ORIGINAL ARTICLE

Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis

Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Or, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators*

ABSTRACT

BACKGROUND

BG-12 (dimethyl fumarate) was shown to have antiinflammatory and cytoprotective properties in preclinical experiments and to result in significant reductions in disease activity on magnetic resonance imaging (MRI) in a phase 2, placebo-controlled study involving patients with relapsing–remitting multiple sclerosis.

METHODS

We conducted a randomized, double-blind, placebo-controlled phase 3 study involving patients with relapsing–remitting multiple sclerosis. Patients were randomly assigned to receive oral BG-12 at a dose of 240 mg twice daily, BG-12 at a dose of 240 mg three times daily, or placebo. The primary end point was the proportion of patients who had a relapse by 2 years. Other end points included the annualized relapse rate, the time to confirmed progression of disability, and findings on MRI.

RESULTS

The estimated proportion of patients who had a relapse was significantly lower in the two BG-12 groups than in the placebo group (27% with BG-12 twice daily and 26% with BG-12 thrice daily vs. 46% with placebo, P<0.001 for both comparisons). The annualized relapse rate at 2 years was 0.17 in the twice-daily BG-12 group and 0.19 in the thrice-daily BG-12 group, as compared with 0.36 in the placebo group, representing relative reductions of 53% and 48% with the two BG-12 regimens, respectively (P<0.001 for the comparison of each BG-12 regimen with placebo). The estimated proportion of patients with confirmed progression of disability was 16% in the twice-daily BG-12 group, 18% in the thrice-daily BG-12 group, and 27% in the placebo group, with significant relative risk reductions of 38% with BG-12 twice daily (P=0.005) and 34% with BG-12 thrice daily (P=0.01). BG-12 also significantly reduced the number of gadolinium-enhancing lesions and of new or enlarging T_2-weighted hyperintense lesions (P<0.001 for the comparison of each BG-12 regimen with placebo). Adverse events associated with BG-12 included flushing and gastrointestinal events, such as diarrhea, nausea, and upper abdominal pain, as well as decreased lymphocyte counts and elevated liver aminotransferase levels.

CONCLUSIONS

In patients with relapsing–remitting multiple sclerosis, both BG-12 regimens, as compared with placebo, significantly reduced the proportion of patients who had a relapse, the annualized relapse rate, the rate of disability progression, and the number of lesions on MRI. (Funded by Biogen Idec; DEFINE ClinicalTrials.gov number, NCT00420212.)

From the Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany (R.G.); the Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland (L.K.); NeuroRx Research (D.L.A.) and Montreal Neurological Institute and Hospital, McGill University (D.L.A., A.B.-O.) — both in Montreal; Queen Mary University of London, Blizard Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, London (G.G.); Medical University of Lodz, Lodz, Poland (K.S.); Georgetown University Hospital, Washington, DC (C.T.); and Biogen Idec, Weston, MA (M.T.S., M.Y., S.I.S., K.T.D.). Address reprint requests to Dr. Gold at the Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Gudrunstr. 56, D-44791 Bochum, Germany, or at ralf.gold@ruhr-uni-bochum.de.

*The Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS (DEFINE) study investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was updated on November 21, 2012, at NEJM.org.

N Engl J Med 2012;367:1098-107.
DOI: 10.1056/NEJMoa1114287

Oral BG-12 (dimethyl fumarate) is being investigated for the treatment of multiple sclerosis. Inflammation and oxidative stress are central pathologic factors in multiple sclerosis.[1,2] Immune cell activation and infiltration into the central nervous system are thought to result in widespread cellular damage, potentially owing to the dysregulated production and release of reactive oxygen and nitrogen species, such as hydrogen peroxide and peroxynitrite, and proinflammatory stimuli.[3] This combination of toxic factors ultimately results in demyelination and neurodegeneration, causing disease activity and progression of disability.

BG-12 has been shown to have beneficial effects in preclinical models of neuroinflammation, neurodegeneration, and toxic oxidative stress, which appear to be mediated predominately through activation of the nuclear 1 factor (erythroid-derived 2)–like 2 (Nrf2) antioxidant response pathway, the primary cellular defense against the cytotoxic effects of oxidative stress.[1,4] BG-12 may also play a role in modulating immune-cell responses by shifting dendritic-cell differentiation,[5] suppressing proinflammatory-cytokine production, or directly inhibiting proinflammatory pathways.[6]

In a randomized, placebo-controlled, 24-week, phase 2 study involving patients with relapsing–remitting multiple sclerosis,[7] BG-12, as compared with placebo, significantly reduced the number of new gadolinium-enhancing lesions, new or enlarging hyperintense lesions on T_2-weighted images, and new hypointense lesions on T_1-weighted images. Here, we report the results of the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS (DEFINE) study, in which two dose regimens of BG-12 were compared with placebo.

METHODS

STUDY OVERSIGHT

We conducted a randomized, double-blind, placebo-controlled, 2-year phase 3 study of BG-12 in patients with relapsing–remitting multiple sclerosis. Members of the advisory committee and the data and safety monitoring committee (see the Study Oversight section in the Supplementary Appendix, available with the full text of this article at NEJM.org) collaborated with the sponsor, Biogen Idec, to develop the protocol and monitor the ongoing study.

Data were collected by the investigators and were analyzed by the sponsor. The investigators and sponsor agreed to maintain data confidentiality during the study. All the authors had early access to the data, participated in person in the data analysis and interpretation, and vouch for the accuracy and completeness of the data and the statistical analysis and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the first author and the senior author representing the sponsor, with support from medical writers from Infusion Communications, who were funded by the sponsor. All the authors participated in writing subsequent drafts of the manuscript and made the decision to submit it for publication. The protocol, including the statistical analysis plan, is available at NEJM.org; the study was conducted and reported as described in the protocol.

PATIENTS

Key eligibility criteria included an age of 18 to 55 years, a diagnosis of relapsing–remitting multiple sclerosis as defined according to the McDonald criteria,[8,9] a baseline score of 0 to 5.0 on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability),[10] and disease activity as evidenced by at least one clinically documented relapse within 12 months before randomization or a brain magnetic resonance imaging (MRI) scan, obtained within 6 weeks before randomization, that showed at least one gadolinium-enhancing lesion. Key exclusion criteria were progressive forms of multiple sclerosis,[9] another major disease that would preclude participation in a clinical trial, abnormal results on prespecified laboratory tests, or recent exposure to contraindicated medications (Table S1 in the Supplementary Appendix).

All patients were fully informed of approved therapies for multiple sclerosis as an alternative to participation in a placebo-controlled trial and provided written informed consent; we also obtained reconsent from patients after a confirmed relapse or progression of disability (after discussion of treatment options as detailed below). The study was approved by central and local ethics committees and was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[11] and the Declaration of Helsinki.[12]

STUDY DESIGN

Patients at 198 sites in 28 countries were randomly assigned, in a 1:1:1 ratio, to receive, in a double-blind fashion, BG-12 at a dose of 240 mg twice daily, BG-12 at a dose of 240 mg three times daily, or placebo (Fig. S1 in the Supplementary Appendix). Randomization was performed centrally and was stratified according to site.

To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial). The examining neurologists conducted neurologic assessments, including assessment of the EDSS score, whereas the treating neurologists were responsible for all aspects of patient care, including the treatment of relapses and other disease symptoms. To ensure that the study-group assignments would not be revealed, patients were instructed to take the assigned study drug at least 4 hours before study visits, in case patients in the BG-12 groups had a side effect of flushing.

All patients were eligible to switch to an alternative therapy for multiple sclerosis if they had completed 48 weeks of the study treatment and had had one or more confirmed relapses after 24 weeks; patients could switch at any time if they had confirmed progression of disability.

STUDY PROCEDURES AND END POINTS

Study visits were scheduled every 4 weeks for safety assessments, including the monitoring of laboratory values; for dispensing of the study drug; and for assessment of adherence to the study drug. During clinic visits every 12 weeks, standardized neurologic assessments, including assessment of the EDSS score, were performed by physicians who were certified either by in-person training or through an online program (www.Neurostatus.net). MRI scans were obtained at screening and at weeks 24, 48, and 96 in a subgroup of patients at sites with full MRI capabilities. All scans were evaluated in a blinded manner at a central reading facility (NeuroRx Research). Unscheduled visits were conducted as needed to evaluate suspected relapses.

The primary end point was the proportion of patients who had a relapse by 2 years. Protocol-defined relapses were new or recurrent neurologic symptoms, not associated with fever or infection, that lasted for at least 24 hours and that were accompanied by new objective neurologic findings according to the examining neurologist's evaluation. All protocol-defined relapses were evaluated by an independent neurologic evaluation committee (see the Study Oversight section in the Supplementary Appendix), whose members reviewed a standardized set of blinded clinical records (which did not include MRI data) from the treating and examining neurologists.

Secondary end points at 2 years included the number of gadolinium-enhancing lesions and of new or enlarging hyperintense lesions on T_2-weighted images, the annualized relapse rate (the total number of relapses divided by the number of patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications), and the time to progression of disability. Disability progression was defined as at least a 1.0-point increase on the EDSS in patients with a baseline score of 1.0 or higher or at least a 1.5-point increase in patients with a baseline score of 0, with the increased score sustained for at least 12 weeks.

STATISTICAL ANALYSIS

All efficacy analyses were performed on data from the intention-to-treat population, which included all patients who underwent randomization and who received at least one dose of the study drug. All statistical tests were two-sided, with an overall type I error rate of 0.05. Sensitivity analyses were performed on the primary end point.

On the basis of data from another clinical trial in which an active drug was compared with placebo in patients with multiple sclerosis,[13] we estimated that 48.0% of patients receiving placebo and 33.6% of patients receiving BG-12 would have at least one relapse during the study. Using a chi-square test with a two-sided alpha level of 0.05, and assuming an estimated dropout rate of 23%, we estimated that we would need to enroll 337 patients in each group for the study to have 90% power to detect the 30% reduction in the percentage of patients with a relapse in each BG-12 group as compared with the placebo group. The primary end point was analyzed with the use of a Cox proportional-hazards model, adjusted for baseline EDSS score, age, region, and number of relapses in the year before study entry. The estimated proportion of patients with a relapse was derived with the use of the Kaplan–Meier product-limit method, which was based on the time-to-first-relapse survival distribution.

For secondary end points, the analyses were conducted in the following ranked order: an analysis of the number of new or newly enlarging hyperintense lesions on T_2-weighted images, with the use of a negative binomial model; an analysis of the number of gadolinium-enhancing lesions, with the use of an ordinal logistic-regression model; an analysis of the annualized relapse rate, with the use of a negative binomial regression model; and an analysis of the time to progression of disability that was sustained for 12 weeks, with the use of a Cox proportional-hazards model. The analytic models included adjustments for region and baseline characteristics, including EDSS score, age, relapse rate, and number or volume of baseline lesions, as appropriate.

A sequential (closed) testing procedure was used to control the overall type I error rate due to multiple comparisons. Formal testing of the comparison of twice-daily BG-12 with placebo was undertaken only if the comparison of thrice-daily BG-12 with placebo was significant ($P \leq 0.05$). Analysis of secondary end points, according to the ranked order, followed an additional sequential testing procedure such that if statistical significance was not achieved for an end point, all lower-ranking end points were also considered to be nonsignificant.

Among patients who switched to an alternative therapy for multiple sclerosis, all the data before the switch were used for the analysis of the clinical end points. For the analyses of MRI end points in these patients, the data before the switch were used and then data after the rescue therapy was initiated were imputed with the use of a constant rate assumption.

Safety analyses were summarized with the use of descriptive statistics for all patients who received at least one dose of the study drug. Among patients who switched to alternative medications, data collected after the switch were excluded from the safety analyses.

RESULTS

PATIENTS

A total of 1237 patients underwent randomization, of whom 1234 received at least one dose of the study drug (intention-to-treat population). The baseline demographic and disease characteristics were generally well balanced across the study groups (Table 1). Patients were 18 to 56 years of age and had received a diagnosis of multiple sclerosis between 0 and 32 years before study entry. Approximately 40% of the patients had previously received approved therapies for relapsing–remitting multiple sclerosis (Table 1). A total of 540 patients were included in the subgroup of patients who underwent MRI. The baseline demographic and disease characteristics of patients in the MRI cohort were similar to those of patients who were not in the MRI cohort and to those of the overall study population (Table S2 in the Supplementary Appendix).

A total of 952 patients (77%) completed the study (78% in the placebo group and 77% in each of the BG-12 groups) (Fig. S2 in the Supplementary Appendix). The rate of discontinuation of the study drug was similar in the three groups (35% in the placebo group and 31% in each of the BG-12 groups), as was the rate of withdrawal from the study (22% in the placebo group and 23% in each of the BG-12 groups) (Table S3 and Fig. S2 in the Supplementary Appendix). The percentage of patients who switched to an approved therapy for multiple sclerosis was low (13% in the placebo group, 6% in the twice-daily BG-12 group, and 5% in the thrice-daily BG-12 group). The mean duration of participation in the study was 83.9 weeks and was similar among the three groups.

EFFICACY

Relapses

The proportion of patients who had at least one relapse of multiple sclerosis by 2 years was significantly reduced with each BG-12 regimen as compared with placebo. On the basis of Kaplan–Meier estimates, 27% of the patients in the twice-daily BG-12 group and 26% in the thrice-daily BG-12 group, as compared with 46% in the placebo group, had a relapse at 2 years ($P<0.001$ for both comparisons) (Table 2 and Fig. 1A). The hazard ratio for the risk of relapse with BG-12 treatment as compared with placebo during the 2-year period was 0.51 for the twice-daily group (95% confidence interval [CI], 0.40 to 0.66) and 0.50 for the thrice-daily group (95% CI, 0.39 to 0.65) ($P<0.001$ for both comparisons), corresponding to a 49% and 50% reduction, respectively, in the risk of relapse. Each BG-12 regimen, as compared with placebo, prolonged the time to a first relapse (time to relapse in the 25th percentile of patients, 38 weeks in the placebo group, as compared with 87 weeks and 91 weeks in the twice-daily and thrice-daily BG-12 groups, respective-

Table 1. Baseline Characteristics of the Intention-to-Treat Population.*

Characteristic	Placebo (N=408)	Twice-Daily BG-12 (N=410)	Thrice-Daily BG-12 (N=416)
Age — yr	38.5±9.1	38.1±9.1	38.8±8.8
Female sex — no. (%)	306 (75)	296 (72)	306 (74)
Weight — kg	71.1±17.0	70.7±18.5	71.3±16.9
Race — no. (%)†			
White	318 (78)	321 (78)	330 (79)
Asian	42 (10)	38 (9)	36 (9)
Black	8 (2)	8 (2)	10 (2)
Other or unknown	40 (10)	43 (10)	40 (10)
Previous use of approved medication for multiple sclerosis — no. (%)‡	172 (42)	162 (40)	168 (40)
Time since diagnosis — yr	5.8±5.8	5.6±5.4	5.1±5.3
Relapses in previous 12 mo — no.	1.3±0.7	1.3±0.7	1.3±0.6
EDSS score at baseline — no. (%)§			
0	21 (5)	29 (7)	24 (6)
1.0 or 1.5	105 (26)	109 (27)	104 (25)
2.0 or 2.5	112 (27)	116 (28)	146 (35)
3.0 or 3.5	97 (24)	82 (20)	85 (20)
4.0 or 4.5	56 (14)	56 (14)	42 (10)
5.0	16 (4)	16 (4)	14 (3)
Mean score on EDSS	2.48±1.24	2.40±1.29	2.36±1.19
MRI findings¶			
Gadolinium-enhancing T_1-weighted lesions — no.	1.6±3.4	1.2±3.3	1.2±4.1
Hyperintense T_2-weighted lesions			
Mean no.	49.2±38.6	47.6±34.7	55.8±44.3
<9 — no. of patients	12	9	14
≥9 — no. of patients	168	167	170

* Plus–minus values are means ±SD. The intention-to-treat population included all patients who underwent randomization and received at least one dose of the study drug. All the baseline characteristics were well balanced among the study groups (nominal P>0.05).
† Race was self-reported.
‡ Approved medications for multiple sclerosis include interferon beta-1a (used in 27% of all randomly assigned patients), glatiramer acetate (15%), interferon beta-1b (14%), and natalizumab (3%). Patients may have received more than one prior medication for multiple sclerosis. Patients may also have received other, nonapproved therapies for multiple sclerosis. (The percentage of patients receiving any medication for multiple sclerosis before study entry was 54 to 56% across treatment groups.)
§ Scores on the Expanded Disability Status Scale (EDSS) range from 0 to 10, with higher scores indicating a greater degree of disability. The baseline score was higher than 5.0 in one patient in each group, and the score was unknown for one patient in the twice-daily BG-12 group.
¶ Magnetic resonance imaging (MRI) was performed in 180 patients in the placebo group, 176 in the twice-daily BG-12 group, and 184 in the thrice-daily BG-12 group.

ly). Sensitivity analyses, performed with the use of logistic regression, in which patients who discontinued the study drug or withdrew from the study without having had a relapse were considered to have had a relapse if the reason for discontinuation or withdrawal was suggestive of a lack of efficacy, showed that BG-12 treatment also reduced the proportion of patients who had a relapse by 2 years (odds ratio for relapse, 0.42 with twice-daily BG-12 and 0.41 with thrice-daily BG-12; P<0.001 for both comparisons). An additional sensitivity analysis that included all proto-

Table 2. Clinical and MRI End Points during the 96-Week Study.*

End Point	Placebo (N=408)	Twice-Daily BG-12 (N=410)	Thrice-Daily BG-12 (N=416)
Patients with relapse at 2 yr — %†	46	27	26
Hazard ratio vs. placebo (95% CI)	—	0.51 (0.40–0.66)‡	0.50 (0.39–0.65)‡
Odds ratio vs. placebo (95% CI)§	—	0.42 (0.31–0.57)‡	0.41 (0.30–0.56)‡
Time to first relapse, 25th percentile — wk¶	38	87	91
Annualized relapse rate at 2 yr			
Adjusted relapse rate (95% CI)‖	0.36 (0.30–0.44)	0.17 (0.14–0.21)	0.19 (0.15–0.23)
Rate ratio vs. placebo (95% CI)	—	0.47 (0.37–0.61)‡	0.52 (0.40–0.67)‡
Confirmed progression of disability at 2 yr			
Patients with progression sustained for 12 wk — %†	27	16**	18
Hazard ratio vs. placebo (95% CI)		0.62 (0.44–0.87)††	0.66 (0.48–0.92)‡‡
MRI assessments			
New or newly enlarging T_2-weighted lesions at 2 yr as compared with baseline			
Adjusted mean no. of lesions (95% CI)	17.0 (12.9–22.4)	2.6 (2.0–3.5)	4.4 (3.2–5.9)
Ratio of adjusted mean no. of lesions in treatment group to adjusted mean no. in placebo group (95% CI)		0.15 (0.10–0.23)‡	0.26 (0.17–0.38)‡
Gadolinium-enhancing T_1-weighted lesions at 2 yr			
Mean no.	1.8±4.2	0.1±0.6	0.5±1.7
Odds ratio vs. placebo (95% CI)	—	0.10 (0.05–0.22)‡	0.27 (0.15–0.46)‡

* Plus–minus values are means ±SD. Clinical results are derived from the 1234 patients in the intention-to-treat population; MRI results are derived from the 469 patients in the MRI cohort with postbaseline data (165 in the placebo group, 152 in the twice-daily BG-12 group, and 152 in the thrice-daily BG-12 group). CI denotes confidence interval.
† The proportion of patients was estimated by Kaplan–Meier analysis.
‡ P<0.001.
§ In this sensitivity analysis based on logistic regression, patients who discontinued the study drug or withdrew from the study without having had a confirmed relapse as assessed by the independent neurologic evaluation committee were considered to have had a relapse if the reason for discontinuation or withdrawal was suggestive of relapse or lack of efficacy; otherwise, they were considered not to have had a relapse.
¶ The 25th percentile of time to first relapse was the time at which the estimated proportion of patients who had a relapse was at least 25%.
‖ The annualized relapse rate included only relapses that were confirmed by the independent neurologic evaluation committee.
** Data were available for 409 patients in this group.
†† P=0.005.
‡‡ P=0.01.

col-defined relapses, regardless of whether they were confirmed by the independent neurologic evaluation committee, showed results that were consistent with those of the primary analysis (Fig. S3 in the Supplementary Appendix).

The annualized relapse rate at 2 years was 0.17 in the twice-daily BG-12 group and 0.19 in the thrice-daily BG-12 group, as compared with 0.36 in the placebo group, representing relative reductions with BG-12 of 53% and 48%, respectively (P<0.001 for both comparisons) (Fig. S4 in the Supplementary Appendix).

Disability

As compared with placebo, BG-12 reduced the risk of confirmed progression of disability that was sustained for 12 weeks by 38% over the 2-year study period in the twice-daily BG-12 group (hazard ratio, 0.62; 95% CI, 0.44 to 0.87; P=0.005) and by 34% in the thrice-daily BG-12 group (hazard ratio, 0.66; 95% CI, 0.48 to 0.92; P=0.01), (Table 2 and Fig. 1B). The estimated proportion of patients with progression of disability was 27% with placebo, 16% with twice-daily BG-12, and 18% with thrice-daily BG-12.

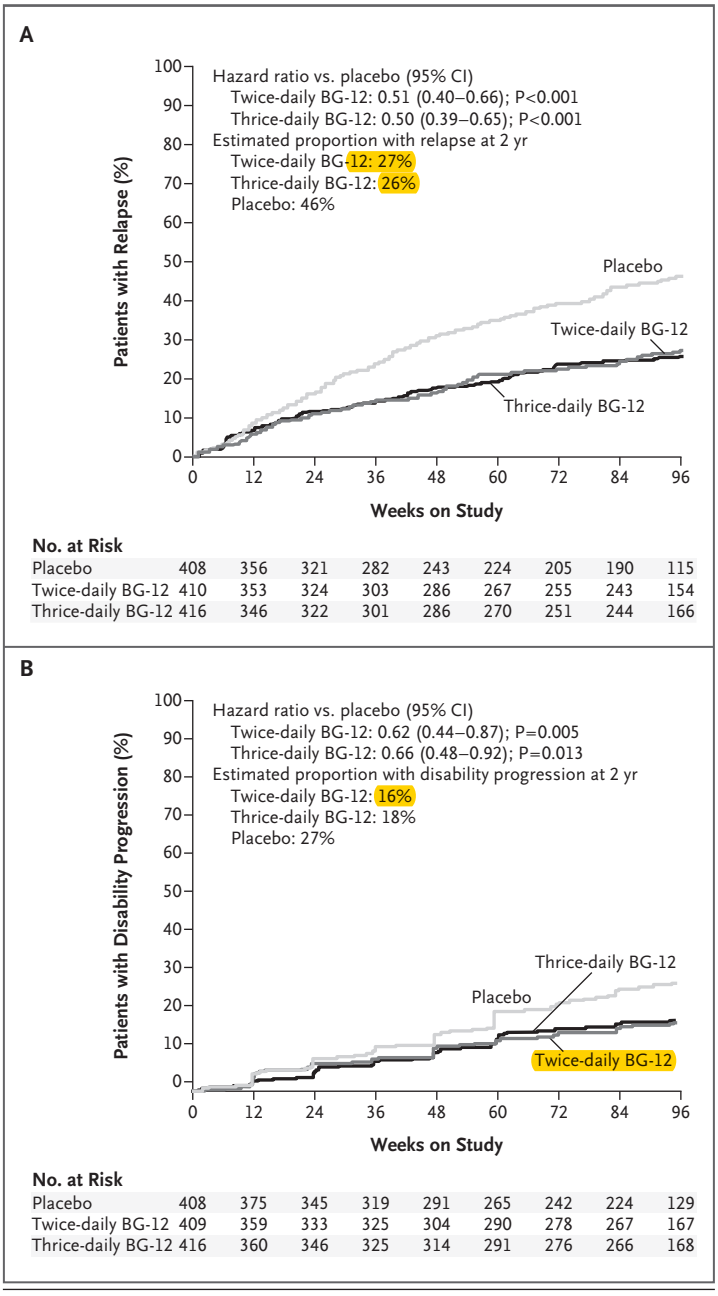

Figure 1. Kaplan–Meier Plot of Primary and Secondary Clinical Outcomes.

Panel A shows the time to the first relapse that was confirmed by the independent neurologic evaluation committee and the proportion of patients with a confirmed relapse among patients in the group that received BG-12 twice daily, the group that received BG-12 thrice daily, and the placebo group. The P values and hazard ratios for a relapse with BG-12 as compared with placebo were calculated with the use of a Cox proportional-hazards model, adjusted for baseline score (≤2.0 vs. >2.0) on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability), age at baseline (<40 years vs. ≥40 years), region, and the number of relapses in the year before study entry. The estimated proportion of patients with a relapse at 2 years is a Kaplan–Meier estimate. Panel B shows the time to confirmed progression of disability in each of the three groups. The P values and hazard ratios for progression with BG-12 as compared with placebo were calculated with the use of a Cox proportional-hazards model, adjusted for baseline score on the EDSS, age at baseline, and region. The estimated proportion of patients with confirmed progression of disease at 2 years is a Kaplan–Meier estimate.

MRI End Points

As compared with placebo, BG-12 reduced the number of new or enlarging hyperintense lesions on T_2-weighted images at 2 years by 85% with the twice-daily regimen and by 74% with the thrice-daily regimen (P<0.001 for both comparisons) and reduced the odds of an increase in the number of gadolinium-enhancing lesions at 2 years by 90% and 73%, respectively (P<0.001 for both comparisons) (Table 2). Larger percentages of patients in the BG-12 groups than in the placebo group were free from gadolinium-enhancing lesions on MRI at 2 years (93% in the twice-daily BG-12 group and 86% in the thrice-daily BG-12 group vs. 62% in the placebo group) (Table S4 in the Supplementary Appendix).

SAFETY

Adverse Events

The overall incidence of adverse events was similar across the three groups (95 to 96%) (Table 3); in the case of most of the patients, the adverse events were of mild or moderate severity. Adverse events that occurred more frequently in patients receiving BG-12 than in patients receiving placebo included flushing, gastrointestinal events (e.g., diarrhea, nausea, upper abdominal pain, abdominal pain, and vomiting), proteinuria, and pruritus (Table 3). The incidences of flushing and gastrointestinal events were highest in the first month of the study and decreased thereafter (Fig. S5 in the Supplementary Appendix). Overall, the incidence of adverse events leading to discontinuation of the study drug was similar across the groups (13% in the placebo group and 16% in each of the BG-12 groups), although discontinuations due to flushing and overall gastrointestinal events occurred more frequently in patients who received BG-12 than in patients who received placebo (discontinuation due to flushing, 2% in the twice-daily BG-12 group and 1% in the thrice-

Table 3. Adverse and Serious Adverse Events.*

Adverse Event	Placebo (N=408)	Twice-Daily BG-12 (N=410)	Thrice-Daily BG-12 (N=416)
	number of patients (percent)		
Any adverse event	387 (95)	395 (96)	396 (95)
Most frequently reported adverse events†			
Flushing	20 (5)	154 (38)	132 (32)
Multiple sclerosis relapse	189 (46)	111 (27)	114 (27)
Diarrhea	55 (13)	62 (15)	78 (19)
Nausea	38 (9)	53 (13)	54 (13)
Upper abdominal pain	28 (7)	40 (10)	52 (12)
Proteinuria	34 (8)	38 (9)	50 (12)
Abdominal pain	22 (5)	46 (11)	37 (9)
Pruritus	19 (5)	42 (10)	34 (8)
Vomiting	24 (6)	40 (10)	30 (7)
Adverse events leading to discontinuation	55 (13)	65 (16)	68 (16)
Death‡	0	1 (<1)	1 (<1)
Any serious adverse event	86 (21)	74 (18)	65 (16)
Most frequently reported serious adverse events§			
Multiple sclerosis relapse	60 (15)	39 (10)	32 (8)
Gastroenteritis	0	4 (<1)	1 (<1)
Gastritis	0	0	3 (<1)
Ovarian cyst	1 (<1)	1 (<1)	2 (<1)
Headache	0	0	2 (<1)
Pneumonia	1 (<1)	2 (<1)	0
Serious infection	7 (2)	10 (2)	8 (2)
Malignant neoplasm	2 (<1)	2 (<1)	2 (<1)

* Adverse and serious adverse events were assessed in the safety population, which in this study was identical to the intention-to-treat population. Additional details regarding serious infections and malignant neoplasms are provided in Table S7 and Table S8, respectively, in the Supplementary Appendix.

† With the exception of a multiple sclerosis relapse, the listed adverse events are those that were reported in 10% or more (rounded up to nearest integer) of patients, with an incidence that was at least 3% higher in either BG-12 group than in the placebo group.

‡ A patient in the twice-daily BG-12 group died in a bicycle accident 3 weeks after withdrawing from the study. A patient in the thrice-daily group died in a motor vehicle accident during the study period.

§ Included are serious adverse events reported in two or more patients treated with BG-12. Further details are provided in Table S6 in the Supplementary Appendix.

daily BG-12 group vs. <1% in the placebo group; and discontinuation due to overall gastrointestinal events, 5% and 6% in the two BG-12 groups, respectively, vs. 1% in the placebo group) (Table S5 in the Supplementary Appendix).

The incidence of serious adverse events was similar across the study groups, with relapse of multiple sclerosis the most frequently reported event (Table 3, and Table S6 in the Supplementary Appendix). Gastroenteritis and gastritis (both of which occurred in <1% of the patients) were the only other serious adverse events reported in more than two patients in either BG-12 group. There were two deaths, both of which were the result of road accidents.

The incidence of infections was similar across the study groups (65% in the placebo group, 64% in the twice-daily BG-12 group, and 68% in the thrice-daily BG-12 group). The most common infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and influenza. The incidence of serious infections was 2% in all the groups (Table 3, and Table S7 in the Supplementary Appendix). No opportunis-

tic infections were observed in the BG-12 groups, and no serious infections were reported in patients with lymphocyte counts of less than 0.5×10^9 per liter. The overall incidence of malignant neoplasms was less than 1% in all the groups (Table 3, and Table S8 in the Supplementary Appendix).

Overall, the incidence of renal adverse events was balanced across the study groups (21% in the placebo group, 22% in the twice-daily BG-12 group, and 25% in the thrice-daily BG-12 group). Proteinuria was the most commonly reported renal event among patients receiving BG-12, with an incidence of 9% in the twice-daily BG-12 group and 12% in the thrice-daily BG-12 group (as compared with 8% in the placebo group) (Table 3); most events were mild and reversible and did not result in discontinuation of treatment. There were no cases of renal failure classified by the investigator as serious adverse events.

Laboratory Assessments and Other Monitoring

In the BG-12 groups, as compared with the placebo group, the mean white-cell count and lymphocyte count decreased over the first year and then plateaued, with mean values remaining within normal limits (Fig. S6 in the Supplementary Appendix); at 1 year, white-cell and lymphocyte counts had decreased from baseline values by approximately 10% and 28%, respectively. White-cell counts of less than 3.0×10^9 per liter or lymphocyte counts of less than 0.5×10^9 per liter (corresponding to National Cancer Institute Common Toxicity Criteria grade 2 or higher leukopenia and grade 3 or higher lymphopenia, respectively) were seen in 4% of the patients in the BG-12 groups as compared with 1% or less of the patients in the placebo group.

We observed an increased incidence of elevations in liver aminotransferase levels, primarily between months 1 and 6. Alanine aminotransferase levels that were three or more times the upper limit of the normal range were seen in 3% of the patients in the placebo group and in 6% of the patients in each BG-12 group, with the difference driven mainly by differences at week 4. No such elevations of aminotransferase levels were concurrent with increases in bilirubin that were more than two times the upper limit of the normal range. There were no reports of hepatic failure. Evaluation of serial electrocardiograms showed no clinically relevant changes in the corrected QT interval or any other electrocardiographic variable.

DISCUSSION

Results from the DEFINE study showed that in patients with relapsing–remitting multiple sclerosis, BG-12, as compared with placebo, significantly reduced the proportion of patients who had a relapse by 2 years, the annualized rate of relapse, and the cumulative progression of disability. The effects of BG-12 were apparent at 12 weeks and were sustained for the duration of the study. A sensitivity analysis of all protocol-defined relapses, rather than only relapses confirmed by an independent neurologic evaluation committee, showed results that were consistent with those of the main analysis. BG-12 also significantly reduced disease activity as assessed by means of MRI findings.

The adverse events that occurred most frequently in patients who received BG-12 were flushing and gastrointestinal events, with the highest incidence of these events in the first month. The incidences of infections and serious infections were similar across all groups. There were decreases in lymphocyte counts and elevations in liver aminotransferase levels in the patients who received BG-12.

These efficacy results are consistent with those of the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) trial, reported in this issue of the *Journal*.[14] The CONFIRM trial was a placebo-controlled, phase 3 study in which twice-daily BG-12 and thrice-daily BG-12 reduced the annualized relapse rate by 44% and 51%, respectively, as compared with placebo, and reduced the estimated proportion of patients with a relapse from 41% with placebo to 29% and 24% with the two doses of BG-12, respectively. Similarly, in the CONFIRM trial, there were fewer multiple sclerosis lesions on MRI scans in patients who received BG-12 than in those who received placebo. In addition, the safety profile of BG-12 in the DEFINE study was similar to that observed in the CONFIRM study.

Interferon beta and glatiramer acetate, which were the initial disease-modifying therapies approved for the treatment of multiple sclerosis and are commonly used as first-line therapies in patients with a relapsing–remitting course, reduce the rate of clinical relapses by approxi-

mately 30%.[15-19] Other treatments associated with greater reductions in clinical relapses (50% to 68%) were subsequently approved.[13,20,21] However, none of these agents provide a cure for multiple sclerosis, and the improved efficacy of these newer agents needs to be weighed against the increased safety concerns associated with them. Because our trial was not a head-to-head study comparing BG-12 with an approved multiple sclerosis therapy, a comparison of the efficacy and safety of BG-12 with those of other therapies is not within the scope of this article.

The observed reductions in the number of brain MRI lesions, the rate of relapse, and the rate of disability progression with BG-12 are consistent with its beneficial effects on the inflammatory damage associated with multiple sclerosis. These data are also consistent with results from preclinical studies, in which BG-12 has been shown to have beneficial effects in animal models through direct neuroprotective and immunomodulatory mechanisms.[1,5] It is difficult to determine whether the therapeutic effect of BG-12 stems predominantly from immunomodulatory mechanisms or from neuroprotective mechanisms.

There remains a considerable unmet need for safe treatment options that are more effective than current first-line agents and are appropriate for a wide spectrum of patients with multiple sclerosis. Further exploration of the mechanism of action of BG-12 may help to guide future clinical studies.

Presented in part at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis (ECTRIMS and ACTRIMS), Amsterdam, October 19–22, 2011.

Supported by Biogen Idec.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in the study; the study-site personnel; the members of the data and safety monitoring committee; the members of the independent neurologic evaluation committee; the staff of NeuroRx Research (Montreal); and Simon Whiteley, Ph.D., and Joshua Safran (Infusion Communications) for assistance with the preparation of an earlier version of the manuscript.

REFERENCES

1. Linker RA, Lee DH, Ryan S, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain 2011;134:678-92.
2. Gilgun-Sherki Y, Melamed E, Offen D. The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. J Neurol 2004;251:261-8.
3. Johnson DA, Amirahmadi S, Ward C, Fabry Z, Johnson JA. The absence of the pro-antioxidant transcription factor Nrf2 exacerbated experimental autoimmune encephalomyelitis. Toxicol Sci 2010;114:237-46.
4. Scannevin RH, Chollate S, Jung MY, et al. Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the Nrf2 pathway. J Pharmacol Exp Ther 2012;341:274-84.
5. Ghoreschi K, Bruck J, Kellerer C, et al. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med 2011;208:2291-303.
6. Loewe R, Holnthoner W, Groger M, et al. Dimethylfumarate inhibits TNF-induced nuclear entry of NF-kappa B/p65 in human endothelial cells. J Immunol 2002;168:4781-7.
7. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008;372:1463-72. [Erratum, Lancet 2009;373:1340.]
8. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005;58:840-6.
9. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996;46:907-11.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-52.
11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH harmonized tripartite guideline — guideline for good clinical practice: E6(R1). Geneva: ICH, June 10, 1996 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf).
12. Declaration of Helsinki — ethical principles for medical research involving human subjects. Ferney-Voltaire, France: World Medical Association (http://www.wma.net/en/30publications/10policies/b3/index.html).
13. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;354:899-910.
14. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367:1087-97.
15. Biogen Idec announces positive top-line results from second phase 3 trial investigating oral BG-12 (dimethyl fumarate) in multiple sclerosis. Press release of Biogen Idec, Weston, MA, October 26, 2011 (http://www.biogenidec.com/PRESS_RELEASE_DETAILS.aspx?ID=5981&ReqId=1621631).
16. PRISMS Study Group. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001;56:1628-36. [Erratum, Neurology 2001;57:1146.]
17. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285-94. [Erratum, Ann Neurol 1996;40:480.]
18. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology 1995;45:1268-76.
19. Vollmer TL, Soelberg Sørensen P, Arnold DL, et al. A placebo-controlled and active comparator phase III trial (BRAVO) for relapsing-remitting multiple sclerosis. Mult Scler 2011;17:Suppl:S507. abstract.
20. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010;362:402-15.
21. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010;362:387-401.