic subgroup (trial 302)

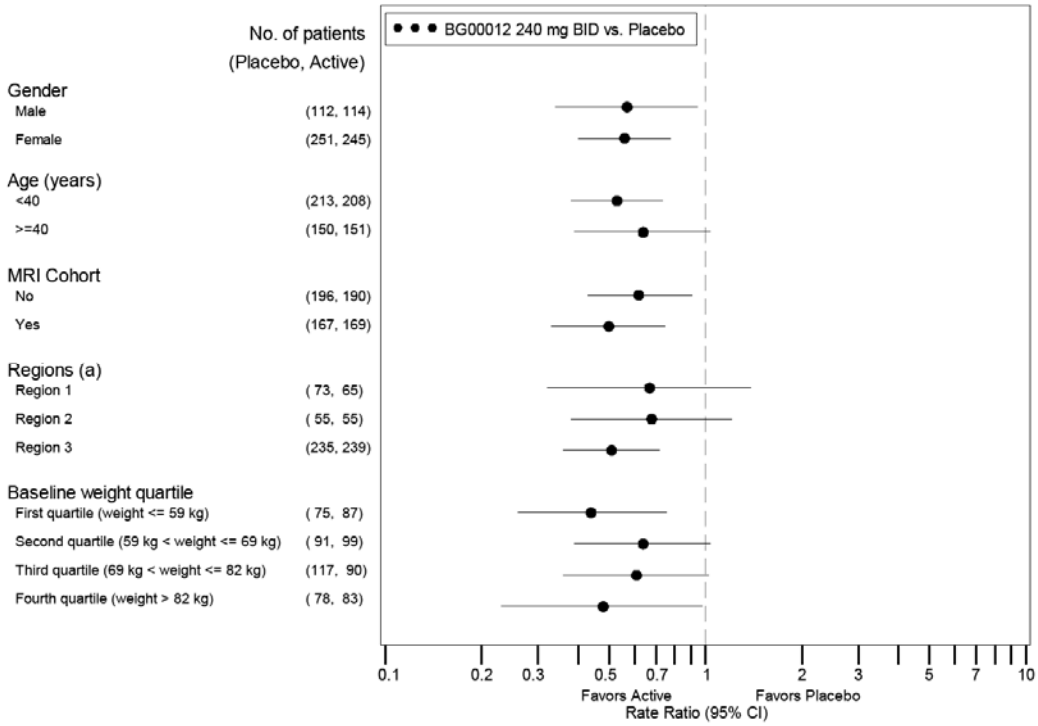
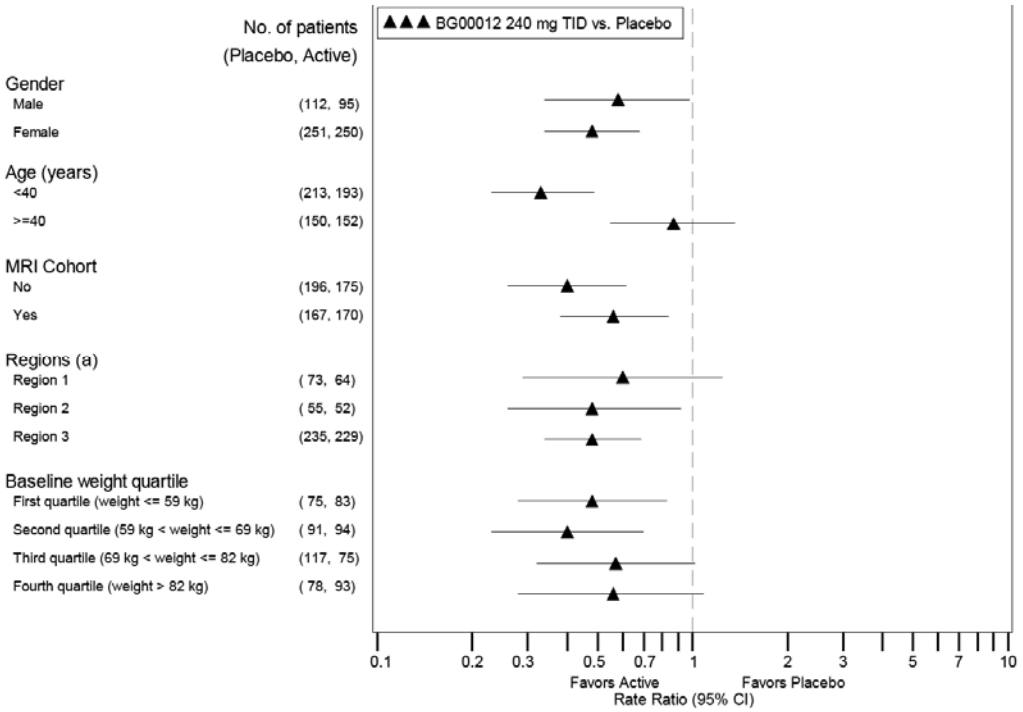


Figure 12: ARR (INEC confirmed) at 2 years- rate ratio for the BG-12 240 mg tid vs. placebo comparison and 95% CI by demographic subgroup (trial 302)



5.3.4 Protocol 109MS303

Study Title: A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG-12 Monotherapy in Subjects with RRMS

Subjects who completed studies 301 and 302 were eligible to enroll in study 303 and be followed for up to 5 years.

Study Design

Study 303 is an ongoing multicenter, parallel-group, randomized, dose blind, rater blind, dose comparison extension study designed to evaluate the long term safety and efficacy of 2 dose regimens of BG-12 in subjects with RRMS. Subjects who were randomized to BG-12 in study 301 or 302 continue on the same BG-12 dose to which they were originally randomized. Subjects who were randomized to placebo in studies 301 or 302 or to GA in trial 302 were re-randomized in a 1:1 ratio to BG-12 240 mg bid or 240 mg tid. The primary objective of study 303 was to evaluate the long term safety profile of BG-12. Efficacy endpoints included ARR, proportion of subjects relapsed, disability progression as measured by the EDSS and visual function every 6 months. Safety assessments occurred during every visit and MRI and quality of life assessments (SF-36 Health Survey and EuroQol-5D) were measured yearly. MRI measures of disease activity in subjects at selected investigational sites based on the availability of the necessary MRI equipment (MRI cohort) were conducted. Eligible subjects were enrolled at week 96 of their parent study (301 or 302) and this visit was considered the baseline visit for the extension study.

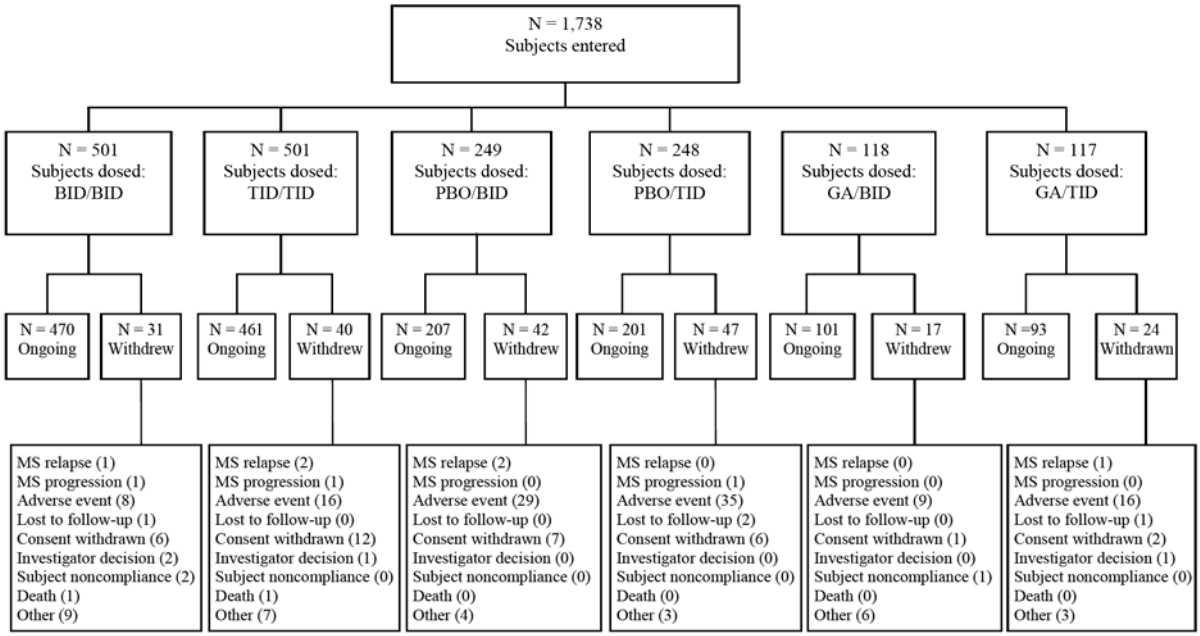
Subjects reported to the study site every 4 weeks for the first 24 weeks, and then every 12 weeks for up to 5 years. Long-term efficacy data based on a data cut-off date of August 3, 2011 was provided for this ongoing study.

5.3.4.1. Efficacy Results Trial 303

5.3.4.1.1 Trial Population

1738 subjects were enrolled in this trial with 6 arms: BG-12 bid/bid (501 subjects), BG-12 tid/tid (501), placebo/BG-12 bid (249), placebo/BG-12 tid (248), GA/BG-12 tid (118) and GA/BG-12 tid (117). For details on why patients withdrew from the study refer to Figure 13.

Figure 13: Overview of Subject Disposition in Trial 303



5.3.4.1.2 Efficacy Analysis

Data sets analyzed

Studies 301 + 302 analysis populations are as follows:
Studies 301 + 302 ITT and safety population (excluded subjects randomized to GA in study 302) were defined as all subjects who were randomized to placebo or BG-12 in studies 301 or 302 and who received at least 1 dose of study treatment in studies 301 or 302. This population was used to analyze efficacy and safety endpoints.

Studies 301 + 302 MRI cohort (excluded subjects randomized to GA in study 302) was defined as subjects in the studies 301 + 302 ITT population who consented to participate in the MRI

substudy and who had any MRI data in studies 301, 302, or 303. This population was used for select MRI analyses that were intended to additionally assess persistence of efficacy in the controlled and uncontrolled studies combined. Study 303 data from the parent studies (301 and 302) were analyzed in a pooled manner since both study's had similar populations and results.

Studies 301, 302, and 303 used the same definition for objective (i.e., protocol-defined) relapses. However, in studies 301 and 302, relapses had to be confirmed by an INEC, a requirement that was not applied in study 303. Therefore, analyses of relapse for the analysis of study 303 were based primarily on objective (i.e., protocol-defined) relapses.

In general, results are presented for the first and second years of studies 301 and 302, and the first year of the extension study 303 for the cohort of subjects who were dosed in study 303. Limited data were available for the second year of dosing in study 303 in terms of both the numbers of subjects treated and the length of observation; therefore, data from the second year of study 303 are not discussed in the study report.

As this is an analysis of an ongoing extension study, the sponsor did not perform formal statistical testing. Analyses are generally descriptive in nature and based on observed data, without imputation for missing values. For relevant analyses (e.g., adjusted ARR) CIs are provided for each treatment group, where appropriate, to characterize the variability around the point estimate. Data after subjects switched to alternative MS medications are excluded.

At the time of data cut off for this report, 1002 subjects who had received BG-12 in the parent studies had continued to receive treatment with BG-12 in the extension study, including 353 who had been treated for ≥1 year in the extension study. The sponsor presented their conclusions about this data concerning long-term (up to 3 years) efficacy of BG-12 which this reviewer will summarize in this section below, but this reviewer points out that in general open label long term extension trials do not provide valid data about efficacy and are generally useful in their contribution to the long term safety profile of a product.

Sponsor's conclusions:

- Analysis of endpoints, including ARR, time to first relapse demonstrated a continued treatment effect (>2 years) with BG-12, administered at 240 mg bid/bid: ARR (0.178, 95% CI 0.150, 0.211) or tid/tid ARR: (0.182, 95% CI 0.153, 0.215)
- In subjects who previously received placebo in the parent studies, 1 year of treatment with BG-12 240 mg bid or tid in study 303 reduced ARR, proportion of subjects relapsed as demonstrated by the yearly ARR over time (refer to Table 30 below).
- MRI data were supportive of the clinical data. In subjects previously treated with BG-12, effects on new/newly enlarging T2 hyperintense, new T1 hypointense, and Gd-enhancing lesions were maintained, while subjects who previously received placebo in the parent studies showed results in the first year of study 303 that were similar to those seen in the first year of BG-12 treatment in the parent studies.

Table 30: ARR with 95% CI for subjects randomized to placebo then active study treatment (trial 303)

	Placebo/ BG-12 BID	Placebo/ BG-12 TID
0 to 1 year	0.346 (0.269, 0.444)	0.355 (0.278, 0.454)
1 to 2 years	0.280 (0.213, 0.368)	0.248 (0.187, 0.329)
2 to 3 years	0.209(0.140, 0.312)	0.145 (0.092, 0.228)

Reviewer's comments: The data above represent the sponsor's conclusions not this reviewer's, as in general, efficacy data from a trial with this design would not be interpretable due to the bias introduced by the fact that patients are aware that they have been assigned to an experimental drug. This trial contributes predominantly safety information to this product's profile.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Treatment of patients with relapsing forms of multiple sclerosis (b) (4)

6.1.1 Methods

Four trials contribute data in support of efficacy for BG-12, a phase 2, one year, placebo controlled dose finding trial (C-1900), a 2 year double blind, placebo controlled dose comparison phase 3 trial (109MS301), a 2 year double blind, placebo controlled dose comparison phase 3 trial with an open label active comparator arm (109MS302), and a 5 year long term open label extension trial that is ongoing (109MS303). Trials 109MS301 and 109MS302 are considered the pivotal efficacy trials.

6.1.2 Demographics

Demography and baseline disease characteristics were generally well balanced between study 301 and 302 and between the 3 treatment groups. Overall 72% of subjects were women, the subjects ranged in age from 18-56 (median, 38) and 55% of subjects were younger than 40 years of age. The majority of subjects (81%) were White.

There was a difference between studies in terms of the regions from which subjects were enrolled. The 3 geographic regions were predefined based on geography and access to health care in each country. Both studies enrolled about 18% of subjects from region 1 (US). In trial 301, the remaining subjects were equally enrolled from regions 2: Canada, W. Europe, Israel, New Zealand and Australia (301 only), South Africa (301 only) and Costa Rica (302 only) and 3:

E. Europe, India, Mexico and Guatemala (301 only) (42%), whereas in study 302, approximately 15% were from region 2 and 66% were from region 3.

Table 31: Demography in terms of distribution of regions between trials and treatment groups

	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Geographic location						
Region 1[1]	64 (16)	65 (16)	72 (17)	73 (20)	65 (18)	64 (19)
Region 2[2]	172 (42)	174 (42)	173 (42)	55 (15)	55 (15)	52 (15)
Region 3[3]	172 (42)	171 (42)	171 (41)	235 (65)	239 (67)	229 (66)

Reviewer's comment: The varied distribution of recruitment between trials of regions may suggest that trial 302 included more patients that had poorer access to medical care than in trial 301. In general, there were no clear differences in the distribution of regions between treatment groups in the individual trials. Both trials included a similar and sufficient percentage of patients from the U.S.

Overall the study populations in terms of baseline disease characteristics and previous treatment history were similar and well balanced. Specifically, 48% of the ITT population of trial 301 and 55% of the ITT population of trial 302 had an EDSS score greater than 2.0. During the 12 months prior to the start of studies 301 and 302, the majority of subjects (92%) had 1 or 2 relapses, and approximately 5% of subjects had 3 or more relapses; the mean number of relapses that occurred during this period was 1.3 The mean time since MS diagnosis was 5.2 years (range: 0 to 33 years).

Compared to trial 301, trial 302 had a higher percentage of MS treatment naïve subjects (60% vs. 45% in trials 302 and 301, respectively). This may have been due to the fact that trial 302 had a higher percentage of subjects from region 3 where access to MS therapies may be limited compared to the other 2 regions.

Comparison of treatment groups in the MRI cohort

In both pivotal trials the treatment groups within the MRI cohort were well balanced in terms of demographic characteristics and baseline MS characteristics, although minor differences were noted. In addition, the demographics and baseline characteristics of the MRI cohort appear representative of the ITT population. Most patients that were screened for eligibility of the pivotal trials did not get screening MRIs so the baseline MRIs of the MRI cohort and the ITT cannot be compared. Inclusion criterion #5 specified that patients either had to have a relapse within the prior 12 months with a prior brain MRI demonstrating a lesion consistent with MS, or have shown evidence of Gd enhancing lesions on a brain MRI performed within 6 weeks prior to randomization. Ninety seven percent of subjects in trials 301 and 302 met this entry criterion by

having a relapse within the year before randomization and therefore did not have an MRI of the brain performed at screening.

Reviewer's comment: The demographics and baseline characteristics of the MRI cohort appear to be representative of the overall ITT population.

6.1.3 Subject Disposition

There was no difference in the percentage of subjects that completed the study between treatment arms of both trials (78%). Yet, there were more patients in the placebo groups compared to the active treatment groups that discontinued study treatment (refer to Table 32). The most common reason for prematurely discontinuing study treatment was similar across trials 301 and 302 with consent withdrawn, "other," or MS relapse being the most common reasons leading to study treatment discontinuation in the placebo group in both studies, and AEs being the most common reason for treatment discontinuation in both studies for both BG-12 dose groups.

Table 32: Trial subject disposition

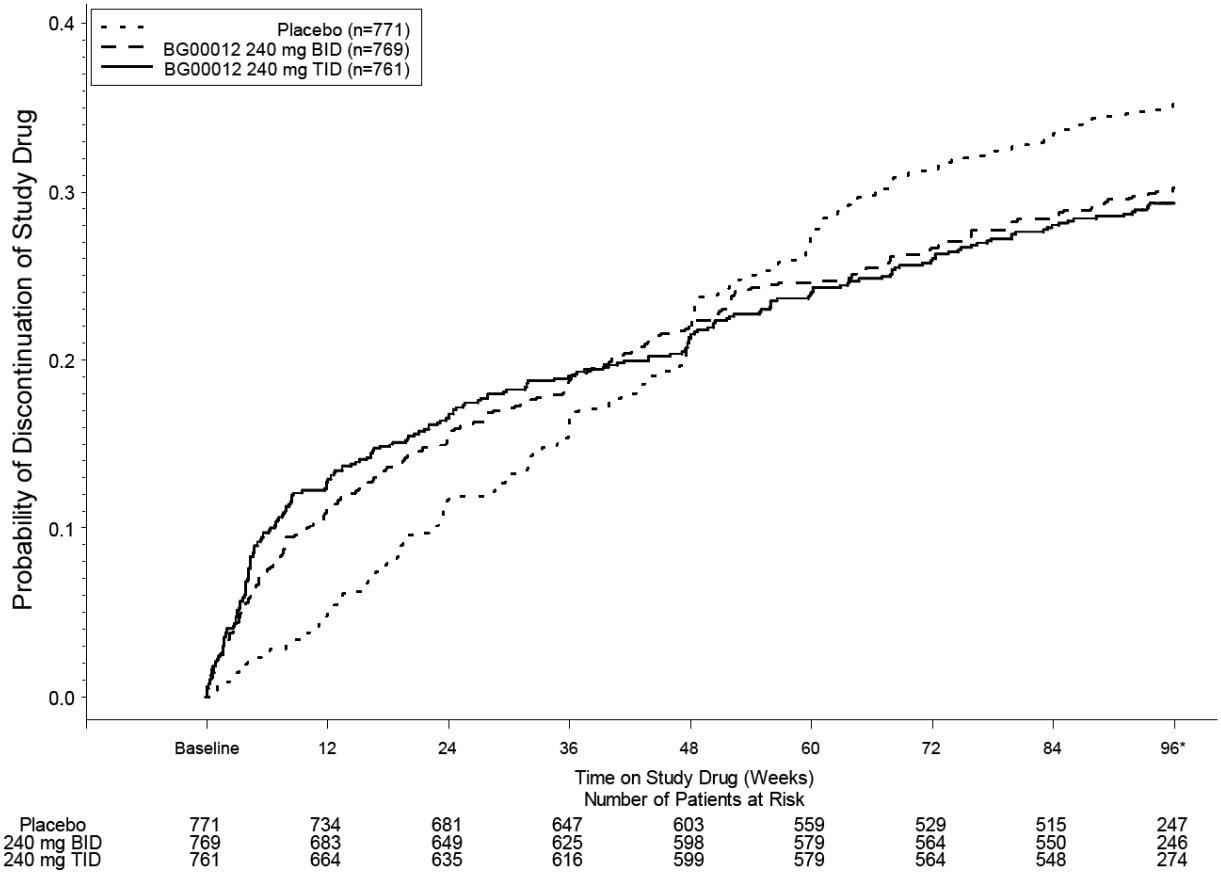
	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. (%) of subjects randomized	410	411	416	363	362	345
No. (%) of subjects dosed	408 (100)	410 (100)	416 (100)	363 (100)	359 (100)	345 (100)
No. (%) of subjects who completed study drug treatment	265 (65)	284 (69)	289 (69)	234 (64)	253 (70)	249 (72)
No. (%) of subjects who discontinued study drug	143 (35)	126 (31)	127 (31)	129 (36)	106 (30)	96 (28)
MS relapse	31 (8)	4 (<1)	10 (2)	18 (5)	6 (2)	3 (<1)
MS progression	14 (3)	7 (2)	7 (2)	8 (2)	7 (2)	5 (1)
Adverse event	22 (5)	61 (15)	56 (13)	21 (6)	36 (10)	38 (11)
Lost to follow-up	7 (2)	9 (2)	11 (3)	7 (2)	8 (2)	4 (1)
Consent withdrawn	34 (8)	18 (4)	18 (4)	14 (4)	9 (3)	15 (4)
Investigator decision	4 (<1)	4 (<1)	2 (<1)	3 (<1)	2 (<1)	1 (<1)
Subject non-compliance	3 (<1)	3 (<1)	9 (2)	9 (2)	4 (1)	3 (<1)
Death	0	0	1 (<1)	0	0	0
Other	28 (7)	20 (5)	13 (3)	49 (13)	34 (9)	27 (8)

The analysis of time to discontinuation revealed differences in the pattern of discontinuation between the placebo and BG-12 groups (Figure 14). During the initial part of the 2-year treatment period, particularly over the first 3 months, treatment discontinuations were more common with BG-12 than with placebo due to AEs associated with initiation of BG-12

treatment. Subsequently, similar rates of discontinuation between the placebo and BG-12 treatment groups were evident up to approximately 1 year of treatment. From approximately 1 year onward, treatment discontinuations were more common in the placebo group than in the BG-12 treatment groups, due to lack of efficacy or higher rates of MS relapses in the placebo group. By the end of the treatment period, more subjects receiving BG-12 than placebo were still on study treatment.

Reviewer's comments: Although the study treatment discontinuation reasons are different for the placebo vs. active treatment groups, this difference suggests that the placebo patients discontinued due to increased MS related activity more often than the patients in the active treatment groups. Such a difference could dilute the treatment effect of the active product. Despite this possible contributor to a diluted treatment effect, the primary analysis remains robustly supportive of efficacy of BG-12 over placebo.

Figure 14: Time to discontinuation of study treatment (pooled data 301 and 302)



The percentage of subjects who switched to alternative MS medications due to disease activity as allowed by the protocols was similar across studies. Approximately 8% of the ITT population of the integrated analysis switched to alternative MS. A greater percentage of subjects in the

placebo group (12%) switched to alternative MS medications compared with subjects in the BG-12 bid group (7%), and BG-12 tid group (6%).

Reviewer's comments: As stated earlier, the reasons and patterns of treatment discontinuation suggest that subjects in the active treatment group were transitioning to alternative treatment and discontinuing treatment less often due to MS relapse than subjects in the placebo group.

6.1.4 Analysis of Primary Endpoints

Both trials included a measure of relapse as their primary endpoint, yet in trial 301, the primary endpoint was the proportion subjects who relapsed at 2 years, while in trial 302 it was the ARR at 2 years. The trial that did not include the ARR as the primary endpoint (301), did include the ARR as a key secondary endpoint and the trial that did not include proportion relapsing as the primary endpoint included it as a key secondary endpoint, so comparisons on these endpoints can be made as well and will be included in this section, although in certain cases they do not represent the primary endpoint.

Table 33: Efficacy results of ARR and proportion relapsing- ITT (trials 301 and 302)

Trial 301				**Trial 302**				
Endpoint	Placebo	240 mg bid	240 mg tid	Endpoint	Placebo	240 mg bid	240 mg tid	GA
Proportion relapsing*	**0.461**	**0.270 p<0.0001**	**0.260 p<0.0001**	**ARR**	**0.401**	**0.224 p<0.0001**	**0.198 p<0.0001**	**0.286 p<0.0001**
ARR	0.364	0.172 p<0.0001	0.189 p<0.0001	Proportion relapsing	0.41	0.291 p=0.002	0.241 p<0.001	0.321 p=0.0097

*Bolded row above represents results for the primary endpoint of the trial

Trial 301 demonstrated a statistically significant treatment effect on the proportion of patients relapsing (as can be seen in Table 33), in BG-12 240 mg bid (0.270) as compared to placebo (0.46) resulting in a 41% reduction (p<0.0001). In addition there was a statistically significant treatment effect on the proportion of patients relapsing in the BG-12 tid (0.260) group as compared to the placebo group (0.461) resulting in a 44% reduction (p<0.0001)

Trial 302 also demonstrated a statistically significant treatment effect on the ARR when the placebo group (0.401) was compared to the BG-12 240 mg bid group (0.224) resulting in a 44% reduction (p<0.0001) on treatment over placebo. A statistically significant treatment effect on the ARR was also identified when the placebo group (0.401) was compared to the BG-12 240 mg tid group (0.198) resulting in a 51% reduction on treatment over placebo (p<0.0001). In addition, this treatment effect was also demonstrated in the trials for which these endpoints were identified as key secondary outcomes (refer to Table 33)

The sponsor's primary analysis for trial 302 was based on the adjusted ARR. In addition the sponsor calculated the unadjusted ARR, the rate ratio (active/placebo) and the percentage reduction (active/placebo) of the ARR. These analyses provided nominally significant values for

the active treatment vs. placebo comparisons as described in detail in section 5.3.2.2 of this review (p value <0.0001 for both active treatment groups vs. placebo). The following sensitivity analyses were performed and were supportive of the robust findings of the primary endpoint.

In trial 301 the following analyses yielded nominally significant findings:

- Patients with unknown relapse status when withdrawn from the study or when discontinued from the study treatment for reasons indicative of MS relapse or lack of efficacy or switched to alternate MS medication were given "relapsed status". This analysis reveals that the proportion of patients relapsing is 45%, 26 %, and 25% in placebo, BG-12 bid, BG-12 tid respectively (p<0.0001).
- An analysis was performed on all patients that completed the trial regardless of whether they transitioned to alternate medications. This analysis reveals that the of proportion of patients relapsing is 42%, 24% and 23% for placebo, BG-12 bid, BG-12 tid respectively (p< 0.0001).
- An analysis was performed on the per protocol population which revealed that the proportion of patients relapsing was 43%, 26% and 25% in the placebo, BG-12 bid, BG-12 tid groups respectively (p< 0.0001).
- An analysis was performed on the ITT population excluding the 23 subjects from the 3 sites with GCP violations. This analysis revealed that the proportion of subjects relapsing were 42%, 24%, 23% in placebo, BG-12 bid and BG-12 tid respectively.

In trial 302 the following analyses yielded nominally significant findings:

- An analysis of data from subjects regardless of whether they transitioned to alternative MS medications revealed that the ARR in placebo, BG-12 bid and BG-12 tid was 0.381, 0.217 and 0.205, respectively (p<0.0001 for both comparisons active treatment vs. placebo).
- An analysis of the per protocol population revealed an ARR of 0.378, 0.220, and 0.197 in placebo, BG-12 bid and BG-12 tid groups, respectively (p<0.0001 for both comparison).

Reviewer's comment: Overall, the sensitivity analyses conducted by the sponsor were supportive of the robust findings of the primary endpoint in both pivotal efficacy trials.

6.1.5 Analysis of Secondary Endpoints

6.1.5.1 Number of New or Newly Enlarging T2 Hyperintense Lesions

In the individual studies, 301 and 302, both BG-12 doses (240 mg bid and tid) significantly reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years compared with placebo.

In study 301, BG-12 bid and tid reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 2 years by 85% and 74%, respectively, compared with placebo (p<0.0001 for both comparisons). In study 302, compared with placebo, treatment with BG-12 240 mg bid and tid significantly reduced the number of new or newly enlarging T2 hyperintense

lesions that developed over 2 years by 71% and 73%, respectively (p<0.0001 for both comparisons).

Table 34: Number of new and newly enlarging T2 hyperintense lesions at 2 years compared to baseline (trial 301 and 302)

	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. of subjects in MRI cohort	180	176	184	167	169	170
No. (%) of subjects with						
0 lesions	45 (27)	68 (45)	62 (41)	17 (12)	38 (27)	43 (31)
1 lesion	8 (5)	26 (17)	28 (18)	7 (5)	24 (17)	21 (15)
2 lesions	3 (2)	14 (9)	11 (7)	4 (3)	16 (11)	13 (9)
3 lesions	8 (5)	10 (7)	5 (3)	5 (4)	11 (8)	12 (9)
4 or more lesions	101 (61)	34 (22)	46 (30)	106 (76)	51 (36)	51 (36)
n (%)	165 (100)	152 (100)	152 (100)	139 (100)	140 (100)	140 (100)
Median	7	1	1	11	2	2
25th, 75th percentile	0, 20	0, 3	0, 5	4, 26	0, 5.5	0, 6
Min, max	0, 106	0, 52	0, 106	0, 119	0, 84	0, 63
Adjusted mean[1]	17.0	2.6	4.4	17.4	5.1	4.7
Lesion mean ratio[2]		0.15	0.26		0.29	0.27
95% CI		0.10, 0.23	0.17, 0.38		0.21, 0.41	0.20, 0.38
Percentage reduction		85	74		71	73
95% CI		77, 90	62, 83		59, 79	62, 80
p-value[3]		<0.0001	<0.0001		<0.0001	<0.0001

Reviewer's comment: BG-12 had a robust treatment effect on the reduction of the number of new and newly enlarging T2 lesions at 2 years compared to placebo in trials 301 and 302.

6.1.5.2 Number of Gd-enhancing lesions at 2 years

Trial 301 ranked this endpoint as a key secondary endpoint to test in their closed testing procedure to control for the type 1 error due to multiplicity. Trial 302 did not name this endpoint as a key secondary endpoint but information about the analysis of this endpoint from trial 302 will be included in this section.

In trial 301 BG-12 bid and tid reduced the odds of having greater Gd-enhancing lesion activity at 2 years by 90% and 73%, respectively, compared with placebo (p<0.0001 for both comparisons). At 2 years, the mean number of Gd-enhancing lesions in the placebo group was 1.8, compared

with 0.1 and 0.5 in the BG-12 bid and tid groups, respectively. The odds ratios obtained from the model were 0.10 (95% CI, 0.05, 0.22; p <0.0001) for BG-12 bid vs. placebo and 0.27 (95% CI, 0.15, 0.46; p <0.0001) for BG-12 tid vs. placebo. This indicated that treatment with BG-12 bid and tid resulted in statistically significant reductions over placebo of 90% and 73%, respectively, in the odds of having greater Gd-enhancing lesion activity at 2 years.

Although the number of Gd enhancing lesions at 2 years was not a key secondary endpoint in trial 302, there was a nominally significant effect on this endpoint for both doses vs. placebo (see Table 35 below). At 2 years, the mean number of Gd enhancing lesions in the placebo group was 2.0, compared to 0.5 and 0.4 in the BG-12 bid and BG-12 tid group, respectively.

Table 35: Number of Gd enhancing lesions at 2 years- MRI cohort (trials 301, 302)

	Trial 301			**Trial 302**		
	Placebo	**BG BID**	**BG TID**	**Placebo**	**BG BID**	**BG TID**
# subjects in MRI cohort	180	176	184	167	169	170
n	165	142	130	144	147	144
Mean (SD)	1.8 (4.15)	0.1 (0.63)	0.5 (1.73)	2.0 (5.59)	0.5 (1.67)	0.4 (1.18)
Odds ratio		0.10	0.27		0.26	0.35
95%		0.05,0.22	0.15,0.46		0.15,0.46	0.20, 0.59
% reduction		90	73		74	65
P value		<0.0001	<0.0001		<0.0001	=0.0001

Reviewer's comment: BG-12 had a robust treatment effect on the reduction of the number of Gd enhancing lesions at 2 years as compared to placebo in both pivotal efficacy trials.

6.1.5.3 New T1 hypointense lesions

Trial 302 ranked this endpoint as a key secondary endpoint to test in their closed testing procedure to control for the type 1 error due to multiplicity. Trial 301 did not name this endpoint as a key secondary endpoint but information about the analysis of this endpoint from trial 301 will be included in this section.

In trial 302, compared to placebo, the number of new T1 hypointense lesions that developed over 2 years was reduced by 57% and 65%, respectively in the BG-12 bid and tid groups (p< 0.0001 for both comparisons). In trial 301, compared to placebo the number of new T1 hypointense non enhancing lesions that developed over 2 years was reduced by 72% and 63%, respectively in the BG-12 bid and BG-12 tid groups (p<0.0001). Refer to Table 36.

Table 36: Number of new T1 hypointense lesions over 2 years- MRI cohort (trial 301 and 302)

	Study 301			Study 302		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. of subjects in MRI cohort	180	176	184	167	169	170
No. (%) of subjects with						
0 lesions	59 (36)	61 (40)	69 (45)	29 (21)	55 (39)	61 (44)
1 lesion	16 (10)	35 (23)	29 (19)	8 (6)	21 (15)	21 (15)
2 lesions	10 (6)	15 (10)	13 (9)	10 (7)	15 (11)	19 (14)
3 to 4 lesions	19 (12)	26 (17)	18 (12)	29 (21)	12 (9)	9 (6)
5 or more lesions	61 (37)	14 (9)	23 (15)	63 (45)	37 (26)	30 (21)
n (%)	165 (100)	151 (100)	152 (100)	139 (100)	140 (100)	140 (100)
Median	2	1	1	4	1	1
25th, 75th percentile	0, 8	0, 3	0, 3	1, 11	0, 5	0, 3
Min, max	0, 36	0, 36	0, 34	0, 47	0, 47	0, 45
Adjusted mean[1]	5.6	1.5	2.1	7.0	3.0	2.4
Lesion mean ratio[2]		0.28	0.37		0.43	0.35
95% CI		0.20, 0.39	0.26, 0.52		0.30, 0.61	0.24, 0.49
Percentage reduction		72	63		57	65
95% CI		61, 80	48, 74		39, 70	51, 76
p-value[3]		<0.0001	<0.0001		<0.0001	<0.0001

Reviewer's comment: BG-12 had a robust treatment effect on the reduction of the number of new T1 hypointense lesions at 2 years as compared to placebo in both pivotal trials although it was named a key secondary endpoint and had a prespecified plan for the statistical analysis to control for the type 1 error rate only in trial 302.

6.1.5.4 Annualized relapse rate/proportion relapsing

Please see section 6.1.4 for a full description of the findings for these endpoints in trials 301 and 302. Since trial 301 included "proportion of relapsing subjects at 2 years" as the primary endpoint and trial 302 included the "ARR at 2 years" as the primary endpoint, both of which are a measure of relapse activity, I included discussions about this endpoint in the primary endpoint section. Please note that in trial 301 the "ARR at 2 years" was a key secondary endpoint and in trial 302, the endpoint "the proportion of relapsing subjects at 2 years" was a key secondary endpoint. As described above in the referenced section, BG-12 at both doses showed a robust effect on both endpoints in both trials over placebo.

6.1.5.5 Disability progression

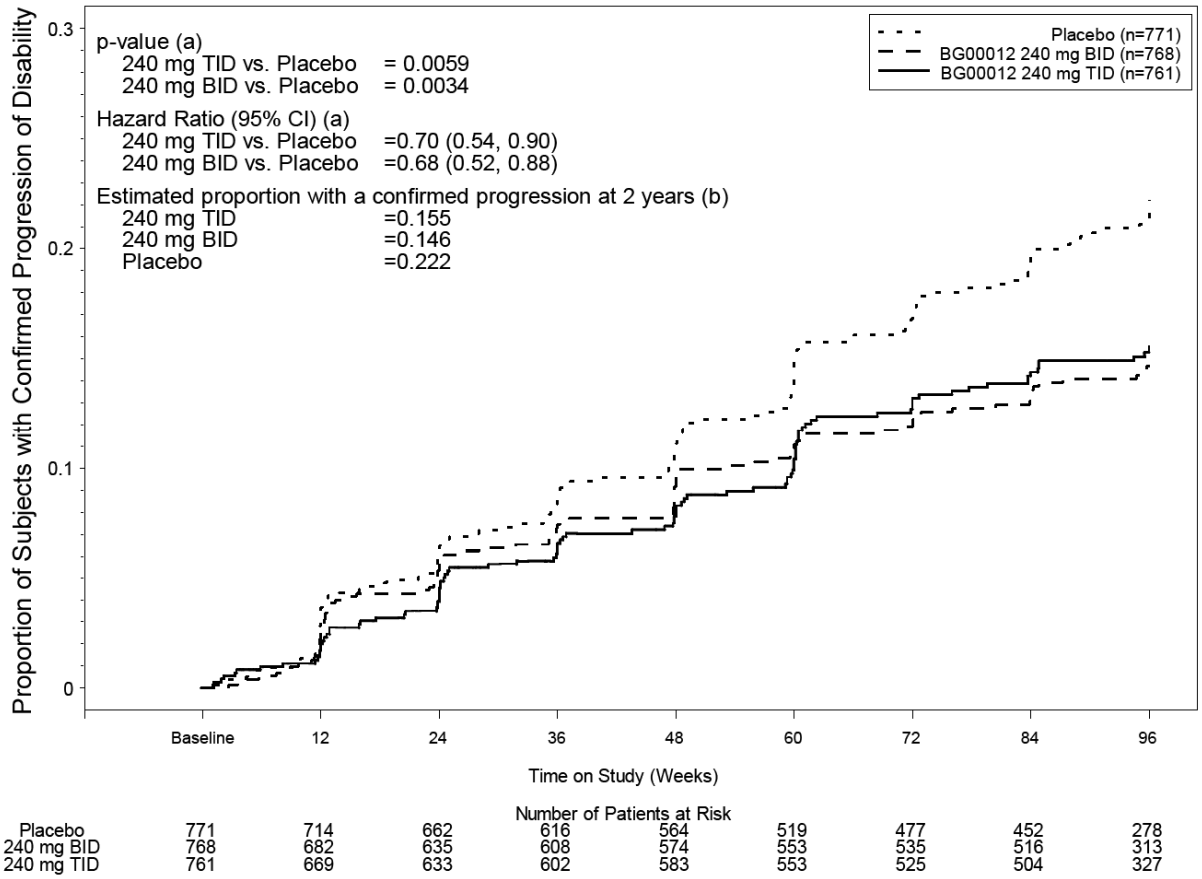
In study 301, both BG-12 doses showed a statistically significant reduction in the time to disability progression. Treatment with BG-12 bid and tid reduced the risk of confirmed (12-week) disability progression at 2 years by 38% (p = 0.0050) and 34% (p = 0.0128), respectively, compared with placebo. Yet this treatment benefit was not shown when 24 week disability confirmation was evaluated in the BG-12 bid vs. placebo comparison (p=0.1893) or the BG-12 tid vs. placebo comparison (p=0.0760). Upon closer inspection of the data, it is evident that among the subjects that progressed in trial 301 after 12 weeks, the proportion without a confirmed progression after 24 weeks was greater in the placebo group (36%) than the BG-12 bid (23%) or BG-12 tid (34%) groups. This may have been due to the fact that a greater proportion of subjects in the placebo group (16%) than the BG-12 bid (14%) and BG-12 tid (11%) group did not have EDSS data at least 24 weeks after the start of the progression, and therefore did not have the opportunity to have their progression confirmed. In addition, 6% of the placebo subjects without a confirmed 24 week progression started on alternative MS medication within 24 weeks after the start of their progression while none of the patients in the BG-12 groups did. Missing data in this case for the 24 week confirmed disability progression and the use of alternative MS medication may have affected the ability to maintain a positive effect on disability progression through the 24 week time point.

Study 302 did not demonstrate a statistically significant treatment effect of BG-12 over placebo in the time to disability progression. In study 302 the Kaplan-Meier estimate of the proportion of subjects who progressed by 2 years was 0.169 in the placebo group, compared with 0.128 and 0.130 in the BG-12 bid and BG-12 tid groups, respectively. The proportion of subjects in the placebo group with confirmed 12 week progression (0.169) was lower than that observed in the placebo group in study 301 (0.271). The sponsor proposes that due to the low placebo disability progression rate, this trial was unable to show a treatment effect for this endpoint. This reviewer notes that although a similar number of patients were enrolled in trial 301 as trial 302, due to the additional treatment arm in trial 302 there were fewer patients per arm. In trial 301 there were approximately 410 patients per arm, and in trial 302 there were approximately 360 patients per treatment arm. This is relevant in terms of the disability progression endpoint which generally requires studies with large numbers of patients of longer duration to detect a treatment effect as compared to the relapse endpoint. Trial 301 may not have had adequate power to detect an effect on disability progression due to the smaller numbers per treatment arm than were randomized in trial 301. In such a case, a pooled analysis may contribute another view of the strength of the data for this endpoint.

Reviewer's comment: Evidence of baseline differences in the two placebo groups in the two trials would support the sponsor's proposal about the placebo disability progression rate being unusually low in trial 302, yet this reviewer was unable to identify such differences. In independent trials a value from one trial cannot be easily generalized to the other trial, so one can not make a different conclusion in trial 302 based on this placebo differential progression rate, by borrowing the placebo progression rate seen in trial 301 and comparing this rate to the active treatment arms in trial 302. In this case, we have one trial that supports efficacy for disability progression and one trial that does not. It can be difficult to demonstrate disability

progression in a 2 year trial since there may be few events in this time period. Although in general it may not be useful to pool data if one trial is clearly negative, the presence of a trend in trial 302 and reduced power to detect a difference due to a smaller number of patients per treatment arm as compared to trial 301, may suggest that pooling may be informative.

Figure 15: Time to sustained progression of disability at 2 years as measured by EDSS (12 week confirmation)-ITT (trials 301 and 302 pooled)



When the data from trials 301 and 302 are pooled (refer to Figure 15 and Table 37), there is a nominally significant difference in the comparison of placebo and BG-12 bid and the comparison of placebo and BG-12 tid for time to 12 week confirmed disability progression.

Table 37: Disability progression in trial 301, 302 and pooled analysis

	Study 109MS301			Study 109MS302			Pooled Analysis (109MS301 + 109MS302)		
	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
No. (%) of subjects	408 (100)	409 (100)	416 (100)	363 (100)	359 (100)	345 (100)	771 (100)	768 (100)	761 (100)
12-week confirmation									
No. (%) progressed	89 (22)	57 (14)	62 (15)	52 (14)	40 (11)	38 (11)	141 (18)	97 (13)	100 (13)
Estimated proportion who progressed[1]	0.271	0.164	0.177	0.169	0.128	0.130	0.222	0.146	0.155
Hazard ratio[2] 95% CI		0.62 0.44, 0.87	0.66 0.48, 0.92		0.79 0.52, 1.19	0.76 0.50, 1.16		0.68 0.52, 0.88	0.70 0.54, 0.90
p-value[3]		0.0050	0.0128		0.2536	0.2041		0.0034	0.0059

Reviewer's comment: The data provided in this submission is supportive of a reduction of the risk of 12 week confirmed disability progression by 2 years in patients on BG-12 as compared to placebo. Substantial evidence is provided by the statistically significant analysis of disability progression in trial 301 with confirmatory evidence provided by the positive trend seen in trial 302 and the nominally significant analysis for disability progression in the pooled analysis of trials 301 and 302 when patients on BG-12 are compared to those on placebo.

6.1.6 Other Endpoints

The Use of IV Steroids

In study 301, the annualized rate of relapse requiring IV steroids over 2 years was reduced by 52% and 51% following treatment with BG-12 bid and tid, respectively, compared with placebo (p =0.0001 for both comparisons). In study 302, the number of relapses that required IV steroid therapy was reduced by 43.6% (p=0.0002) and 48.6% (p<0.0001) following treatment with BG-12 bid and BG-12 tid, respectively, over placebo.

Reviewer's comment: This analysis is supportive of efficacy and suggests that patients on BG-12 required less rescue medication with steroids during the pivotal trials.

Brain Atrophy

Brain atrophy is an exploratory endpoint that was evaluated in both trial 301 and 302. For trial 301, at 2 years, the median percentage change in brain volume from 6 months was -0.660% in the placebo group compared with -0.460% in the bid group (p=0.0214 for the placebo vs. bid comparison) and -0.550% in the tid group (p = 0.2478 for the placebo vs. TID comparison). Although the comparison between placebo and BG-12 bid represents a nominally significant change, this change represents a numerically small percent change of 0.2. In trial 302, there were no significant changes indentified in brain atrophy between treatment groups. Between 6 months and 2 years, a median change of -0.765% was seen in the placebo group compared with -0.720% in the BG-12 bid group (p=0.8306 for the placebo vs. BG-12 bid comparison) and -0.745% the BG-12 tid group (p=0.5621 for the placebo vs. BG-12 tid comparison) .

Reviewer's comment: This endpoint continues to be exploratory and in this trial does not clearly support efficacy.

6.1.7 Subpopulations

Analyses of efficacy endpoints for a number of different subpopulations have been performed by the sponsor for the individual phase 3 studies 301 and 302. Demographic subgroups were pre-defined based on age, gender, baseline weight quartiles, inclusion in the MRI cohort and region. Subgroups based on baseline disease characteristics were also pre-defined by the number of relapses experienced by the subject in the year prior to study entry, baseline McDonald criteria, prior treatment with an MS medication, baseline EDSS score, baseline T2 hyperintense lesion volume and the presence of baseline Gd-enhancing lesions.

In studies 301 and 302, for each of the 3 clinical endpoints evaluated, the effect of BG-12 bid and tid treatment was generally consistent across all subgroups, although BG-12 treatment effect appeared to be greater among subjects younger than 40 years of age and in subjects with a baseline EDSS score of ≤2. The BG-12 bid and tid treatment effect also appeared to be greater among subjects who were naïve to MS treatment. With respect to MRI endpoints, the effect of BG-12 bid and tid treatment was generally consistent across all subgroups in both studies.

Efficacy based on EDSS (≤2.0 versus >2)

Trial 301
Among subjects with a baseline EDSS score ≤2.0, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 65% and 66%, respectively; the ARR at 2 years by 71% and 67%, respectively; and the risk of confirmed (12-week) disability progression by 48% and 50%, respectively.

Among subjects with a baseline EDSS score of >2.0, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 29% and 32%, respectively; the ARR at 2 years by 30% and 26%, respectively; and the risk of confirmed (12-week) disability progression by 27% and 15%, respectively.

Trial 302
Among subjects with baseline EDSS score ≤2.0, treatment with BG-12 bid and tid reduced the ARR at 2 years by 52% and 66%, respectively, over placebo. Reductions of 37% over placebo were observed among subjects with baseline EDSS scores >2.0 in both the BG-12 bid and tid groups.

Table 38: Summary of ARR (INEC confirmed) at 2 years by EDSS score (trials 301 and 302 pooled)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Baseline EDSS			
<= 2.0			
n	362	373	383
Adjusted relapse rate (95% CI) (a)	0.357 (0.291,0.438)	0.132 (0.102,0.170)	0.122 (0.094,0.159)
Rate ratio (active/placebo) (95% CI) (a)		0.368 (0.272,0.499)	0.342 (0.251,0.466)
> 2.0			
n	409	395	378
Adjusted relapse rate (95% CI) (a)	0.398 (0.335,0.472)	0.265 (0.217,0.323)	0.276 (0.227,0.335)
Rate ratio (active/placebo) (95% CI) (a)		0.666 (0.525,0.845)	0.693 (0.547,0.879)
Baseline EDSS			
<= 3.5			
n	635	635	651
Adjusted relapse rate (95% CI) (a)	0.375 (0.324,0.433)	0.178 (0.150,0.212)	0.173 (0.145,0.207)
Rate ratio (active/placebo) (95% CI) (a)		0.476 (0.384,0.589)	0.463 (0.373,0.573)
> 3.5			
n	136	133	110
Adjusted relapse rate (95% CI) (a)	0.396 (0.283,0.554)	0.270 (0.185,0.394)	0.327 (0.224,0.477)
Rate ratio (active/placebo) (95% CI) (a)		0.683 (0.460,1.013)	0.826 (0.551,1.239)

Reviewer's comment: The treatment effect of BG-12 over placebo on the ARR is more marked in patients with an EDSS ≤ 2 at baseline compared to patients with an EDSS>2 at baseline, and in patients with an EDSS≤ 3.5 at baseline than in patients with an EDSS at baseline > 3.5.

Efficacy based on baseline age (<40 versus ≥40 Years)

Trial 301
Among subjects <40 years of age at baseline, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 59% and 56%, respectively; the annualized relapse rate at 2 years by 63% and 59%, respectively; and the risk of confirmed (12-week) disability progression at 2 years by 62% and 38%, respectively .

Among subjects ≥40 years at baseline, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 26% and 37%, respectively; the annualized relapse rate at 2 years by 34% and 29%, respectively; and the risk of confirmed (12-week) disability progression by 9% and 32%, respectively.

Trial 302
Treatment with BG-12 bid and tid reduced the ARR at 2 years by 47% and 67%, respectively, over placebo among subjects <40 years of age at baseline, and by 36% and 13%, respectively, over placebo among subjects aged ≥40 years.

Reviewer's comment: There was a greater treatment effect on the clinical endpoints among patients < 40 than those ≥40 in both trials. Most notable is the difference in the treatment effect in trial 301 for the BG-12 bid group for the risk of disability progression in which

patients < 40 have a 62% reduction and those that are ≥ 40 only had a 9% reduction as compared to placebo.

Efficacy based on prior treatment with a medication for MS

Trial 301
Among MS treatment-naïve subjects, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 63% and 56%, respectively; the ARR at 2 years by 67% and 61%, respectively; and the risk of confirmed (12-week) disability progression by 62% and 54%, respectively.

Among subjects who had received prior medications for the treatment of MS, BG-12 bid and tid treatment reduced the risk of relapse over 2 years by 35% and 45%, respectively; ARR at 2 years by 39% and 37%, respectively; and the risk of confirmed (12-week) disability progression by 17% and 17%, respectively.

Trial 302
Treatment with BG-12 bid and tid reduced the ARR by 53% and 55% over placebo among subjects who had received prior MS treatment and by 36% and 46%, respectively, among subjects who had not previously received MS treatment.
The treatment effect of BG-12 on the MRI efficacy endpoints (number of new or newly enlarging T2 hyperintense lesions, the number of Gd-enhancing lesions and the number of new T1 hypointense lesions) was also generally consistent across the subgroups defined by demographics and baseline disease characteristics.

Analysis of the primary endpoint per region
In general, the treatment effect on the primary endpoint in both pivotal trials was preserved when evaluated by region (refer Table 39 and Table 40).

Table 39: Summary of proportion of subjects relapsed (INEC confirmed) at 2 years by region- ITT (trial 301)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Regions (c)			
Region 1			
n	64	65	72
Estimated proportion of subjects relapsed (a)	0.319	0.142	0.198
Hazard ratio (active/placebo) (95% CI) (b)		0.35 (0.14,0.84)	0.62 (0.29,1.32)
Region 2			
n	172	174	173
Estimated proportion of subjects relapsed (a)	0.503	0.291	0.276
Hazard ratio (active/placebo) (95% CI) (b)		0.51 (0.35,0.73)	0.47 (0.32,0.68)
Region 3			
n	172	171	171
Estimated proportion of subjects relapsed (a)	0.468	0.293	0.266
Hazard ratio (active/placebo) (95% CI) (b)		0.57 (0.39,0.82)	0.52 (0.35,0.76)

Table 40: Summary of ARR (INEC confirmed) at 2 years by region- ITT (trial 302)

	Placebo	BG00012 240 mg BID	BG00012 240 mg TID
Regions (b)			
Region 1			
n	73	65	64
Adjusted relapse rate	0.302	0.202	0.183
(95% CI) (a)	(0.189,0.484)	(0.115,0.355)	(0.104,0.320)
Rate ratio (active/placebo)		0.669	0.604
(95% CI) (a)		(0.322,1.392)	(0.292,1.250)
Region 2			
n	55	55	52
Adjusted relapse rate	0.468	0.318	0.226
(95% CI) (a)	(0.318,0.687)	(0.207,0.489)	(0.135,0.377)
Rate ratio (active/placebo)		0.680	0.483
(95% CI) (a)		(0.382,1.211)	(0.255,0.915)
Region 3			
n	235	239	229
Adjusted relapse rate	0.375	0.192	0.181
(95% CI) (a)	(0.298,0.472)	(0.146,0.254)	(0.136,0.242)
Rate ratio (active/placebo)		0.512	0.483
(95% CI) (a)		(0.362,0.725)	(0.337,0.693)

Analysis of the ARR in the MRI cohort as compared to the non MRI cohort
When comparing the MRI cohort to the non MRI cohort in terms of the ARR analysis, the treatment effect, expressed by percentage reduction in ARR, was numerically higher in the non MRI cohort than the MRI cohort for the BG-12 bid vs. placebo comparison. Although the ARR and the percentage reduction in ARR are numerically different between the MRI and non-MRI cohort, a generally consistent and relevant treatment effect for both doses was observed in both studies, with reductions in the ARR versus placebo that ranged from 37% to 60%. Despite these numerical differences, the 95% confidence intervals for the ARR rate ratio and percentage reductions largely overlap between the MRI and non-MRI cohort for dose groups, suggesting generally consistent treatment effects and lack of a qualitative difference.

Reviewer's comment: The data presented in this submission suggests that although some baseline differences exist in the MRI cohort and the non MRI cohort and some numerical differences were seen in the analysis of the ARR in these two groups, these differences are not sufficient to consider the MRI cohort non representative of the general population of MS patients studied in this trial.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor conducted a phase 2 dose finding trial to assess dose response of BG-12 on MRI and clinical endpoints. This trial included four treatment arms; placebo, BG-12 120 qd, BG-12 120 mg tid and BG-12 240 mg tid. The primary endpoint in this phase 2 dose finding trial was the total number of new Gd enhancing lesions over 4 scans at week 12-24 on MRI in MS patients on BG-12 compared to placebo. The efficacy analysis was performed on the ITT (n=256), as well as, the efficacy evaluable population (n=223). The data from this trial indicated that the comparison of the treatment effect on MRI endpoints between 120 mg tid vs. placebo and 240

mg tid vs. placebo were both nominally significant (p=0.036, p<0.001 respectively). These changes were associated with a 40% and 73% reduction in the total number of Gd enhancing lesions as compared to baseline, respectively. Although the ARR was measured in this trial, there was no nominally significant effect on this endpoint, nor was there an indication of a dose response. Therefore, this trial suggested that the optimal dose to take into the phase 3 program was somewhere between the two highest doses studied in this trial. The sponsor took the 240 mg tid dose and a lower dose, 240 mg bid, into their phase 3 trials.

In the phase 3 pivotal trials, both active doses studied showed comparable effects statistically and numerically as compared to placebo on the primary endpoint. For example in trial 301, the BG-12 bid vs. placebo comparison (HR 0.51) and the BG-12 tid comparison vs. placebo (HR 0.50) for the proportion of subjects relapsed at 2 years both had a p value for this comparison of <0.0001. For trial 302, The ARR for the BG-12 bid vs. placebo comparison (0.244) and the BG-12 tid comparison (0.198) both were associated with a p value of <0.0001.

Efficacy of the key secondary MRI endpoints in trials 301 and 302 were comparable for the two active dose groups compared to placebo; these analyses were associated with a p value <0.0001 for the pre-specified analyses of all the MRI endpoints. The treatment effect of BG-12 on disability progression, a key secondary endpoint in both trials, was comparable in trial 301 for both active doses vs. placebo comparisons and as described above demonstrated statistically significant differences of similar magnitude in trial 301. The treatment effect of BG-12 on disability progression was also comparable in trial 302 for both doses of BG-12 vs. placebo but in this trial neither dose was able to demonstrate a statistically significant treatment effect over placebo.

Based on this information, the sponsor concluded that comparable efficacy was shown with both active doses of BG-12, therefore based on safety considerations, the sponsor would attempt to take the BG-12 bid dose to market.

Reviewer's comment: Based on the efficacy and dose finding data presented in this submission, the BG-12 240 mg bid dose is the most appropriate dose to take to market.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The phase 2 dose finding trial C-1900, identified statistically significant improvements on Gd enhancing lesions at 12 weeks in the BG-12 tid group as compared to placebo and this finding was maintained at 24 weeks.

Trial 301
The Kaplan-Meier estimate of the proportion of subjects relapsed over the first year was 31% in the placebo group, compared with 16.7% in the BG-12 bid group and 17.8% in the tid group. The hazard ratios obtained from the model were 0.49 (95% CI, 0.36, 0.67; p <0.0001) for BG-12 bid vs. placebo and 0.54 (95% CI, 0.40, 0.73; p <0.0001) for BG-12 tid vs. placebo, representing reductions of 51% and 46%, respectively, over placebo.

The ARR over 1 year was reduced by 50% and 44% following treatment with BG-12 bid and tid, respectively, compared with placebo ($p < 0.0001$ and $p = 0.0002$, respectively). At 2 years the ARR was reduced by 53% and 48% in the BG-12 bid vs. placebo and BG-12 tid vs. placebo comparison, respectively. Thus, the reduction in the risk of relapse over 1 year was thus comparable to that observed over 2 years, demonstrating that BG-12 has a robust effect on relapse at 1 year and this effect was maintained over the 2-year study period.

BG-12 bid and tid reduced the number of new or newly enlarging T2 hyperintense lesions at 1 year by 84% and 75%, respectively ($p < 0.0001$ for both comparisons), compared with placebo. In addition, BG-12 bid and tid reduced the odds of having greater Gd-enhancing lesion activity at 1 year by 92% and 87%, respectively, compared with placebo ($p < 0.0001$ for both comparisons).

Trial 302

The annualized relapse rate at 1 year was evaluated as a tertiary endpoint. Treatment with BG-12 bid and BG-12 tid reduced the ARR at 1 year by 43.3% ($p=0.0002$) and 46% ($p < 0.0001$), respectively, over placebo. Significant reductions over placebo were sustained during the second year of the study, with reductions of 33.9% ($p=0.0468$) and 48.7% ($p=0.0032$) in the BG-12 bid and tid groups, respectively, between year 1 and year 2.

BG-12 bid and tid reduced the number of new or newly enlarging T2 hyperintense lesions at 1 year by 67% and 70%, respectively as compared to ($p<0.0001$ for both comparisons). BG-12 bid and tid treatment reduced the risk of having greater Gd enhancing lesion activity by 87.3% and 77.4%, respectively over placebo at 1 year ($p < 0.0001$ for both comparisons).

Reviewer's comment: Efficacy of BG-12 on the endpoint, the ARR, was demonstrated in both trials 301 and 302 at the end of one year and was maintained through the end of the second year. In addition measurement of key secondary MRI endpoints identified a treatment effect at 6 months that was maintained over the course of the 2 year trial.

6.1.10 Discussion of the Presence of Withdrawal Effects

The potential for withdrawal effects with BG-12 was assessed using relapse data. The majority of subjects who completed studies 301 and 302 enrolled in study 303 without interruption of study treatment. For subjects who completed studies 301 and 302 and chose not to enroll in study 303, there was a 1 month follow-up period post dose. The sponsor evaluated these patients to determine if the reduced ARR obtained during the study treatment period was maintained after withdrawal. For the purposes of this analysis, the sponsor performed this analysis on subjects either who prematurely discontinued study treatment and were followed for at least 1 day, and subjects who completed the 2 year study treatment period, and was off treatment for at least 1 day.

This analysis included 1044 subjects. Of these subjects 58%, 54%, and 55% of subjects had up to 1 month of follow-up data, and 42%, 46% and 45% had greater than 1 month follow-up data in the placebo, BG-12 bid, and BG-12 tid groups, respectively. The total number of subject-years

of follow-up in this analysis was approximately 52, 67, and 60 in the placebo, BG-12 bid, and BG-12 tid groups, respectively.

Based on the analysis, the adjusted ARR for subjects following the last dose was 0.178 (95% CI, 0.094, 0.338) in the placebo group, compared with 0.119 (95% CI, 0.061, 0.233) in the BG-12 bid group and 0.210 (95% CI, 0.118, 0.373) in the BG-12 tid group. As shown, the ARR post dose was similar and lower than at baseline across treatment groups.

Reviewer's comment: Limited data is available on the persistence of efficacy after withdrawal of study treatment, since this data provides information only up to 1 month post treatment. Similar results were seen in all 3 treatment groups for the ARR. It is reassuring to see that no obvious rebound occurs during this 1 month period in patients on active treatment vs. placebo, but measurement during a longer period of follow-up would provide more support that this persistence of efficacy is not a short term finding.

6.1.11 Additional Efficacy Issues/Analyses

Analysis of the primary endpoint by the presence of the adverse event of flushing
Due to the observation that a high percentage of subjects on active study treatment in the pivotal trials experienced flushing as an AE, this reviewer wanted to evaluate if the presence of this adverse event which had the potential of unblinding patients in the trials, may have introduced bias and inflated the treatment effect in this subset of patients. The Agency statistician conducted an efficacy analysis to compare the magnitude and direction of the treatment effect on the primary endpoint for patients that reported flushing as an AE vs. those that did not. As can be seen in Table 41 and Table 42 below, the treatment effect was preserved in both subgroups in both trials, although numerically both trials had a slightly greater effect size in the groups with flushing.

Table 41: Estimated proportion of relapsing patients based on the presence of the adverse event of flushing (trial 301)

	Placebo	BG-12 BID	BG-12 TID
With flushing	0.46	0.22	0.23
Without flushing	0.46	0.31	0.28

Trial 302 had similar findings concerning this subgroup analysis as trial 301 for the BG-12 bid vs. placebo comparisons although in the BG-12 tid groups there was no real numerical difference in the ARR between patients that did report a flushing adverse event vs. those that did not.

Table 42: Estimated ARR based on the presence of the adverse event of flushing (trial 302)

	Placebo	BG-12 BID	BG 12-TID
With flushing	0.46	0.12	0.22
Without flushing	0.46	0.25	0.20

Reviewer's comment: The treatment effect on the ARR was preserved in patients that may have had potential unblinding due to the adverse event of flushing, although there was a numerical difference in both trials favoring patients that reported flushing, most consistently seen in the BG-12 bid vs. placebo comparison.

Efficacy in patients with dose reduction/dose interruptions

In order to evaluate whether a short term (generally 1 month) dose reduction or dose interruption would affect efficacy in the pivotal trials, the Agency asked the sponsor to provide an analysis of the number and conditions under which patients implemented dose reductions or interruptions of BG-12. In addition the sponsor was asked to provide an analysis of the primary endpoint by patients with dose adjustments to evaluate whether this dose adjustment may have had an impact on the treatment effect.

The sponsor provided the following data for trial 301:

- The number (percentage) of patients in the ITT population with a dose reduction for at least 1 month was 11(3%) in placebo, 20 (5%) in BG-12 bid and 35 (8%) in BG-12 tid groups.
- Most subjects only had one instance of dose reduction for at least 1 month: 8 (73%) in placebo, 20 (100%) in BG-12 bid and 35 (100%) in BG-12 tid group. Of these subjects, most had a dose increase following this dose reduction: 10 (91%) in placebo, 18 (90%) in BG-12 bid and 32 (91%) in BG-12 tid group.
- The number (percentage) of patients in the ITT population with a dose interruption for at least 1 month was 5 (1%) in placebo, 6 (1%) in the BG-12 bid group and 6 (1%) in the BG-12 tid group.

The sponsor provided the following data for trial 302:

- The number (percentage) of patients in the ITT population with a dose reduction for at least 1 month was 7 (2%) in placebo, 16 (4%) in BG-12 bid and 17 (5%) in the BG-12 tid group.
- Most subjects had one instance of a dose reduction for 1 month: 7 (100%) in placebo, 14 (88%) in BG-12 bid group and 16 (94%) in BG-12 tid group. Of these subjects, most had a dose increase after a dose reduction for at least one month: 6 (86%) in placebo, 14 (88%) in BG-12 bid and 14 (82%) in the BG-12 tid group.
- In the ITT population, the number (percentage) of patients with a dose interruption for at least 1 month was 4 (1%) in placebo, 1 (<1%) in BG-12 bid and 3 (<1%) in the BG-12 tid group.

The blinded study drug accountability CRF pages captured the number of capsules that remained in the wallet on each day but did not capture the reason for dose reductions or dose interruptions. The sponsor acknowledges that this represents a limitation of the analyses of adverse events leading to dose reduction and states that they are not able to summarize the reasons for these dose modifications.

The sponsor provided the following analysis of the primary endpoint for trials 301 and 302 on patients that had at least a 1 month dose interruption or reduction in study drug by treatment group.

For trial 301, the subgroup of subjects with a dose interruption/reduction for at least one month was as follows: 7 patients in the placebo group, 16 patients in the BG-12 BID group and 17 patients in the BG-12 tid group were included. For the analysis for patients without a dose interruption/reduction for at least one month, 356 patients in the placebo group, 343 patients in the BG-12 bid group and 328 patients in the BG-12 tid group were included.

Table 43: Summary of proportion of subjects relapsed (INEC confirmed) at 2 years by dose reduction/interruption status (trial 301)

Trial 301						
	Dose reduction/ interruption			No dose reduction/ interruption		
	Placebo	BG BID	BG TID	Placebo	BG BID	BG TID
n	11	20	35	397	390	381
Hazard ratio (active/placebo)		0.85	1.62		0.51	0.46
95% CI		0.19,3.78	0.43, 6.06		0.39, 0.66	0.36, 0.61
% reduction (active/placebo)		14.6	-62.3		49.2	53.5
95% CI		-278, 80.7	-506, 56.5		34.4, 60.6	39.4, 64.4

For trial 302, the subgroup of subjects with a dose interruption/reduction for at least one month was as follows: 7 patients in the placebo group, 16 patients in the BG-12 bid group and 17 patients in the BG-12 tid group were included. For the analysis for patients without a dose interruption/reduction for at least one month, 356 patients in the placebo group, 343 patients in the BG-12 bid group and 328 patients in the BG-12 tid group were included.

Table 44: Summary of ARR (INCEC confirmed) at 2 years by dose reduction/interruption status (trial 302)

Trial 302						
	Dose reduction/ interruption			No dose reduction/ interruption		
	Placebo	BG BID	BG TID	Placebo	BG BID	BG TID
n	7	16	17	356	343	328
Total # relapses	5	5	6	207	119	100
Unadjusted ARR	0.409	0.192	0.217	0.377	0.266	0.199
Adjusted ARR	0.269	0.074	0.240	0.389	0.224	0.193
95% CI	0.109,0.664	0.021,0.267	0.110,0.522	0.318,0.477	0.177,0.283	0.150,0.248
% reduction (active/placebo)		72.5	10.9		42.6	50.4

95% CI		-9.8, 93.1	-134, 66.1		24.1, 56.6	33.5, 63.0

Reviewer's comment: The analyses in Table 43 and Table 44 above, of subjects that had dose interruptions/reductions, includes a very small number of patients with highly variable data, and therefore no conclusions can be made about the preservation of efficacy in these groups as compared to the group without a dose reduction/interruption. What is reassuring is that a small percentage of subjects in each trial required a dose reduction/interruption and of those a large percentage went on to continue study drug at their randomized dose. One may conclude from this information that the reduction/interruption of the study drug for this period of time, more commonly resulted in the resumption of the original dose rather than drug discontinuation.

Analysis of efficacy in patients with reduced lymphocytes
Information provided in the original NDA submission, suggested that approximately 30% of patients reported the adverse event of lymphopenia during the trial. This reviewer requested an additional analysis from the sponsor to determine if the magnitude of the treatment effect on the primary endpoint was shifted in the subgroup of patients with reduced lymphocytes vs. those without this adverse event. For this analysis, the sponsor defined lymphocyte reduction as a post baseline lymphocyte count below the lower limit of normal (LLN). Since there were only a small number of patients in the placebo group with reduction of lymphocytes in this range, the sponsor grouped the placebo patients from trial 301 and 302 and included them in the analyses.

For trial 301, the analysis was performed on the primary endpoint, the proportion of subjects with an INEC-confirmed relapse at 2 years. The analysis of the primary endpoint of patients that had post baseline lymphocyte counts < LLN included all 408 patients in the placebo group, 146 patients in the BG-12 bid group and 109 patients in the BG-12 tid group. The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 46.1% in the placebo group compared with 23.9% in the BG-12 bid group and 21.8% in the BG-12 tid group. The hazard ratios obtained from the model were 0.45 (95% CI, 0.31, 0.64) for BG-12 bid vs. placebo and 0.43 (95% CI, 0.28, 0.66) for BG-12 tid vs. placebo. The corresponding percentage reductions vs. placebo were 55.4% for BG-12 bid and 57.1% for BG-12 tid.

The analysis of the proportion of subjects relapsed at 2 years with no post-baseline lymphocyte count < LLN included all 408 patients in the placebo group, 264 patients in the BG-12 bid group and 307 patients in the BG-12 tid group. The Kaplan-Meier estimate of the proportion of subjects relapsed at 2 years was 46.1% in the placebo group compared with 28.9% in the BG-12 bid group and 27.9% in the BG-12 tid group. The hazard ratios obtained from the model were 0.55 (95% CI, 0.41, 0.74) for BG-12 bid vs. placebo and 0.53 (95% CI, 0.40, 0.70) for BG-12 tid vs. placebo. The corresponding percentage reductions vs. placebo were 44.7% for BG-12 bid and 47.1% for BG-12 tid.

Table 45: Summary of the proportion of subjects relapsed (INEC confirmed) at 2 years by the presence of minimum post baseline lymphocyte count <LLN (trial 301)

Trial 301						
	Lymphocytes <LLN			No report of lymphocytes< LLN		
	Placebo	BG BID	BG TID	Placebo	BG BID	BG TID
n	408	146	109	408	264	307
% relapsed	42	24	21	42	24	23
Hazard ratio (active/placebo)		0.45	0.43		0.55	0.53
95% CI		0.31,0.64	0.28,0.66		0.41, 0.74	0.40, 0.70
% reduction (active/placebo)		55.4	57.1		44.7	47.1
95% CI		35.7, 69	33.6, 72.3		26.0, 58.7	30.2, 59.9

For trial 302, the analysis was performed on the primary endpoint, the ARR at 2 years based on INEC-confirmed relapses. This analysis of patients with post baseline lymphocyte count < LLN included all 363 patients in the placebo group, 139 patients in the BG-12 bid group, and 108 patients in the BG-12 tid group. The adjusted ARR at 2 years was 0.379 in the placebo group compared with 0.199 in the BG-12 bid group and 0.181 in the BG-12 tid group. The rate ratios were 0.525 (95% CI, 0.365, 0.756) for the BG-12 bid - placebo comparison and 0.477 (95% CI, 0.313, 0.727) for the BG-12 tid - placebo comparison. The corresponding percentage reductions vs. placebo were 47.5% for BG-12 bid and 52.3% for BG-12 tid.
The analysis of the ARR in patients with no post-baseline lymphocyte count < LLN included all 363 patients in the placebo group, 220 patients in the BG 12 bid group, 237 patients in the BG-12 tid group. The adjusted ARR at 2 years was 0.398 in the placebo group compared with 0.238 in the BG-12 bid group and 0.207 in the BG-12 tid group. The rate ratios vs. placebo were 0.599 (95% CI, 0.429, 0.835) for BG-12 bid and 0.520 (95% CI, 0.372, 0.727) for BG-12 tid. The corresponding percentage reductions versus placebo were 40.1% for BG-12 bid and 48.1% for BG-12 tid.

Table 46: Summary of ARR (INEC confirmed) at 2 years by the presence of minimum post baseline lymphocyte count <LLN (trial 302)

Trial 302						
	Lymphocytes <LLN			No report of lymphocytes< LLN		
	Placebo	BG BID	BG TID	Placebo	BG BID	BG TID
n	363	139	108	363	220	237
Total # relapses	212	51	35	212	73	71
Unadjusted ARR	0.378	0.209	0.182	0.378	0.236	0.211
Adjusted ARR	0.379	0.199	0.181	0.398	0.238	0.207
95% CI		0.141,0.281	0.121,0.271	0.326,0.486	0.178,0.318	0.155,0.276

% reduction (active/placebo)		47.5	52.3		40.1	48.0
95% CI		24.4,63.5	27.3,68.7		16.5, 57.1	27.3, 62.6

Reviewer's comment: The treatment effect was preserved in both subgroups of patients with and without lymphocyte reductions on BG-12 below the LLN as compared to placebo, yet numerically the treatment effect was mildly greater in those subjects that did report the adverse event of lymphocyte reduction.

7 Review of Safety

Please see the Agency safety review for this NDA by Dr. Gerard Boehm.

8 Postmarket Experience

BG-12 is an investigational product that has not been approved or marketed in other countries; therefore, there is no postmarket information.

9. Appendices

9.1 Labeling Recommendations

Please refer to approved label.

9.2 Advisory Committee Meeting

Not applicable.

9.3 Pediatric Review Committee (PeRC) Meeting

A deferral for pediatric study initiation was requested by the sponsor until after the phase 3 adult data in this NDA are reviewed so that evidence for safety and efficacy can be accumulated prior to the initiation of pediatric studies. When pediatric studies are initiated, the sponsor plans to study the 240 mg bid dose based on the findings in the phase 3 trials. Their plan for pediatric studies is to conduct a bridging phase 3 trial to evaluate the safety, tolerability and the effect on disease course of BG-12 in subjects aged 10-17 years (b) (4) Patients under age 10 years will not be included in the deferral request because the sponsor plans to ask for a pediatric waiver in patients aged 0-9 years of age.

Please refer to section 1.4 of this review which describes the PMR that the Agency plans to request from the sponsor for pediatric studies. The final decision of PeRC concerning the specific pediatric trial the Agency will require of the sponsor is pending.

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/s/

HEATHER D FITTER
11/08/2012

WILLIAM H Dunn
03/25/2013