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Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

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ABSTRACT

BACKGROUND

BG-12 (dimethyl fumarate) is in development as an oral treatment for relapsing–remitting multiple sclerosis, which is commonly treated with parenteral agents (interferon or glatiramer acetate).

METHODS

In this phase 3, randomized study, we investigated the efficacy and safety of oral BG-12, at a dose of 240 mg two or three times daily, as compared with placebo in patients with relapsing–remitting multiple sclerosis. An active agent, glatiramer acetate, was also included as a reference comparator. The primary end point was the annualized relapse rate over a period of 2 years. The study was not designed to test the superiority or noninferiority of BG-12 versus glatiramer acetate.

RESULTS

At 2 years, the annualized relapse rate was significantly lower with twice-daily BG-12 (0.22), thrice-daily BG-12 (0.20), and glatiramer acetate (0.29) than with placebo (0.40) (relative reductions: twice-daily BG-12, 44%, P<0.001; thrice-daily BG-12, 51%, P<0.001; glatiramer acetate, 29%, P=0.01). Reductions in disability progression with twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate versus placebo (21%, 24%, and 7%, respectively) were not significant. As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the numbers of new or enlarging T_2-weighted hyperintense lesions (all P<0.001) and new T_1-weighted hypointense lesions (P<0.001, P<0.001, and P=0.002, respectively). In post hoc comparisons of BG-12 versus glatiramer acetate, differences were not significant except for the annualized relapse rate (thrice-daily BG-12), new or enlarging T_2-weighted hyperintense lesions (both BG-12 doses), and new T_1-weighted hypointense lesions (thrice-daily BG-12) (nominal P<0.05 for each comparison). Adverse events occurring at a higher incidence with an active treatment than with placebo included flushing and gastrointestinal events (with BG-12) and injection-related events (with glatiramer acetate). There were no malignant neoplasms or opportunistic infections reported with BG-12. Lymphocyte counts decreased with BG-12.

CONCLUSIONS

In patients with relapsing–remitting multiple sclerosis, BG-12 (at both doses) and glatiramer acetate significantly reduced relapse rates and improved neuroradiologic outcomes relative to placebo. (Funded by Biogen Idec; CONFIRM ClinicalTrials.gov number, NCT00451451.)

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Multiple sclerosis is a chronic demyelinating and neurodegenerative disease of the central nervous system, which is commonly treated with parenteral agents (interferon beta and glatiramer acetate). Oxidative stress and proinflammatory stimuli are important pathologic factors in multiple sclerosis.[1-3] Experimental data suggest that BG-12, an oral formulation of dimethyl fumarate, has antiinflammatory and cytoprotective properties that are mediated through activation of the nuclear factor (erythroid-derived 2)–like 2 transcriptional pathway, among others.[3-6]

Here, we report the results of the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) trial, a randomized, multicenter, double-blind, 2-year study evaluating the efficacy and safety of BG-12, at a dose of 240 mg two or three times per day, versus placebo in patients with relapsing–remitting multiple sclerosis. A rater-blinded, active agent approved for relapsing–remitting multiple sclerosis (subcutaneous glatiramer acetate at a dose of 20 mg per day) was also included as a reference comparator, to allow a relative benefit–risk assessment of BG-12 through comparison of the active-treatment groups with the placebo group.

Methods

Study Oversight

The study was approved by central and local ethics committees and conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[7] and the Declaration of Helsinki.[8] An advisory committee participated in study design and oversight of study conduct, a data and safety monitoring committee reviewed all pertinent benefit–risk data, and an independent neurologic evaluation committee, whose members were unaware of the study-group assignments, provided confirmation of relapses of multiple sclerosis (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Data were gathered by the investigators and were analyzed by the sponsor (Biogen Idec), and data remained confidential during the study. All the authors were involved in all stages of manuscript development and vouch for the completeness and accuracy of the data. The first draft was cowritten by the first and last authors (the latter is a representative of the sponsor), with assistance from a medical-communications agency paid by the sponsor. The study was conducted in accordance with the study protocol, which is available at NEJM.org.

Patients

Key eligibility criteria were a diagnosis of relapsing–remitting multiple sclerosis (McDonald criteria[9]), an age of 18 to 55 years, a score of 0 to 5 on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability),[10] and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization. Key exclusion criteria were progressive forms of multiple sclerosis,[11] other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to glatiramer acetate or contraindicated medications (see the Supplementary Appendix for additional details).

Patients were informed of approved therapies[12] for multiple sclerosis, and they provided written informed consent. Reconsent was required after a confirmed relapse or confirmed disability progression.

Study Design

Patients at 200 sites in 28 countries were randomly assigned in a 1:1:1:1 ratio to receive oral placebo, BG-12 at a dose of 240 mg two times daily, BG-12 at a dose of 240 mg three times daily, or subcutaneous daily injections of 20 mg of glatiramer acetate for 96 weeks (Fig. S1 in the Supplementary Appendix). Patients receiving glatiramer acetate were aware of their treatment assignment. All study management and site personnel, investigators, and patients were unaware of assignment to the BG-12 and placebo groups; examining neurologists, technicians at the magnetic resonance imaging (MRI) reading center, and members of the independent neurologic evaluation committee were unaware of all study-group assignments. Each site used separate examining and treating neurologists, thereby maintaining rater blinding for all study groups, including the group that received glatiramer acetate. To ensure that the assignments to the BG-12 and placebo groups would not be revealed, patients in those groups were instructed not to take the study medication within 4 hours before each study visit, since a flushing reaction is known to be more common with BG-12.[13] Patients could switch to an alternative medication

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for multiple sclerosis if they had two confirmed relapses and had completed 48 weeks of study treatment or if they had confirmed disability progression (see the Supplementary Appendix).

STUDY PROCEDURES AND END POINTS

Standardized neurologic assessments, including an EDSS assessment, were performed every 12 weeks and at the time of suspected relapse (evaluated during unscheduled visits). MRI scans were obtained in a subset of patients at sites with MRI capabilities, at screening and at weeks 24, 48, and 96, and were evaluated in a blinded manner at a central MRI reading center.

The primary efficacy end point was the annualized relapse rate at 2 years, based on protocol-defined relapses (new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days) that were confirmed by the independent neurologic evaluation committee. Secondary efficacy end points included the number of new or enlarging hyperintense lesions on T_2-weighted images, the number of new hypointense lesions on T_1-weighted images, the proportion of patients with a relapse, and the time to disability progression, each at 2 years. Disability progression was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later. Tertiary end points included a comparison of the relative benefits and risks of BG-12 or glatiramer acetate versus placebo and the number of gadolinium-enhancing lesions at 2 years (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We estimated that a sample of 308 patients per group would provide approximately 84% power at a two-sided significance level of 0.05 to detect a 25% relative reduction in the 2-year annualized relapse rate, with the assumption of an annualized relapse rate of 0.61 in the placebo group. A sequential (closed) testing procedure was used to control for overall type I error due to multiple comparisons (see the Supplementary Appendix).

Primary and secondary end points were analyzed in the intention-to-treat (ITT) population (all randomly assigned patients who received study treatment) and in the MRI cohort (patients in the ITT population for whom any postbaseline MRI data were available), with the use of two-sided statistical tests at a significance level of 0.05.

The annualized relapse rate (total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications) was analyzed with the use of a negative binomial regression model adjusted for baseline EDSS score, age, region (regions were defined on the basis of not only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry. Four sensitivity analyses were performed (see the Supplementary Appendix).

Negative binomial regression was used for analysis of the total number of new or enlarging hyperintense lesions on T_2-weighted images and the total number of new hypointense lesions on T_1-weighted images at 2 years. A Cox proportional-hazards model was used for analysis of the proportion of patients with clinical relapse and the time to disability progression. Models were adjusted for region, EDSS score, age, relapse rate, and volume of lesions, as appropriate.

In general, analyses of primary and secondary end points were based on all observed data before patients switched to alternative multiple sclerosis medications, with analyses of MRI end points additionally based on missing data imputed with the use of a constant-rate assumption. The study was not designed to test the superiority or noninferiority of BG-12 versus glatiramer acetate. Safety was analyzed with the use of descriptive statistics for the safety population (all patients who received at least one dose of the study medication), excluding data obtained after patients switched to alternative multiple sclerosis medications.

RESULTS

PATIENTS

Of 1430 randomly assigned patients, 1417 were included in the ITT population (Fig. S2 in the Supplementary Appendix). Baseline demographic and disease characteristics were similar among the four study groups (Table 1) and between the MRI cohort (681 patients) (Table S1 in the Supplementary Appendix) and non-MRI cohort (736 patients). Approximately 29% of patients had re-

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Table 1. Baseline Demographic and Disease Characteristics (ITT Population).*

Characteristic	Placebo (N=363)	Twice-Daily BG-12 (N=359)	Thrice-Daily BG-12 (N=345)†	Glatiramer Acetate (N=350)†
Age — yr	36.9±9.2	37.8±9.4	37.8±9.4	36.7±9.1
Female sex — no. (%)	251 (69)	245 (68)	250 (72)	247 (71)
Weight — kg	72.6±16.9	71.9±17.9	72.5±17.8	71.4±19.1
Race — no. (%)‡				
White	305 (84)	304 (85)	292 (85)	290 (83)
Asian	28 (8)	28 (8)	26 (8)	25 (7)
Black	9 (2)	2 (<1)	5 (1)	11(3)
Other or unknown	21 (6)	25 (7)	22 (6)	24 (7)
Time since diagnosis — yr	4.8±5.0	4.9±5.1	4.6±5.2	4.4±4.7
Any prior approved DMT — no. (%)§	111 (31)	101 (28)	100 (29)	103 (29)
Relapses in previous 12 mo — no.	1.4±0.8	1.3±0.6	1.4±0.7	1.4±0.6
EDSS score at baseline — no. (%)¶				
0	13 (4)	15 (4)	15 (4)	18 (5)
1.0 or 1.5	78 (21)	85 (24)	84 (24)	77 (22)
2.0 or 2.5	111 (31)	94 (26)	94 (27)	96 (27)
3.0 or 3.5	98 (27)	105 (29)	99 (29)	99 (28)
4.0 or 4.5	50 (14)	47 (13)	42 (12)	46 (13)
5.0	13 (4)	12 (3)	11 (3)	14 (4)
Mean score on EDSS¶	2.6±1.2	2.6±1.2	2.5±1.2	2.6±1.2

* All baseline characteristics were well balanced among the study groups (nominal P>0.05). Plus–minus values are means ±SD. DMT denotes disease-modifying therapy, EDSS Expanded Disability Status Scale, and ITT intention to treat.
† One patient randomly assigned to the thrice-daily BG-12 group took glatiramer acetate throughout the study. This patient was counted in the thrice-daily BG-12 group of the ITT population and in the glatiramer acetate group of the safety population.
‡ Race was self-reported.
§ Prior exposure to interferon beta-1a (in 21% of the ITT population), interferon beta-1b (11%), natalizumab (1%), and glatiramer acetate (<1%) was balanced across groups; one patient was randomly assigned to glatiramer acetate who had previously been exposed to the drug. Patients may have received more than one prior multiple sclerosis medication. Patients may also have received other, nonapproved therapies for multiple sclerosis (the proportion of patients receiving any multiple sclerosis medication before the study was 40 to 41% across study groups).
¶ Scores on the EDSS range from 0 to 10, with higher scores indicating a greater degree of disability. One patient in the twice-daily BG-12 group had a baseline score higher than 5.0.

ceived an approved disease-modifying therapy before study entry.

Study completion rates were similar across study groups (overall rate in the ITT population, 80%), with a mean time in the study of 86.1, 84.4, 84.1, and 88.5 weeks in the placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively. The rate of study-drug discontinuation was higher in the placebo group than in the other groups (36% vs. 30% in the twice-daily BG-12 group, 28% in the thrice-daily BG-12 group, and 25% in the glatiramer acetate group) (Table S2 in the Supplementary Appendix), as was the proportion of patients who switched to alternative multiple sclerosis medications (11% vs. 7%, 8%, and 6%, respectively).

EFFICACY

Clinical End Points

The frequency of relapses of multiple sclerosis was significantly reduced by twice-daily and thrice-daily BG-12, with an adjusted annualized relapse rate at 2 years (primary end point) of 0.22 and 0.20, respectively, representing reductions relative to placebo (annualized relapse rate, 0.40) of 44% and 51% (P<0.001 for both comparisons). Glatiramer acetate also reduced the annualized relapse rate (0.29; relative reduction, 29% vs. placebo;

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P=0.01) (Fig. 1A and Table 2). Similar results were obtained in four sensitivity analyses that used different definitions of relapse or that included data after patients switched to alternative medications, findings that show the robustness of the results for the primary end point (Fig. S3 in the Supplementary Appendix).

As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the risk of relapse, by 34% (P=0.002), 45% (P<0.001), and 29% (P=0.01), respectively (Table 2). The Kaplan–Meier estimate of the proportion of patients with a relapse at 2 years was 41% in the placebo group as compared with 29%, 24%, and 32% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively (Fig. S4 in the Supplementary Appendix). Similar findings were observed in sensitivity analyses (Fig. S5 in the Supplementary Appendix).

Disability progression was not significantly reduced with twice-daily BG-12, thrice-daily BG-12, or glatiramer acetate, as compared with placebo (relative reduction, 21% [P=0.25], 24% [P=0.20], and 7% [P=0.70], respectively) (Fig. 1B and Table 2). The Kaplan–Meier estimate of the proportion of patients with disability progression was 17% in the placebo group as compared with 13%, 13%, and 16% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively. In a preplanned sensitivity analysis, 24-week confirmed disability progression was not significantly reduced versus placebo in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups (38% [P=0.06], 33% [P=0.12], and 13% [P=0.55], respectively), with an estimated proportion of patients with disability progression of 13% in the placebo group versus 8%, 9%, and 11% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively (Table S3 in the Supplementary Appendix).

MRI End Points

As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the mean number of new or enlarging hyperintense lesions on T_2-weighted images at 2 years, by 71%, 73%, and 54%, respectively (P<0.001 for all comparisons) (Table 2, and Fig. S6A in the Supplementary Appendix), and reduced the mean number of new hypointense lesions on T_1-weighted images, by 57% (P<0.001), 65% (P<0.001), and 41% (P=0.002), respectively (Table 2, and Fig. S6B in the Supplementary Appendix). The percentage of patients free from new or enlarging hyperintense lesions on T_2-weighted images at 2 years was higher with twice-daily BG-12 (27%), thrice-daily BG-12 (31%), or glatiramer acetate (24%) than with placebo (12%); corresponding percentages free from new hypointense lesions on T_1-weighted images were 39%, 44%, and 34% versus 21%.

The odds of having more gadolinium-enhancing lesions at 2 years was also significantly reduced by twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate treatment as compared with placebo, by 74%, 65%, and 61%, respectively (P<0.001 for all comparisons) (Table 2, and Fig. S6C in the Supplementary Appendix).

Benefits and Risks of BG-12 versus Glatiramer Acetate

In the prespecified comparison of the relative efficacy of each active treatment with placebo, the estimated treatment effects of both doses of BG-12 were numerically similar to or larger than those of glatiramer acetate across efficacy end points (Table 2). In a post hoc direct evaluation of the relative benefit of BG-12 versus glatiramer acetate, estimates and 95% confidence intervals excluded unity for some comparisons (Fig. S7 in the Supplementary Appendix). Nominal P values for comparisons of twice-daily BG-12 and thrice-daily BG-12 with glatiramer acetate were as follows: annualized relapse rate, P=0.10 and P=0.02, respectively; new or enlarging hyperintense lesions on T_2-weighted images, P=0.007 and P=0.002; new hypointense lesions on T_1-weighted images, P=0.08 and P=0.003; proportion of patients with a relapse, P=0.58 and P=0.09; and time to disability progression, P=0.44 and P=0.37.

SAFETY

The overall incidence of adverse events was similar across study groups (87 to 94%) (Table 3). Adverse events reported more frequently with BG-12 than with placebo included flushing, gastrointestinal events (diarrhea, nausea, and upper abdominal pain), upper respiratory tract infections, and erythema. For flushing, which included events of flushing and hot flush, the incidence was 35% with twice-daily BG-12 and 28% with thrice-daily BG-12 versus 6% with placebo and 3% with glatiramer acetate; for gastrointestinal events, the incidence was 36% with twice-daily BG-12

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