CLINICAL INVESTIGATION

BG-12 (dimethyl fumarate) in the treatment of multiple sclerosis

BG-12 was recently approved in the USA, Canada and Australia as an oral treatment for relapsing–remitting multiple sclerosis after positive results from two large pivotal Phase III studies. Approval is also imminent in the EU, where BG-12 has received a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use in March 2013. The active ingredient, dimethyl fumarate, is thought to act mainly by inducing NF-E2 p45-related factor, thereby reducing oxidative stress, which is considered to be one of the pathogenic mechanisms in multiple sclerosis. The agent is not only highly effective at reducing relapse rate but also appears to slow disability progression across a wide variety of patient groups. With the oral route of administration and a good safety profile, BG-12 will likely become a valuable treatment option for multiple sclerosis patients and neurologists.

Keywords: BG-12 • clinical development • dimethyl fumarate • emerging therapies • relapsing–remitting multiple sclerosis

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Multiple sclerosis (MS) is thought to be an inflammatory disease of the CNS in which demyelination, gliosis and axonal loss lead to a variety of neurologic symptoms [1,2]. In the early stages, most patients have the relapsing–remitting form (RRMS) in which relapses or exacerbations are followed by recovery to a similar level of disability [3].

At present, MS remains an incurable disease. The main aim of therapy is to slow accumulation of disability and prevent the patient from entering the progressive form of the disease [4], where much fewer treatment options are available. Another aim of therapy is to reduce the number of relapses a patient experiences, partly because this may have an impact on disability progression (although the link between relapses and accumulation of disability is disputed [5]) and partly because relapses in themselves represent considerable disease and economic burden [6]. Traditional disease-modifying therapies such as the interferons and glatiramer acetate have modest efficacy [7,8], while their parenteral route of administration also represents a burden to the patient [9]. Newly approved agents for MS have brought new hope to patients with MS. Some are oral agents, which will likely be more acceptable to MS patients [10], while others have much less frequent (and hence more convenient) dosing regimens [11]. Nevertheless, many of these new agents require close safety monitoring and may not be appropriate or effective in all patients. There therefore remains a need for effective new agents with convenient dosing. In this sense, BG-12 represents an important addition to the neurologist's armamentarium [2,12]. The present review will discuss the current status of BG-12, its putative mechanism of action and the clinical development program for MS. Finally, the position of BG-12 among the approved MS agents will be considered.

Current status of BG-12

The active substance of BG-12 is dimethyl fumarate, a fumaric acid ester with a molecular weight of 144.13 that exists as a white to off-white powder that is highly soluble in water.

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BG-12 was approved by the US FDA in the USA as a twice-daily (b.i.d.) oral treatment for relapsing–remitting MS in March 2013 and the US launch followed shortly afterwards, in May 2013. In addition, approval has been granted in Canada and Australia. In March 2013, the product also received a positive opinion from the European Medicines Agency, and the marketing authorization in Europe was granted by the European Commission in January 2014.

Non-clinical & clinical pharmacology

Putative mechanism of action

Most new therapies for relapsing–remitting MS are biologic agents that aim to reduce or modulate inflammation by targeting leukocytes, leukocyte migration, or chemokines and cytokines and their receptors [13]. BG-12 in contrast is a small molecule that acts mainly by alleviating the oxidative stress thought to play a major role in the process of axonal injury in patients with MS [14]. Given that the transcription of NF-E2 p45-related factor (Nrf2) has been implicated in antioxidative and neuroprotective effects, investigators became interested in this factor as a potential therapeutic target. Many compounds have been shown to induce Nrf2 *in vitro*, but most are associated with considerable safety concerns [15]. The compound was found to be effective in ameliorating experimental autoimmune encephalitis, a widely used animal model of MS [16,17]. Dimethyl fumarate or monomethyl fumarate treatment also significantly improved astrocyte and neuron viability after toxic oxidative challenge in a concentration-dependent manner [18], suggesting that cytoprotective effects may also be in operation. Experiments have also shown that dimethyl fumarate can inhibit maturation of dendritic cells by reducing the production of inflammatory cytokines such as IL-12 and IL-6 and expression of MHC class II, CD80 and CD86 [19]. This in turn led to fewer activated T-cells characterized by decreased interferon-γ and IL-17 production. The same authors also demonstrated that dimethyl fumarate can interfere with NF-κb signaling by p65 nuclear translocalization and phosphorylation and also by dimethyl-fumarate-mediated suppression of ERK1 and ERK2. Ultimately, dimethyl fumarate appears to inhibit maturation of dendritic cells and subsequent Th1 and Th17 cell differentiation, suggesting additional anti-inflammatory mechanisms may be operating [20].

Non-clinical toxicity

The standard carcinogenic and mutagenic test batteries did not identify any particular safety concerns. Kidney toxicity was, however, observed in repeat-dose experiments in mice, rats, dogs and monkeys. Findings indicative of renal damage included renal tubule epithelia regeneration, renal tubular hyperplasia, cortical atrophy and interstitial fibrosis, even at doses similar to those observed in humans after receiving the recommended dose levels. Nevertheless, careful monitoring of renal function in humans has so far not detected any renal safety signals of note.

Pharmacokinetics

Dimethyl fumarate is rapidly hydrolyzed by esterases before reaching systemic circulation and so serum concentrations of dimethyl fumarate and fumaric acid remain below the limit of detection. Median time to maximum concentration (T_{max}) of the active metabolite, monomethyl fumarate, is between 2 and 2.5 h. The AUC was generally not affected by food intake although the peak concentration (C_{max}) was approximately 40% lower when administered after a high-fat, high-calorie meal. The incidence of flushing is reduced by approximately 25% when the drug is administered after a meal, although the drug may be taken with or without food according to the US labelling.

Metabolism of the active metabolite, monomethyl fumarate, does not involve the P450 (CYP) system, and so the potential for drug–drug interactions is thought to be low. Indeed, single doses of interferon β-1a, glatiramer acetate or aspirin had no effect on the pharmacokinetic parameters of monomethyl fumarate.

Clinical development for MS

Phase II proof-of-concept study

The first Phase IIb study was conducted in 257 patients with RRMS [21]. Patients were randomized to BG-12 (120 mg once daily [n = 64], 120 mg three times daily [t.i.d.; n = 64], or 240 mg t.i.d. [n = 64]) or placebo (t.i.d. [n = 65]) for 24 weeks. At 24 weeks, patients in the placebo group switched to BG-12 240 mg t.i.d. in a dose-blinded safety extension (i.e., patients in the placebo group remained unaware of their initial treatment assignment and patients in the active-treatment arms continued with their assigned dose and were unaware of their assignment). The primary outcome measure was total number of new gadolinium-enhancing lesions on brain MRI scans at weeks 12, 16, 20, and 24. The authors found that the 240 mg t.i.d. regimen of BG-12 reduced the total number of new lesions by 69% compared with placebo at week 24 (1.4 vs 4.5; $p < 0.0001$). The annualized relapse rate, a secondary outcome measure, was reduced by 32% compared with placebo (0.44 vs 0.65) although the difference was not significant ($p = 0.227$). In the other treatment arms, numerical treatment effects were observed, but the differences versus placebo were not significant. Abdominal pain,

Table 1. Characteristics of the study populations in the DEFINE and CONFIRM pivotal Phase III studies.

Regimen (n)	Age (years)	Sex		Weight (kg)	Race†				PDMT (n; %)	TFD (years)	Relapses (previous 12 months)	EDSS at baseline (mean)	Available MRIs (n)‡	MRI characteristics	
		Female (n; %)	Male (n; %)		White (n; %)	Asian (n; %)	Black (n; %)	Other/ unknown (n; %)						Gd-enhancing T_1 weighted lesions	Hypointense T_2 weighted lesions
DEFINE [24]															
Placebo (408)	38.5 ± 9.1	306 (75)	102 (25)	71.1 ± 17.0	318 (78)	42 (10)	8 (2)	40 (10)	172 (42)	5.8 ± 5.8	1.3 ± 0.7	2.48 ± 1.24	180	1.6 ± 3.4	49.2 ± 38.6
BG-12 b.i.d. (410)	38.1 ± 9.1	296 (72)	114 (28)	70.7 ± 18.5	321 (78)	38 (9)	8 (2)	43 (10)	162 (40)	5.6 ± 5.4	1.3 ± 0.7	2.40 ± 1.29	176	1.2 ± 3.3	47.6 ± 34.7
BG-12 t.i.d. (416)	38.8 ± 8.8	306 (74)	110 (26)	71.3 ± 16.9	330 (79)	36 (9)	10 (2)	40 (10)	168 (40)	5.1 ± 5.3	1.3 ± 0.6	2.36 ± 1.19	184	1.2 ± 4.1	55.8 ± 44.3
CONFIRM [25]															
Placebo (363)	36.9 ± 9.2	251 (69)	112 (31)	72.6 ± 16.9	305 (84)	28 (8)	9 (2)	21 (6)	111 (31)	4.8 ± 5.0	1.4 ± 0.8	2.6 ± 1.2	167	2.7 ± 7.7	Not reported
BG-12 b.i.d. (359)	37.8 ± 9.4	245 (68)	114 (32)	71.9 ± 17.9	305 (85)	28 (8)	2 (<1)	25 (7)	101 (28)	4.9 ± 5.1	1.3 ± 0.6	2.6 ± 1.2	169	2.7 ± 6.2	Not reported
BG-12 t.i.d. (345)	37.8 ± 9.4	250 (72)	95 (28)	72.5 ± 17.8	292 (85)	26 (8)	5 (1)	22 (6)	100 (29)	4.6 ± 5.2	1.4 ± 0.7	2.5 ± 1.2	170	1.9 ± 5.0	Not reported
Glatiramer acetate (350)	36.7 ± 9.1	247 (71)	103 (29)	71.4 ± 19.1	290 (83)	25 (7)	11 (3)	24 (7)	103 (29)	4.4 ± 4.7	1.4 ± 0.6	2.6 ± 1.2	175	2.4 ± 6.8	Not reported

†Self reported.

‡MRI data not available for all patients.

b.i.d.: Twice daily; EDSS: Expanded Disability Status Scale; PDMT: Previous disease-modifying therapy; TFD: Time from diagnosis; t.i.d.: Three times daily.

flushing, and hot flush were reported more frequently in the active-treatment group compared with placebo.

In a subgroup analysis of the Phase IIb study to determine the influence of different patient characteristics, Kappos *et al.* [22] reported that BG-12 significantly reduced the number of gadolinium-enhancing lesions compared with placebo among patients with Expanded Disability Status Scale (EDSS) score ≤ 2.5 (74%), EDSS score > 2.5 (63%), no gadolinium-enhancing lesions (80%), ≥ 1 gadolinium-enhancing lesion (55%), age < 40 years (49%), age ≥ 40 years (89%), female patients (81%), disease duration ≤ 6 years (81%) and disease duration > 6 years (54%). These findings suggested that BG-12 is effective over a wide range of patients.

In a retrospective analysis of the evolution of new gadolinium-enhancing lesions that evolved to T1-hypointense lesions (147 lesions in the BG-12 group and 221 in the placebo group), MacMannus *et al.* [23] reported that conversion was 34% lower in the BG-12 treatment group compared with placebo (29% for BG-12 vs 44% for placebo; odds ratio: 0.51; 95% CI: 0.43–0.61; p < 0.0001). This raises the intriguing possibility of an axon-protective effect in which axonal damage is limited by treatment.

Pivotal Phase III studies

Two pivotal Phase III trials have been conducted with BG-12 to support approval in the treatment of relapsing forms of MS: the DEFINE study [24] and the CONFIRM study [25]. Both were randomized placebo-controlled studies in which patients were assigned to either oral BG-12 (240 mg b.i.d. or t.i.d.) or placebo. The randomized, double-blind phase lasted 2 years in both cases. In the case of the CONFIRM study, patients were also assigned to an open-label glatiramer acetate arm (20 mg daily) although the study was not designed to make head-to-head efficacy comparisons with the blinded arms. To help maintain blinding in the blinded arms, patients were not to take their study medication within 4 h of a study visit given that flushing reactions were a commonly known reaction to BG-12.

The inclusion and exclusion criteria were very similar for the two studies. Patients had to have RRMS as per the McDonald criteria [26] and have active disease (a relapse in the preceding 12 months or at least one new gadolinium-enhancing lesion on brain MRI within 6 weeks of randomization). Their baseline EDSS score had to be below 5.0 and patients with progressive forms of MS were excluded. In addition, certain prespecified laboratory abnormalities and certain other concomitant diseases were also grounds for exclusion.

Women accounted for between 72 and 75% of patients in the CONFIRM study and between 68 and 72% in the DEFINE study. A greater proportion of patients in the CONFIRM study were white (84–85%) compared with the DEFINE study (78–79%). The majority of patients had a baseline EDSS score of ≥2.0. Fewer patients in the CONFIRM study (29–31%) had received previous disease-modifying therapy compared with those in the DEFINE study (40–42%) and the time since diagnosis was also shorter in the CONFIRM study (4.4–4.9 vs 5.1–5.8 years). In general, other patient characteristics were balanced across groups and across studies (Table 1). MRI evaluations were only available for a subset of patients in each study (given that MRI was not routinely available in all participating centers).

In both studies, the primary end point was based on relapses; in the case of the DEFINE study it was proportion of patients with at least one relapse after 2 years of treatment and in the case of the CONFIRM study, it was the annualized relapse rate after 2 years. Secondary efficacy end points included disability progression and new/enlarging T2 hyperintense lesions. Relapses were defined (in the protocol) as new or recurrent neurologic symptoms with no associated fever or infection that lasted for more than 24 h and were accompanied by new objective neurologic findings. In both studies, relapses were adjudicated by an independent neurologic evaluation committee.

The efficacy results are summarized in Table 2. For both studies, the annualized relapse rate at 2 years and proportion of patients with relapse at 2 years was significantly lower in both BG-12 dose groups compared with placebo. In the case of disability progression at 2 years, significant treatment effects were observed for both BG-12 dose groups in the DEFINE study. In the case of the CONFIRM study, a numerical effect was seen in favor of BG-12 versus placebo, but these differences were not significant. A likely explanation for this is the lower proportion of patients with disability progression in the placebo group of the CONFIRM study (17%) compared with the DEFINE study (27%), making the study unpowered to detect a statistical difference. This may perhaps be linked to differences in the populations of the two studies (in the CONFIRM study, fewer patients had received previous disease-modifying therapy and the mean disease duration was lower, suggesting that the CONFIRM study enrolled patients with more incipient disease).

Although the CONFIRM study included a glatiramer acetate treatment arm, it was not designed to directly compare the treatment effects of BG-12 and glatiramer acetate. A prespecified comparison of the relative efficacy of each active treatment with placebo did show numerically larger effects compared with placebo (Table 2). Direct *post hoc* comparisons were performed and generally showed numerical benefit

Table 2. Efficacy outcomes for the Phase III trials with BG-12.

Regimen (n)	Annualized relapse rate at 2 years		Relapse at 2 years		Disability progression at 2 years		Gd-enhancing T_1-weighted lesions at 2 years (n)†	Mean (n)	Odds ratio vs placebo (95% CI)
	Rate (95% CI)	Reduction vs placebo (%; 95% CI)	%	Hazard ratio vs placebo (90% CI)	Confirmed progression (%)	Hazard ratio vs placebo			
DEFINE [24]									
Placebo (408)	0.36 (0.30–0.44)	–	46	–	27	–	180	1.8 ± 4.2	–
BG-12 b.i.d. (410)	0.17 (0.14–0.21)	47 (37–61)	27	0.51 (0–40–0.66)	16‡	0.62 (0.44–0.87)	176	0.1 ± 0.6	0.10 (0.05–0.22)
BG-12 t.i.d. (416)	0.19 (0.15–0.23)	52 (40-67)	26	0.50 (0.39–0.65)	18	0.66 (0.48–0.92)	84	0.5 ± 1.7	0.27 (0.15–0.46)
CONFIRM [25]									
Placebo (363)	0.40 (0.33–0.49)	–	41	–	17	–	167	2.0 ± 5.6	–
BG-12 b.i.d. (359)	0.22 (0.18–0.28)	44.0 (26.0–57.7)	29	0.66 (0.51–0.86)	13	0.79 (0.52–1.19)	169	0.5 ± 1.7	0.26 (0.15–0.46)
BG-12 t.i.d. (345)	0.20 (0.16–0.25)	50.5 (33.8–63.1)	24	0.55 (0.42–0.73)	13	0.76 (0.50–1.16)	170	0.4 ± 1.2	0.35 (0.20–0.59)
Glatiramer acetate (350)	0.29 (0.23–0.35)	28.6 (6.9–45.2)	32	0.71 (0.55–0.92)	16	0.93 (0.63–1.137)	175	0.7 ± 1.8	0.39 (0.24–0.65)

†MRI data only available for certain centers.
‡n = 409.
b.i.d.: Twice daily; t.i.d.: Three times daily.

in favor of BG-12 and significant effect was observed for two secondary outcomes (Independent Neurology Evaluation Committee confirmed relapses at the 240 mg t.i.d. dose level and for new/enlarging T2 enhanced lesions for both dose groups).

Subgroup analyses

With the rationale that MS is a heterogeneous condition and that patients have a wide range of baseline characteristics that might have an influence on the efficacy of treatment, an extensive subgroup analysis of DEFINE was carried out [27]. Analyses of the primary and secondary end points were prespecified for the following demographic subgroups: gender, age (<40 years or ≥40 years at baseline), inclusion in MRI cohort, region (USA; Western Europe, Canada, Australia, New Zealand, Israel, and South Africa; or Eastern Europe, India, Guatemala and Mexico), and baseline weight by quartile (≤58 kg, >58 to ≤68 kg, >68 to ≤81 kg, or > 81 kg). In addition, prespecified analyses were conducted for number of relapses in the preceding 12 months (≤1 or ≥2), baseline McDonald criteria (1 or 2–4), prior MS therapy, baseline EDSS score (≤2.0 or > 2.0), baseline T2 hyperintense lesion volume (≤median or >median, only for cohort with MRI data) and presence of baseline gadolinium-enhancing lesions (only for cohort with MRI data). An additional exploratory stratification by EDSS score ≤3.5 and >3.5 was also included in accordance with regulatory guidelines [28].

For all subgroups and both dose regimens, there was a numerical treatment effect in favor of BG-12 compared with placebo for proportion of patients with relapse at 2 years. These differences were statistically significant (upper 95% CI of hazard ratio < 1) in all cases except for age ≥ 40 years and EDSS > 3.5 for BG-12 t.i.d. and except for EDSS > 3.5 and baseline T2 lesion volume ≤ median for BG-12 b.i.d. When proportion of patients with disease progression was considered, a numerical treatment effect in favor of BG-12 t.i.d. compared with placebo was observed for all subgroups, although the differences were only statistically significant for age < 40 years, ≤1 relapse in 1 year, 1 McDonald criterion, no prior MS therapy, and baseline EDSS score ≤2.0 and ≤3.5. In the case of BG-12 b.i.d., there was a numerical treatment effect favoring BG-12 in all subgroups except baseline T2 lesion volume ≤median and absence of baseline gadolinium-enhancing lesions. Statistically significant differences compared with placebo were observed for the same subgroups as BG-12 t.i.d. Taken together, the results of these subgroup analyses suggest that BG-12

is effective in a wide variety of patients and are consistent with the subgroup analyses reported for the Phase IIb study [22]. Response to disease-modifying therapy has been suggested to be greater in younger patients [29], and the findings reported in this subgroup analysis would seem to support this in that the numerical treatment effect was greater in patients under 40 years both for proportion of patients with relapse at 2 years and proportion of patients with disease progression. However, a numerical treatment effect was also seen in patients with prior MS treatment and EDSS ≤3.5, so disease severity, rather than age itself, could be the important factor in determining response.

In further analyses of the pivotal studies, the efficacy observed overall is maintained for patients with newly diagnosed disease [30] and for those who have already received prior MS treatment [31], providing further evidence for the broad-ranging efficacy of BG-12.

Long-term efficacy

Long-term efficacy and safety data are of course important in a chronic disease like MS. In the case of BG-12, these data will be generated by a 5-year, long-term study (the ENDORSE study [32]). Patients who completed the pivotal Phase III studies as per protocol were offered the possibility of entering the study. Those on active treatment continued at the dose they had been assigned while patients receiving placebo crossed over to an active dose group. The preliminary results appear to be consistent with the 2 year placebo-controlled, blinded data [33]. The study is expected to be complete by the middle of 2016.

Health-related quality of life

Health-related quality of life (HRQoL) is a global concept that attempts to measure a patient's general well-being. Some symptoms of MS such as bodily pain and low vitality are not captured by disability end points such as the EDSS score [34]. These symptoms nevertheless may have an impact on quality of life and so it is important to gauge their impact through measurement of HRQoL. HRQoL also takes into account side effects and convenience of dosing, among other things.

Both pivotal studies included HRQoL outcomes as tertiary end points (measured using the Mental Component Summary [MCS] and Physical Component Summary [PCS] of the Short Form 36 Health Survey [SF-36]) and a measurement of the patients' global impression of well-being (Visual Analog Scale [VAS]). The results have been reported separately from the primary publication by Kappos *et al.* [35] (DEFINE) and Kita *et al.* [36] (CONFIRM).

In the DEFINE study, at 2 years, statistically significant improvements were observed for SF-36 PCS scores in both BG-12 dose groups compared with placebo ($p < 0.001$ for both) [35]. Likewise, improvements were seen in the SF-36 MCS scores, although the difference compared with placebo was only significant for the t.i.d. group ($p < 0.002$). There were also significant improvements compared with placebo in both BG-12 dose groups for mean VAS score ($p = 0.003$ for the b.i.d. group and $p < 0.001$ for the t.i.d. group).

In the case of the CONFIRM study, the SF-36 PCS score significantly improved compared with placebo for the BG-12 b.i.d. dose group ($p = 0.0217$) and the glatiramer acetate group ($p = 0.0259$) but only showed a trend towards improvement in the BG-12 t.i.d. dose group ($p = 0.0519$) [36]. Non-significant trends towards improvement were observed in both BG-12 dose groups for MCS scores. All arms showed a significant improvement in mean VAS scores ($p = 0.0003$ for the b.i.d. group, $p=0.0025$ for the t.i.d. group and $p<0.0001$ for glatiramer acetate). It should be noted that the glatiramer acetate group was unblinded and so the results for this agent should be interpreted with caution.

Taken together, the results of these studies further support the use of BG-12 in patients with RRMS. An additional Phase IV study (the PROTEC study [37]) is planned with HRQoL end points.

Comparative efficacy

The sharp increase in the number of MS therapies available makes it increasingly difficult for the neurologist to select the most appropriate therapy. This difficulty is compounded because very few head-to-head trials are available (in part because many of these new drugs have only very recently been approved), and when studies have been conducted, the comparator is usually an interferon [38,39]. In the case of BG-12, a glatiramer acetate treatment arm was included in the CONFIRM study, but as a reference arm and the study was not designed for a head-to-head comparison [2,25].

In an attempt to palliate the lack of knowledge of the relative efficacy of the new MS agents, Hutchinson *et al.* [40] performed a systematic review of the efficacy and safety of BG-12 and other disease-modifying therapies using a mixed treatment comparison approach, which in essence uses the results for the different placebo arms to leverage a comparison between the active arms of different trials. Their literature search identified 27 studies that were included in the quantitative analysis. In their comparison, they considered the b.i.d. regimen as this is the regimen licensed for BG-12 in the USA.

The efficacy results are summarized in Figures 3 and 4 of Hutchinson's paper [40]. A significantly greater

Table 3. Adverse events reported during Phase III studies.

Regimen (n)	Any AE (n; %)	Most frequently reported AEs†									AEs leading to discon. (n; %)	Death (n; %)	Any SAE (n; %)	SI (n; %)	Malignancies (n; %)
		Flushing (n; %)	Diarrhea (n; %)	Nausea (n; %)	URTI (n; %)	UAP (n; %)	Prot. (n; %)	Pruritus (n; %)	AP (n; %)	Vomiting (n; %)					
DEFINE [24]															
Placebo (408)	387 (95)	20 (5)	55 (14)	38 (9)	53 (13)	28 (7)	34 (8)	19 (5)	22 (5)	24 (6)	55 (13.5)	0 (0)	86 (21)	7 (2)	2 (<1)
BG-12 b.i.d. (410)	395 (96.3)	154 (38)	65 (15.9)	53 (13)	63 (15)	40 (10)	38 (9)	42 (10)	46 (11)	40 (10)	1 (0.2)	74 (18.0)	111 (27.1)	10 (2)	2 (<1)
BG-12 t.i.d. (416)	396 (95.2)	132 (32)	78 (18.8)	54 (13)	51 (12)	52 (12)	50 (12)	34 (8)	37 (9)	30 (7)	68 (16.3)	1 (0.2)	65 (15.6)	8 (2)	2 (<1)
CONFIRM [25]															
Placebo (363)	333 (91.7)	13 (4)	28 (7.7)	29 (8)	34 (9)	17 (5)	25 (7)	11 (3)	15 (4)	13 (4)	38 (10.5)	1 (0.3)	79 (21.8)	5 (1)	1 (<1)
BG-12 b.i.d. (359)	338 (94.2)	110 (31)	45 (12.5)	40 (11)	36 (10)	36 (10)	29 (8)	20 (6)	27 (8)	25 (7)	44 (12.3)	0 (%)	61 (17.0)	7 (2)	0
BG-12 t.i.d. (344)‡	316 (91.9)	83 (24)	50 (14.5)	51 (15)	47 (14)	33 (10)	35 (10)	24 (7)	26 (8)	23 (7)	41 (11.9)	1 (0.3)	54 (15.7)	7 (2)	0
Glatiramer acetate (351)‡	304 (86.6)	6 (2)	14 (4.0)	15 (4)	27 (8)	4 (1)	30 (9)	7 (2)	4 (1)	8 (2)	35 (10.0)	1 (0.3)	60 (17.1)	4 (1)	4 (1)
DEFINE [24] **and CONFIRM** [25]															
Total BG-12 treated	1445 (95)	479 (31)	235 (15)	198 (13)	197 (13)	161 (11)	152 (10)	120 (8)	136 (9)	118 (8)	218 (14)	3 (<1)	254 (17)	32 (2)	4 (<1)

Reported in ≥10% of patients and with an incidence ≥3% higher in any BG-12 group compared with placebo in either study.

One patient assigned to BG-12 t.i.d. was treated with glatiramer acetate throughout the study.

AE: Adverse event; AP: Abdominal pain; b.i.d.: Twice daily; Discon.: Discontinuation; Prot.: Proteinuria; SAE: Serious adverse event; SI: Serious infection; t.i.d.: Three times daily; UAP: Upper abdominal pain; URTI: Upper respiratory tract infection.

Data taken from [44].

treatment effect on relapses was found for BG-12 compared with pooled interferons, glatiramer acetate 20 mg, and teriflunomide (7 and 14 mg). A numerically greater treatment effect was observed for fingolimod versus BG-12 (not significant) and a significantly greater treatment effect was observed for natalizumab versus BG-12. In the case of prevention of sustained disease progression, there was a numerical treatment effect in favor of BG-12 versus pooled interferons, glatiramer acetate, teriflunomide (both doses) and fingolimod, though the differences were not significant. In the comparison with natalizumab, there was a slightly greater, non-significant, treatment effect in favor of this drug versus BG-12.

The authors also investigated safety, and found that abdominal pain (5.1%), diarrhea (7.6%) and flushing (20.0%) were reported with ≥5% greater annual incidence among BG-12 treated patients compared with comparator-treated patients. In contrast, adverse events (AEs) with a 5% higher annual incidence among patients treated with at least one comparator were flu-like symptoms, headache, fatigue, depression, influenza, increased alanine transaminase, leukopenia and lower respiratory tract infection. These differences in AEs do not reflect the whole safety picture, given that treatments may be associated with low incidences of AEs that are nevertheless serious or sometimes fatal. This is the case with progressive multifocal leukoencephalopathy with natalizumab [41], cardiac events with fingolimod [42], or autoimmune disorders with alemtuzumab (Table 3) [43].

Clearly, there are limitations with this type of analysis. Many of the studies are not heterogeneous in terms of study conduct, patient population and end points. A covariate analysis was performed to investigate the robustness of the findings. 'Publication year' (two of the studies were conducted more than 20 years previously) and 'relapse in prior 1 year' were found to be significant covariates for relapse rate in both the univariate and bivariate analyses. Despite the caveats, the findings may provide interesting indicators of comparative efficacy while we await the results of head-to-head trials.

Potential safety issues

In the case of BG-12, data are available from the clinical development program, which included more than 2600 patients treated for up to 4 years. An integrated analysis of the placebo-controlled studies presented recently at the 29th Congress of the European Committee for Treatment and Research in MS showed that although a greater percentage of BG-12 patients with grade 3 or 4 lymphopenia was observed compared with placebo, lymphopenia was not clearly associated with an overall increased risk of infections, serious infections, or opportunistic infections [45]. Overall, there was no evidence of an increased risk of serious infections or opportunistic infections among patients on active treatment. The US labeling thus recommends that patients should be monitored for lymphopenia [46].

Besides lymphopenia, the only other warning and precaution included in the US prescribing information is the possibility of flushing [46]. This is a well-known side effect of the drug. In general, the onset of flushing starts soon after administration and is usually mild or moderate in intensity and resolves over time without further intervention. Administration of BG-12 with food may reduce the incidence of flushing by reducing the C_{max} (but not AUC) of the active metabolite. In the clinical studies with BG-12, 3% of patients discontinued due to flushing. An integrated analysis of data from the two Phase III studies suggested that flushing was generally mild to moderate in intensity and occurred largely early on during treatment (in the first month) and rarely led to discontinuation of treatment [47]. Although not mentioned in the US prescribing information, gastrointestinal events such as abdominal pain, nausea/vomiting and diarrhea were also a frequently reported adverse event associated with BG-12 treatment. As for flushing, these events were generally mild or moderate, occurred early on in the course of treatment, and rarely led to discontinuation. Many patients took symptomatic treatment to alleviate the discomfort of these events.

The renal toxicity observed in the toxicology program has not been reflected in the clinical findings to date.

Outlook for BG-12

For many years, the interferons and glatiramer acetate were the only available therapies for RRMS. Their efficacy is modest [2,7], but neurologists are generally very familiar with these therapies and their potential side effects. The approval of natalizumab in 2006 and the steady approval of other new agents since then have changed the landscape of MS therapy. This exciting new era has also brought with it uncertainty as very few head-to-head trials are available and long-term data are still being generated (by the ENDORSE study in the case of BG-12). Likewise, as yet we still have very limited data from observational studies, which provide an indication of how a therapy performs in the real world, away from the carefully controlled environment of a clinical trial.

One setting in which BG-12 may be used is after switching from first (interferon-β, glatiramer acetate, teriflunomide) or second-line treatment (fingolimod, natalizumab, mitoxantrone). Natalizumab is a highly effective therapy but seroconversion to JC virus-positive may necessitate discontinuation of this therapy and so the question of which disease-modifying therapy to administer after natalizumab discontinuation is one that neurologists are likely to have to face [48]. The results of

a study of a switch from natalizumab to fingolimod have already been published [49]. Study IIT6 [50] is an investigator initiated, observational study of disease stability after a switch to BG-12 from natalizumab. Lack of efficacy may also be the driver for a switch from first-line treatment. Another observational study, the RESPOND study [51] is currently recruiting patients to assess the effect of a switch to BG-12 on patients with suboptimal response to glatiramer acetate.

Unlike many other new agents such as fingolimod and alemtuzumab, BG-12 is also indicated as first-line treatment regardless of disease activity given its good safety profile and lack of onerous follow-up (for progressive multifocal leukoencephalopathy with natalizumab, autoimmune disorders with alemtuzumab and cardiac conditions with fingolimod). Given the potency of BG-12, many neurologists will surely be tempted to turn to BG-12 from the outset, particularly if the long-term data being generated by the ENDORSE study prove encouraging.

A further attractive feature of BG-12 is the oral route of administration. Oral administration may help improve patient adherence [52], which is an important consideration in any chronic treatment. A planned observational study (PROTEC [37]) has included patient reported adherence among the secondary end points and so should provide further data on this point. In short, BG-12 looks set to be an extremely valuable treatment option for a wide variety of patients with RRMS.

Acknowledgement

Biogen Idec reviewed the final manuscript prior to publication.

Financial & competing interests disclosure

Ó Fernández has received honoraria as consultant in advisory boards, and as chairmen or lecturer in meetings, and has also participated or participates at present in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering, Merck-Serono, Teva, Novartis, Actelion, Almirall and Allergan. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Executive summary

- BG-12 is formulated as gelatin capsules containing slow release granules providing convenient, twice daily, oral dosing for patients with relapsing–remitting multiple sclerosis (RRMS). The oral route of administration may help improve treatment adherence compared with therapies requiring frequent parenteral dosing.
- The high efficacy of BG-12 was demonstrated in 2 pivotal Phase III trials (DEFINE and CONFIRM), with statistically significant improvements compared with placebo in relapse rates and, in the case of the DEFINE study, in disability progression.
- A lack of head-to-head trials limits any statements about the comparative efficacy of BG-12 with respect to other new therapies for RRMS. Nevertheless, a mixed treatment comparison suggests that BG-12 is at least as efficacious as most other new therapies.
- In the BG-12 clinical development program, over 2600 patients were treated with the drug. 6 months after the launch of the drug in the USA, more than 35,000 patients have been dosed globally in clinical practice, clinical trials and free drug patients. To date, no major safety issues have been identified. The good safety profile of BG-12 may help distinguish it from other new therapies for RRMS.

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