Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study

*Ludwig Kappos, Ralf Gold, David H Miller, David G MacManus, Eva Havrdova, Volker Limmroth, Chris H Polman, Klaus Schmierer, Tarek A Yousry, Minhua Yang, Mefkûre Eraksoy, Eva Meluzinova, Ivan Rektor, Katherine T Dawson, Alfred W Sandrock, Gilmore N O'Neill, for the BG-12 Phase IIb Study Investigators**

Summary

Background Oral fumarate (BG00012) might have dual anti-inflammatory and neuroprotective effects. Our aim was to assess the efficacy and safety of BG00012 in patients with relapsing-remitting multiple sclerosis.

Methods 257 patients, aged 18–55 years, with relapsing-remitting multiple sclerosis were randomly assigned to receive 120 mg once daily (n=64), 120 mg three times daily (n=64), or 240 mg three times daily (n=64) BG00012, or placebo (n=65) for 24 weeks. During an extension period of 24 weeks for safety assessment, patients treated with placebo received BG00012 240 mg three times daily. The primary endpoint was total number of new gadolinium enhancing (GdE) lesions on brain MRI scans at weeks 12, 16, 20, and 24. Additional endpoints included cumulative number of new GdE lesions (weeks 4–24), new or enlarging T2-hyperintense lesions, new T1-hypointense lesions at week 24, and annualised relapse rate. Analysis was done on the efficacy-evaluable population. Safety and tolerability were also assessed. This study is registered with ClinicalTrials.gov, number NCT00168701.

Findings Treatment with BG00012 240 mg three times daily reduced by 69% the mean total number of new GdE lesions from week 12 to 24 compared with placebo (1·4 *vs* 4·5, p<0·0001). It also reduced number of new or enlarging T2-hyperintense (p=0·0006) and new T1-hypointense (p=0·014) lesions compared with placebo. BG00012 reduced annualised relapse rate by 32% (0·44 *vs* 0·65 for placebo; p=0·272). Adverse events more common in patients given BG00012 than in those given placebo included abdominal pain, flushing, and hot flush. Dose-related adverse events in patients on BG00012 were headache, fatigue, and feeling hot.

Interpretation The anti-inflammatory effects and favourable safety profile of BG00012 warrant further long-term phase III studies in large patient groups.

Funding Biogen Idec, Inc.

Lancet 2008; 372: 1463–72

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*Members listed at end of paper

University Hospital Basel, Basel, Switzerland (Prof L Kappos MD); **University Clinic Bochum at St Josef Hospital, Bochum, Germany** (Prof R Gold MD); **Institute of Neurology, University College London, London, UK** (Prof D H Miller MD, D G MacManus MSc, K Schmierer PhD, T A Yousry MD); **General Teaching Hospital, Prague, Czech Republic** (E Havrdova MD); **City Hospital of Cologne, Cologne, Germany** (V Limmroth MD); **VU Medical Centre, Amsterdam, the Netherlands** (Prof C H Polman MD); **Biogen Idec, Cambridge, MA, USA** (M Yang MS, K T Dawson MD, A W Sandrock MD, G N O'Neill MB); **University of Istanbul, Istanbul, Turkey** (Prof M Eraksoy MD); **Motol Hospital, Charles University, second Medical School, Prague, Czech Republic** (E Meluzinova MD); **and Masaryk University, Brno, Czech Republic** (I Rektor MD)

Correspondence to:
Prof Ludwig Kappos, University Hospital Basel, Neurology and Department of Biomedicine, Petersgraben 4, CH 4031, Basel, Switzerland
lkappos@uhbs.ch

Introduction

BG00012, an oral formulation of dimethyl fumarate, might have novel and complex effects on the pathobiology of multiple sclerosis. Preclinical experiments have shown that dimethyl fumarate and its primary metabolite monomethyl fumarate can activate the nuclear-factor-E2-related factor-2 (Nrf2) transcriptional pathway,[1] which controls phase-2 detoxifying enzyme gene expression, and is crucial for oxidative stress response and immune homoeostasis.[2 4] Activation of the Nrf2 pathway defends against oxidative-stress-induced neuronal death,[5 8] protects the blood–brain barrier,[9] and supports maintenance of myelin integrity[10] in the CNS. Dimethyl fumarate induces expression of phase-2 detoxification enzymes in astroglial and microglial cells.[11] It also inhibits expression of cytokines and adhesion molecules implicated in the inflammatory response in vitro.[11 13] These data suggest that BG00012 could have dual neuroprotective and anti-inflammatory effects.

An oral formulation of fumaric acid (Fumaderm, Biogen Idec Gmbh, Ismaning, Germany) showed effectiveness in patients with chronic plaque psoriasis, a disorder associated with immune dysfunction.[14] In a pilot study in patients with relapsing-remitting multiple sclerosis, this formulation also reduced the number and volume of gadolinium enhancing (GdE) lesions on brain MRI scans compared with baseline.[15] On the basis of these preliminary findings, we have tested the efficacy and safety of three doses of BG00012 versus placebo in a multicentre, randomised, double-blind, placebo-controlled, dose-ranging, phase IIb study in patients with relapsing-remitting multiple sclerosis.

Methods

Patients

257 patients were recruited from 43 centres in the Czech Republic, Germany, Hungary, Netherlands, Poland, Russia, Sweden, Switzerland, Turkey, and UK, between Nov 24, 2004, and March 31, 2005. Participants were aged 18–55 years with a diagnosis of relapsing-remitting multiple sclerosis by McDonald criteria,[16] a baseline Expanded Disability Status Scale (EDSS) score between 0 and 5,[17] and either at least one relapse within 12 months of randomisation and a previous cranial MRI scan showing

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lesions consistent with multiple sclerosis, or GdE lesions on MRI scans done within 6 weeks of randomisation.

Women with child-bearing potential had to use appropriate birth control, and were excluded from the study if they were pregnant or breastfeeding. Patients were excluded if they had progressive forms of multiple sclerosis or serious medical disorders, either concurrently (ie, HIV or hepatitis) or by history (ie, malignant disease or anaphylactic reactions, drug or alcohol abuse within 2 years of randomisation, or a relapse of multiple sclerosis within 50 days of randomisation, or no stabilisation from a previous relapse at the time of randomisation, or both). Patients were excluded if they had been previously treated with fumaric acid, FAG-201, BG00012, cladribine, T-cell or T-cell-receptor vaccination, total lymphoid irradiation, or therapeutic monoclonal antibodies apart from natalizumab. Patients were also excluded if they received mitoxantrone or cyclophosphamide within 1 year; cyclosporine, azathioprine, methotrexate, natalizumab, intravenous immunoglobulin, plasmapheresis, or other investigational drugs within 6 months; glatiramer acetate or interferon beta within 3 months; or corticosteroid (oral or intravenous), 4-aminopyridine, or related products within 30 days of randomisation.

Study design and outcome measures

This randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study was a 24-week, blinded, placebo-controlled treatment period (part 1), followed by 24 weeks for dose-blinded safety assessment (part 2) (figure 1). Recruitment started Nov 24, 2004, and the trial ended May 22, 2006. During the first 24 weeks, patients were randomly assigned to receive oral BG00012 120 mg once daily, 120 mg or 240 mg three times daily, or placebo. During the following 24 weeks, patients who received BG00012 in the first 24 weeks were maintained on the same BG00012 dose, and patients who received placebo in the first 24 weeks were given BG00012 240 mg three times daily. Patients who were randomly assigned to BG00012 240 mg three times daily received 120 mg three times daily for the first week and 240 mg three times daily from week 2.

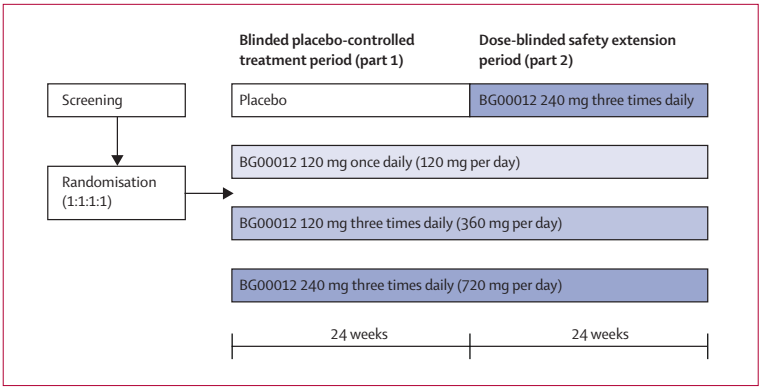

Figure 1: **Study design**

BG00012 and placebo were administered as enteric-coated microtablets in gelatin capsules, which had identical appearance and taste. Daily medication was given in blister packs of six tablets, with different numbers of tablets containing placebo or the active drug to preserve the blinding. In the extension phase, all patients received a new set of medication. During both study periods, reduction to one capsule three times daily for 1 month was allowed for patients unable to tolerate higher doses. Moreover, dosing interruptions were needed for elevated liver or renal function tests, or decreased white blood cell counts. After dose interruption, patients were examined every 2 weeks and allowed to resume dosing when laboratory values returned to normal. Patients with abnormal values for more than 4 consecutive weeks permanently discontinued the study drug.

The study protocol was approved by independent ethics committees, and the study was done in accordance with the Declaration of Helsinki, International Conference of Harmonisation and Good Clinical Practice guidelines, and local regulations. Enrolled patients provided written informed consent.

Study procedures and endpoints

To prevent unblinding of treatment assignment, separate study personnel were assigned to treat patients and to assess drug efficacy. A treating neurologist was responsible for routine neurological care, assessing and treating adverse events, and analysing laboratory test results. Neurologists not otherwise involved in the care of study participants assessed patients at scheduled and unscheduled relapse examinations. These examining neurologists were trained and certified in EDSS examination after attending special training courses, viewing a DVD-ROM,[18] and successfully passing a multiple choice test.

Patients attended clinics every 4 weeks during both study periods. Patients were instructed not to take their medication within 4 h before clinic visits because of the possibility for study unblinding due to flushing. Brain MRI scans were done at baseline and at weeks 4, 8, 12, 16, 20, and 24. Participating imaging sites were equipped with MRI systems operating at 1·0 or 1·5 Tesla. For all patients, 46 contiguous 3-mm-thick axial images of the brain were acquired with a dual echo fast (turbo) spin echo (FSE) sequence (repetition time [TR] 2500–3300 ms, echo time 1 [TE1] 10–40 ms, echo time 2 [TE2] 80–100 ms) to provide proton density and T2-weighted images. Furthermore, a conventional spin echo sequence (TR 500–700 ms, TE 10–20 ms) was undertaken before and after injection of gadolinium-based contrast medium to provide T1-weighted images in the corresponding spatial location to the FSE scans. We used a field of view of 250 mm together with a reconstructed image matrix of 256×256, resulting in an in-plane spatial resolution of 0·97×0·97 for all images.

All scans were analysed from hard-copy film by two trained observers (KS and DGM) under the supervision of an experienced neuroradiologist (TAY) at a

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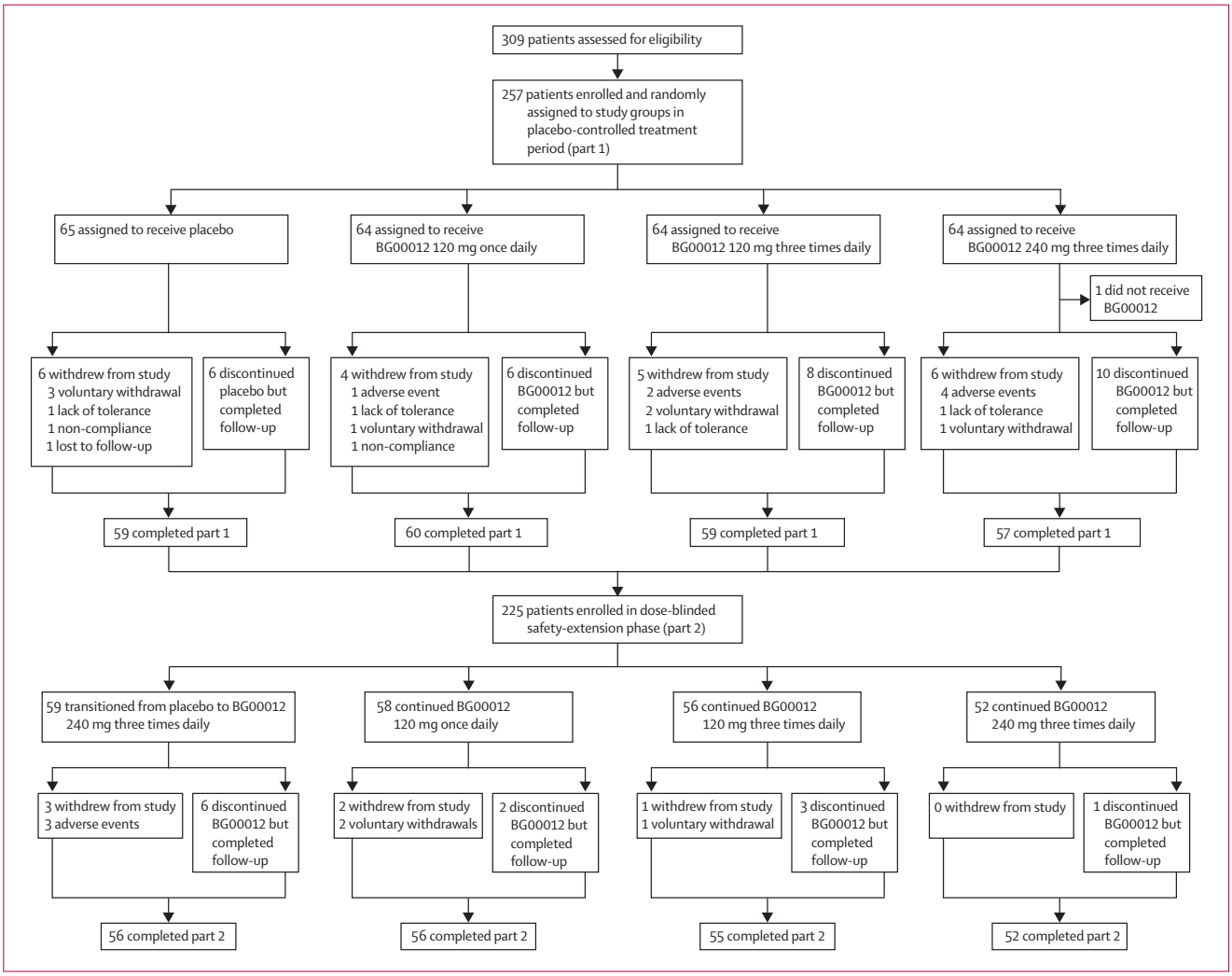

Figure 2: **Trial profile**

central reading centre. New GdE lesions, compared with the previous scan, were identified and marked every month on postcontrast T1-weighted sequences. For new or enlarging T2 lesions, the week-24 scan was compared with the baseline (week-0) scan. The proton-density weighted scan was marked, although the second echo, a more heavily T2-weighted sequence, was also reviewed to confirm the presence of a new lesion. Enlarging T2 lesions were defined as those that appeared larger on two contiguous slices or showed at least twice the diameter compared with the baseline scan. New T1-hypointense black-hole lesions were identified and marked on the unenhanced T1-weighted scans at week 24 compared with the baseline scans.

EDSS scores were assessed at baseline and at weeks 12, 24, 36, and 48. Patients were monitored for relapses at all clinic visits, and suspected relapses were assessed on unscheduled visits. The treating neurologist was contacted within 48 h of symptom onset, and the assessment was done within 72 h; EDSS scores were reviewed during unscheduled visits. Relapses were defined as new or recurrent neurological symptoms lasting for 24 h or longer, not associated with fever or infection, and accompanied by new objective neurological findings on examination. At the neurologists' discretion, patients with relapses were treated per protocol with intravenous methylprednisolone 1000 mg per day for 3 or 5 days.

Haematology, blood chemistry, and urinalysis were done every 4 weeks. Electrocardiographs were done at screening and at weeks 12, 24, 36, and 48. All adverse events were documented throughout the study, regardless of severity or relation to study drug. Patients discontinuing BG00012 during the first or the second part of the study were encouraged to remain in the study until week 24

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	Placebo, N=65	BG00012 120 mg once daily, N=64	BG00012 120 mg three times daily, N=64	BG00012 240 mg three times daily, N=63
Age (years)	35·6 (8·2)	34·8 (10·2)	36·3 (9·5)	37·3 (9·1)
Sex (female)	36 (55%)	42 (66%)	44 (69%)	42 (67%)
Ethnic origin (white)	64 (98%)	62 (97%)	64 (100%)	60 (95%)
Median time since symptom onset (year) (IQR)	6 (4·0–11·0)	7 (4·0–11·5)	5 (3·0–9·0)	6 (4·0–12·0)
Median number of relapses				
Previous 1 year	1	1	1	1
Previous 3 years	2	2	2	3
EDSS score	2·67 (1·23)	2·52 (1·11)	2·51 (1·02)	2·87 (1·33)
Number of GdE lesions				
0	38 (58%)	30 (47%)	30 (47%)	41 (65%)
1	10 (15%)	19 (30%)	7 (11%)	10 (16%)
2	10 (15%)	3 (5%)	10 (16%)	4 (6%)
3	3 (5%)	3 (5%)	3 (5%)	2 (3%)
≥4	4 (6%)	9 (14%)	14 (22%)	6 (10%)
Mean	1·6 (6·6)	1·4 (2·1)	2·5 (4·2)†	1·3 (3·4)

Data are n (%) or mean (SD), unless otherwise stated. EDSS=Expanded Disability Status Scale. GdE=gadolinium enhancing. IQR=interquartile range. *Intention-to-treat population. †p=0·045 versus placebo; p=not significant versus BG00012 120 mg once daily; p=0·019 versus BG00012 240 mg three times daily based on logit regression.

Table 1: **Demographics and baseline clinical characteristics***

or 48, respectively, and to continue protocol-scheduled assessments.

The primary endpoint was the total number of new GdE lesions over four scans at weeks 12, 16, 20, and 24 (calculated as the sum of the scans): this time was selected on the basis of an apparent latency to clinical effect from the pilot study of multiple sclerosis.[15] Secondary MRI endpoints included the cumulative number of new GdE lesions from week 4 to 24, and the numbers of new or enlarging T2-hyperintense lesions and new T1-hyperintense lesions at week 24. The efficacy of BG00012 on relapses and disability progression, and its safety and tolerability, were also assessed.

Statistical analysis

Mean and variability estimates to calculate sample size were derived from summary data from placebo-treated patients with relapsing-remitting multiple sclerosis in other clinical studies (mean=8·6, SD=12·7).[19] The standard deviation for the group treated with the active compound was calculated by assuming a negative binomial distribution of the number of MRI lesions on the basis of the mean in the calculation. A sample size of 65 patients per group had 80% power to detect a treatment effect of 55% reduction or more on the total number of new GdE lesions, when comparing the mean of the placebo group with that of the two groups treated with the two highest doses of active drug combined. This sample size calculation assumed that the total lesion number was from four consecutive scans and was based on a two-group Satterthwaite *t* test of equal means and unequal variances. Additionally, we assumed an alpha value of 0·05 with no adjustment for multiple comparisons. The calculation was done with Nquery (version 5.0) statistical software (Statistical Solutions, Saugus, MA, USA).

MRI endpoints were analysed with the non-parametric Wilcoxon rank sum test. Annualised relapse rate was analysed with a Poisson regression model adjusted for the number of relapses in the 12 months before study entry, and proportion of relapse-free patients was analysed with Fisher exact test. No formal statistics were done on EDSS scores. MRI analyses are reported for the efficacy-evaluable population (ie, patients who had no missing MRI data). MRI scans must have been done before or at least 24 days after steroid treatment. Clinical efficacy analyses are reported for the intention-to-treat population, defined as all patients who were randomised and received at least one dose of drug. All statistical tests were two-sided, with an alpha value of 0·05; no adjustment (type I error rate) for multiple comparisons was made. The safety population included all patients who received at least one BG00012 dose. Differences in adverse-event reporting between all BG00012 groups combined versus placebo group were calculated with the Fisher exact test.

Role of the funding source

The employees of Biogen Idec Inc listed as authors participated with the other authors in the study design and statistical analysis of the data. These authors reviewed and approved the manuscript. The corresponding author had full access to all study data and had final responsibility for submission of the publication.

Results

257 patients were randomly assigned to receive BG00012 120 mg once daily, or 120 mg or 240 mg three times daily, or placebo. One patient, who was randomly assigned to the highest dose of BG00012, withdrew before receiving the drug (figure 2). Patients were well-matched for

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demographic and baseline disease characteristics (table 1). The mean number of baseline GdE lesions was higher for the BG00012 120 mg three times daily group than for all other treatment groups (table 1).

During the first 24 weeks, more patients receiving BG00012 120 mg and 240 mg three times daily discontinued study drug than patients receiving BG00012 120 mg once daily or placebo (figure 2). Overall, 21 of 256 patients who received the drug withdrew from the first part of the study. An additional ten patients who completed the first part of the study did not enter in the second part. During the second 24 weeks, more patients changing from placebo to BG00012 240 mg three times daily prematurely discontinued study drug than patients maintaining their original treatment. Overall, six patients withdrew from this part of the study. 235 patients completed their study visits during the first 24 weeks and 219 completed the second 24 weeks.

Patients receiving BG00012 240 mg three times daily had fewer total new GdE lesions (69% reduction) at weeks 12, 16, 20, and 24 combined compared with those receiving placebo (1·4 *vs* 4·5, p<0·0001) (figure 3). Similarly, a sensitivity analysis of the intention-to-treat population on this endpoint showed that patients receiving this dose of BG00012 had fewer new GdE lesions compared with those receiving placebo (1·3 *vs* 4·8, p<0·0001). Although treatment with BG00012 led to fewer total new GdE lesions in patients receiving 120 mg once daily (3·3) and three times daily (3·1) than placebo (4·5), these treatment group differences were not significant.

From week 4 to 24, patients receiving BG00012 240 mg three times daily had fewer cumulative new GdE lesions (44% reduction) than those receiving placebo (table 2). BG00012 240 mg also reduced the mean number of new or enlarging T2-hyperintense lesions (48% reduction) during the first 24 weeks compared with placebo. During this period, no new T2 lesions developed in 63% of patients receiving this dose of BG00012 compared with 26% of those receiving placebo. Furthermore, the mean number of T1-hypointense lesions after 24 weeks of treatment was lower (53% reduction) in the BG00012 240 mg three times daily dose group compared with the placebo group. No significant differences were seen between the lower BG00012 dose groups (ie, 120 mg once daily and 120 mg three times daily) and the placebo group on any of the MRI endpoints assessed.

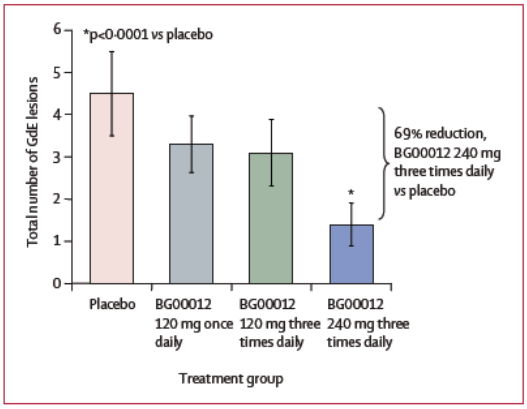

Figure 3: **Mean total number of GdE lesions from scans at weeks 12, 16, 20, and 24 combined**
Vertical bars=SE.

During the first part of the study, the annualised relapse rate for patients who received BG00012 240 mg three times daily decreased by 32% (table 2). The proportion of relapse-free patients was close between the two groups. A similar percentage of patients in every treatment group was treated with intravenous methylprednisolone per protocol for relapses (n=11 [17%] in the placebo group; n=9 [14%] in the BG00012 120 mg once daily group; n=11 [17%] in the BG00012 120 mg three times daily group; and n=6 [10%] in the BG00012 240 mg three times daily group). During the second part of the study, the

	Placebo*	BG00012 120 mg once daily	BG00012 120 mg three times daily	BG00012 240 mg three times daily
MRI†				
Number of new GdE lesions (weeks 12–24)	54	59	56	54
Mean	4·5 (7·4)	3·3 (5·1)	3·1 (5·9)	1·4 (3·8)
Median (IQR)	2·0 (0–5·0)	1·0 (0–4·0)	1·0 (0–3·5)	0·0 (0–1·0)
p value *vs* placebo	..	0·266	0·068	<0·0001
Number of new GdE lesions (weeks 4–24)	53	55	54	52
Mean	6·6 (11·4)	6·2 (8·9)	6·7 (10·9)	3·7 (11·2)
Median (IQR)	3·0 (0–7·0)	3·0 (0–7·0)	2·0 (0–7·0)	0·0 (0–3·0)
p value *vs* placebo	..	0·943	0·801	0·002
Number of new GdE lesions per patient, per scan (weeks 12–24)	54	59	56	54
Mean	1·13 (1·84)	0·83 (1·29)	0·78 (1·48)	0·35 (0·94)
Median (IQR)	0·50 (0–1·25)	0·25 (0–1·00)	0·25 (0–0·88)	0·00 (0–0·25)
p value‡	..	0·266	0·068	<0·0001

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