BG-12 in Multiple Sclerosis

J. Theodore Phillips, MD, PhD[1] Robert J. Fox, MD[2]

[1] Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, Texas
[2] Department of Neurology and Neurological Institute, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, Ohio

Address for correspondence J. Theodore Phillips, MD, PhD, Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, TX 75204 (e mail: ted.phillips@baylorhealth.edu).

Semin Neurol 2013;33:56 65.

Abstract

Dimethyl fumarate (DMF) is an orally administered agent that has been used for over 40 years for the treatment of psoriasis. Recent work demonstrates both DMF immunomodulatory and neuroprotective actions in vitro and in animal models of autoreactive central nervous system inflammation and neurodegeneration. DMF acts through chemical modification of the repressor protein Keap1, allowing stabilization and nuclear translocation of the transcription factor Nrf2, with subsequent downstream activation of a cascade of several cytoprotective and antioxidant pathways. Additionally, suppression of transcription factor NF-κB-mediated proinflammatory signaling results in the inhibition of proinflammatory responses and induction of anti-inflammatory cytokines. BG-12 is an orally administered, enteric-coated microtablet preparation of DMF. In two phase III, relapsing-remitting multiple sclerosis (MS) trials, BG-12 led to a 44 to 53% reduction in annualized relapse rate and a 71 to 85% reduction in new T2 lesions on magnetic resonance imaging. The most common side effects of BG-12 are cutaneous flushing and gastrointestinal symptoms, with the highest incidence in the first month after starting treatment. No serious safety signals were seen during the phase II and III trials, including no increased risk of opportunistic infections or cancer. Altogether, BG-12's novel mechanism of action appears to provide a favorable balance of efficacy, safety, and tolerability for treatment of relapsing MS.

Keywords
- multiple sclerosis
- BG-12
- dimethyl fumarate
- fumaric acids
- NF-E2-related factor 2

For almost 20 years, disease-modifying therapies have been available for treatment of relapsing forms of multiple sclerosis (MS). The current standard, first-line therapies for MS are interferon beta 1 (IFNβ 1; Avonex, Biogen Idec, Weston, Massachusetts; Betaseron/Betaferon, Bayer HealthCare, Leverkeusen, Germany; Extavia, Novartis, Basel, Switzerland; Rebif, EMD Serono, Inc., Rockland, Massachusetts) and glatiramer acetate (GA; Copaxone, Teva Pharmaceuticals, Petah Tikva, Israel). Phase III clinical trials found each to reduce the rate of clinical relapses by approximately 30% relative to placebo.[1 4] Side effects include skin reactions (predominantly subcutaneous therapies) and flu-like side effects and hepatic irritation (IFNβ 1 therapies). A distinct advantage of these therapies is their excellent long-term safety and reasonable tolerability, although their efficacy is modest and all are administered by injection (subcutaneous or intramuscular).

Recently, three additional therapies have emerged as important long-term disease-modifying therapies for relapsing MS. Natalizumab (Tysabri, Biogen Idec, Weston, Massachusetts) is a monoclonal antibody that inhibits leukocyte trafficking into the central nervous system (CNS). Natalizumab has excellent efficacy in reducing clinical relapses, new brain lesions on magnetic resonance imaging (MRI), and delaying sustained progression of disability.[5,6] Two drawbacks of natalizumab include its monthly intravenous administration and its association with progressive multifocal leukoencephalopathy (PML), a potentially fatal CNS infection.[7] Fingolimod (Gilenya, Novartis, Basel, Switzerland), a second contemporary therapy, is a sphingosine receptor

Issue Theme Current and Emerging Therapies for Multiple Sclerosis; Guest Editor, B. Mark Keegan, MD, FRCP(C)

DOI http://dx.doi.org/10.1055/s 0033 1343796. ISSN 0271 8235.

modulator that both reduces leukocyte egress from peripheral lymphoid tissue and may have direct immunomodulating effects within the CNS.[8] Fingolimod shows beneficial relapse, disability progression and MRI effects. A head-to-head study showed fingolimod is more effective than IFNβ 1.[9] However, fingolimod is associated with cardiac side effects (mostly initial bradycardia events), macular edema, and increased risk of some infections (most notably respiratory infections and herpes virus infections). A third therapy, teriflunomide (Aubagio, Genzyme, Cambridge, Massachusetts) has been recently approved for relapsing MS in the United States. Teriflunomide inhibits new pyrimidine synthesis and rapid proliferation of activated lymphocytes through its action on dihydroorotate dehydrogenase.[10] Teriflunomide shows beneficial relapse, disability progression, and MRI effects. Gastrointestinal disturbances, hair thinning, and mild-moderate elevations in alanine aminotransferase levels have been noted more commonly with teriflunomide than placebo. Based on animal studies, the U.S. Food and Drug Administration (FDA) has also issued an alert concerning possible teratogenic effects in humans.[11]

Despite the availability of many disease-modifying therapies for relapsing MS, none have the ideal treatment triad: strong efficacy, good tolerability, and excellent safety. The BG-12 preparation of dimethyl fumarate (DMF) may come closer to offering that ideal treatment triad.

Initial Clinical Experience with Fumaric Acids

Fumaric acid (FA) is an intermediate in the citric acid cycle used by cells to produce energy. In 1946, food chemists recognized its acid regulatory properties and fruit-like taste. FA is still routinely used as a food acidulent in beverages, baking powders, and candy (**Table 1**).

The medicinal use of fumaric acids (FA) is credited to German chemist Walter Schweckendiek, who suffered from psoriasis. In the late 1950s, Schweckendiek turned to his professional expertise in chemistry to search for treatments for his skin condition. He proposed that psoriasis resulted from a defect in carbohydrate metabolism involving the citric acid cycle and its oxidative steps, and predicted improvement through ingestion of FA.[12] However, his first treatment attempts with oral FA were disappointing owing to significant gastrointestinal irritation. To improve gastrointestinal absorption and tolerability, Schweckendiek[13] synthesized a mixture of FA ester (FAE) salts that did prove effective in treating his psoriasis, and also demonstrated less irritant side effects. Gunther Schafer, a general practitioner, later promoted a standardized treatment regimen using an FAE mixture and restricted diet, and subsequently reported encouraging open-label results with over 70% of 900 psoriasis patients showing improvement.[14] Despite the lack of data supporting the metabolic defect hypothesis, efficacy and safety of FAE in psoriasis were subsequently demonstrated in two randomized, double-blinded, placebo-controlled studies.[15,16] These studies were performed using a proprietary preparation of FAE (120 mg dimethyl fumarate [DMF], 87 mg monoethyl fumarate calcium salt, 5 mg monoethyl fumarate magnesium salt, and 3 mg monoethyl fumarate zinc salt per enteric-coated tablet). In 1994, the Swiss company Fumapharm (acquired by Biogen Idec, Weston, Massachusetts) received German regulatory approval for this FAE preparation (called Fumaderm) for the treatment of psoriasis. Fumaderm is currently one of the most widely prescribed systemic therapies for psoriasis in Germany, with visible improvement typically noted within 6 weeks. Fumaderm is generally well tolerated; cutaneous flushing and gastrointestinal upset are the most commonly reported side effects. A small study has

Table 1 Timeline of development of BG-12/DMF in multiple sclerosis

1946: Fumaric acids are recognized by food chemists for their acid regulatory properties and fruit-like taste.
1960s–1980s: German chemist Walter Schweckendiek and general practitioner Gunther Schafer develop fumaric acid ester-based regimen to treat psoriasis.[12,14]
1994: The Swiss company Fumapharm receives German regulatory approval for Fumaderm, which is a proprietary formulation of dimethyl fumarate and several fumarate ester salts.
~ 2000: Bochum neurologist Horst Przuntek observes that MS patients with psoriasis appear to have stabilized MS after starting Fumaderm.
2002: A patent is filed for the use of fumaric acids in the treatment of MS.
2003: Fumapharm establishes collaboration with Biogen Idec to develop fumaric acids in MS.
2006: Schilling and colleagues show DMF or MMF effectively prevents chronic EAE.[24]
2006: Schimrigk and colleagues publish a case series of 10 MS patients treated with Fumaderm.[51]
2007: A placebo-controlled phase II trial shows a robust reduction in MRI lesions with BG-12,[70] and two phase III trials in relapsing remitting MS get underway.[52,53]
2011: Linker and colleagues demonstrate fumaric acid esters activate the Nrf-2 antioxidant pathway and exert neuroprotective effects in EAE-associated neuroinflammation.[25]
2011–2012: Both phase III trials report positive results on clinical and MRI outcomes.[52,53]

Abbreviations: DMF, dimethyl fumarate; EAE, experimental autoimmune encephalomyelitis; MMF, monomethyl fumarate; MRI, magnetic resonance imaging; MS, multiple sclerosis.

found acceptable long-term safety in psoriasis patients treated for 10 to 14 years.[17]

DMF Mechanisms of Action

Pharmacokinetics

Comparative studies have shown that DMF ($C_6H_8O_4$; MW 141.1) is the key FAE component accounting for therapeutic benefit in psoriasis.[18] DMF is rapidly hydrolyzed to monomethyl fumarate (MMF; also known as MHF, methylhydrogen fumarate) by esterases in the alkaline environment of the small intestine.[19] In healthy volunteers and psoriasis patients, time to detectable MMF in blood is somewhat delayed with food intake, but without effect on maximum blood concentration 5 to 6 hours later.[20] Plasma FA levels remain unchanged by FAE ingestion. MMF is detectable in blood after a variable period of 60 minutes or more, whereas DMF is subject to a strong first-pass metabolism and is not systemically detectable at any time after oral DMF ingestion.[20,21] MMF is further metabolized (50% protein-bound; serum half-life 36 h[22]) in the citric acid cycle to yield water and carbon dioxide. DMF is highly lipophilic and may be absorbed by intestinal tissue, where it is at least partially metabolized to MMF. DMF can also conjugate directly to intracellular glutathione and be released systemically as a (possibly bioactive) glutathione conjugate, which is further metabolized to DMF-mercapturic acid and detectable in urine.[23] Additionally, DMF may also be released unaltered into the portal circulation and taken into venous blood cells, or hydrolyzed to MMF in the plasma. These scenarios suggest that DMF could still have biologically relevant activities in vivo (in addition to MMF) despite undetectable free-plasma DMF after ingestion. A small amount of unaltered MMF is excreted in urine and feces. FAEs do not appear to be nephrotoxic. Cytochrome p450-dependent pathways are not involved in FAE metabolism, and drug interactions have not been reported.

In Vivo Effects of DMF and Experimental Models of Demyelination and Neurodegeneration

Efficacy of FAEs in the prevention of myelin-oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) in mice was first identified in 2006.[24] MOG-EAE is an animal model of inflammatory demyelination that also displays features resembling several neurodegenerative aspects of MS. Either DMF or MMF given preventatively in acute MOG-EAE led to decreased CNS inflammatory infiltrates and increased serum interleukin-10 (IL-10; an anti-inflammatory cytokine). Linker and colleagues later confirmed the preventative effects of DMF given during the acute phase of MOG-EAE, and extended these findings to demonstrate a therapeutic effect in established, chronic MOG-EAE.[25] However, in contrast to findings in acute phase EAE, DMF did not significantly decrease inflammatory infiltrates when administered during the chronic phase of MOG-EAE. Interestingly, clinical benefit in this model appeared to result primarily from reduction in demyelination with relative preservation of myelin and axons. This interesting, but unexpected, outcome was suggested to reflect the rescue of neurons and glial (astrocytes) cells from oxidative stress-induced cell death through neuroprotection that is mediated by DMF-induced activation of the nuclear factor-(erythroid-derived 2-) related factor-2 (Nrf2) pathway. Similarly, other studies have now also demonstrated DMF-induced, Nrf2-dependent cytoprotection of neurons and astrocytes.[26–28]

Evidence of oxidative stress is readily apparent within the CNS in EAE and MS.[29–31] Glutathione, a major intracellular reactive oxygen species (ROS) scavenger, is decreased within CNS inflammatory foci,[32] and a variety of antioxidant proteins, including Nrf2, are increased in MS lesions.[33] The importance of the Nrf2 pathway in regulating CNS inflammation is emphasized by the observation of significantly worsened EAE in Nrf2 (/) knockout mice.[25,34] Also, DMF neuroprotective effects are not inducible in Nrf2 (/) mice.

The effects of DMF or MMF have also been examined in other models of demyelination and neurodegeneration. In the cuprizone model of toxic, noninflammatory demyelination, DMF or MMF demonstrated minimal or no significant impact on demyelination or remyelination.[35] In contrast to EAE, no obvious protective effects of DMF or MMF on CNS cellular elements were found in this model. However, in an experimental model of neurodegeneration with similarities to Huntington's disease, the transgenic mouse strains R6/2 and YAC128 showed preservation of striatal and motor cortex neurons and improved short- and long-term motor outcomes with DMF treatment.[36] Apparent DMF-associated neuroprotection has also been observed in a rat model of excitotoxic neurodegeneration induced by intrastriatal malonate injection.[37] In this model, DMF treatment resulted in reduction of striatal lesion volume and improved abnormal apomorphine-induced rotational behavior compared with vehicle controls.

DMF Effects on the Immune System

After dismissal of the initial citric acid cycle defect hypothesis, early explanations of FAE therapeutic effects focused on the proinflammatory T-cell (Th1) theory of certain autoimmune disorders, including psoriasis[38] and MS.[39] In addition to antiproliferative effects on keratinocytes,[40] FAEs were found to have direct effects on multiple components of the immune system. MMF induces anti-inflammatory cytokines IL-4, IL-5, IL-10, and IL-1RA production by human peripheral blood mononuclear cells, without stimulation of proinflammatory cytokines IL-2, interferon gamma (IFNγ), or IL-12.[41–43] Other studies found that DMF or MMF may decrease production of IFNγ and IL-12,[44] as well as decrease expression of cytokine-induced endothelial cell adhesion molecules ICAM-1, VCAM-1, and E-selectin.[45] In vitro differentiation of antigen-presenting, monocyte-derived dendritic cells (mDCs) is inhibited by DMF or MMF, resulting in decreased mDC production of IL-6, IL-10, IL-12, TNFα, and decreased T-cell production of proinflammatory IFNγ and IL-17.[46–49]

DMF, but not MMF, may induce apoptosis in cultured mDCs and activated T cells.[50] Possibly related, a transient 4% increase in CD4+ T cell apoptosis was reported in Fumaderm-treated RRMS patients during the first 12 weeks of therapy.[51] Apoptosis may therefore explain in part the mild decrease in circulating

lymphocyte count observed in psoriasis[16] and MS[52,53] patients treated with Fumaderm or BG-12, respectively.

Subcellular Mechanisms of Action

Twenty years ago, a systematic study of different compounds capable of inducing phase II detoxifying enzymes (e.g., NAD (P)H quinone oxidoreductase-1; NQO1) identified DMF, among others, to be highly effective.[54] A common structural feature among these inducing compounds is that of a so-called Michael acceptor, which reflects the compound's relatively electrophilic nature. As such, DMF and several other Michael acceptor compounds were shown to activate an electrophile-responsive element (EpRE) located in the 5′ flanking region of the mouse glutathione S-transferase Ya subunit gene.[55] EpRE is also known, perhaps more commonly, as ARE (antioxidant-responsive element).[56,57]

Further work showed that the effect of DMF and MMF on ARE/EpRE is actually indirect. Under normal conditions, ARE/EpRE is not active; however, under cellular stress conditions, Nrf2 activates ARE/EpRE.[58] Nrf2 is normally not available for downstream regulatory interactions as it is targeted for rapid ubiquitin E3 ligase–(Cul3-) directed proteasomal degradation through its usual bound interaction with the cytosolic repressor Keap1 (Kelch-like ECH-associated protein 1). DMF or MMF S-alkylates Cys151 of cysteine-rich Keap1, thereby blocking the interaction of Keap1 and Nrf2, which prevents Nrf2 ubiquitination and leads to Nrf2 stabilization, phosphorylation, nuclear translocation, and subsequent Nrf2 nuclear activation of ARE/EpRE.[59] Therefore, Keap1 can be considered a critical intracellular redox sensor; therefore, it is sensitive to inorganic and organic hydroperoxides, peroxynitrite, and other electrophilic molecular species generated by oxidative stress and tissue damage.[60] ARE/EpRE activation results in an increase in synthesis of many antioxidation-related proteins such as NQO1, heme oxygenase-1 (HO-1), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM), peroxiredoxin-1 (Prx1), glutathione S-transferase Mu-1 (GSTM1), thioredoxin (Trx), thioredoxin reductase (TrxR), and various heat shock proteins.[60] ARE/EpRE activation also enhances other prosurvival processes such as phase II detoxification, nucleotide excision repair, and autophagy inhibition. Nrf2 signaling is ultimately terminated through a combination of Nrf2 nuclear export processes dependent on Fyn-mediated Nrf2 phosphorylation, as well as removal of Nrf2-activating signals through the action of the induced antioxidant enzymes.[60]

DMF and MMF also enhance glutathione synthesis through the Nrf2 signaling pathway, despite initial reduction of intracellular glutathione stores through direct reaction with glutathione.[26,28,61,64] Importantly, initial glutathione reduction in mDCs results in preferential induction of type II mDCs promoting Th2 differentiation, and also blocks STAT1 phosphorylation, thereby reducing proinflammatory mDC IL-12 production.[49]

NF-kB, a key redox-sensitive, proinflammatory nuclear transcription factor, is inhibited by DMF or MMF through Nrf2-mediated induction of phase II antioxidants, with subsequent reduction of intracellular ROS accumulation in immune-activated cells, and inhibition of NF-kB upstream signal mediators Akt, NIK, and IKK.[60,65] Through these indirect inhibitory actions of DMF and MMF on NF-kB, proinflammatory gene expression is suppressed. DMF also inhibits NF-kB activity through suppression of ERK1/2 and downstream MSK1 kinase activities, and subsequent reduction of p65 (RelA) phosphorylation, nuclear translocation, and target gene transactivation.[48,66] In addition, recent work suggests that DMF may be capable of suppressing inflammation through one or more Nrf2-independent pathways.[67]

MMF, but not DMF, also competitively binds and activates the high-affinity nicotinic acid (NA) receptor GPR109A, with subsequent production of prostanoids.[68] This interaction appears to account for commonly encountered MMF- (and NA-) induced cutaneous flushing. COX-1 and COX-2 inhibitors were found to decrease early- and late-phase flushing, respectively, which prompted a recent successful study with aspirin to lessen flushing after DMF ingestion.[69]

Summary of DMF Mechanisms of Action

DMF is a small electrophilic molecule that is rapidly converted in the gut to MMF, its major bioactive metabolite. MMF alkylates the intracellular redox sensor Keap1, resulting in stabilization and nuclear translocation of Nrf2, which in turn activates the gene regulatory element ARE/EpRE with subsequent downstream induction of a variety of antioxidant and cytoprotective proteins. Through reduction of intracellular ROS by several of these induced phase II proteins, proinflammatory activities of NF-kB are reduced. DMF direct effects on lymphocytes and dendritic cells induce Nrf2-related pathways, inhibit proinflammatory cytokine production, and promote a shift from Th1 (and Th17) to Th2-like immune activities. Other non-Nrf2 mediated pathways may be involved in DMF anti-inflammatory effects as well. DMF direct effects on neurons and glia (primarily astrocytes) induce Nrf2-related pathways that promote neuroprotection and cell survival. Therefore, DMF-associated net beneficial effects in MS are expected to result from combined anti-inflammatory and neuroprotective actions.

Early Studies of BG-12 in Multiple Sclerosis

The idea of using FAEs therapeutically in MS was reportedly born in the late 1990s at St. Josef Hospital, Ruhr University, Bochum, Germany, when neurology chair Horst Przuntek noticed that the disease course of two of his MS patients appeared to stabilize after they started treatment of their concomitant psoriasis with Fumaderm [R. Gold, personal communication, 2012]. His colleague Sebastian Schimrigk then conducted an open-label, phase I trial of Fumaderm in 19 MS patients, which found a 95% reduction in number of gadolinium-enhancing (Gd+) lesions over 48 weeks.[51]

Gastrointestinal side effects from Fumaderm led to its further refinement into BG-12, which is an enteric-coated, microtablet preparation of DMF. A U.S. patent was filed in 2002 for the use of FAE in the treatment of MS, and a formal collaboration with between Fumapharm and Biogen Idec was established in October 2003.

Subsequently, a 48-week, 257 patient phase IIb clinical trial in relapsing-remitting MS was conducted (ClinicalTrials.gov identifier: NCT00168701). Participants were randomized to three different doses of BG-12 (120 mg daily, or 120 mg three times daily [360 mg/d], or 240 mg three times daily [720 mg/d]) or placebo for 24 weeks, followed by a 24-week dose-blinded safety extension (placebo switched to BG-12 240 mg three times daily).[70] The primary outcome was its effect on new Gd+ lesions, where the highest dose of BG-12 showed a 69% reduction ($p < 0.0001$) in lesion number compared with placebo. The middle dose group (120 mg three times daily) did not show a significant reduction in lesions, but was probably handicapped by a 56% higher baseline MRI disease activity relative to the placebo group. When the primary outcome is instead expressed as the within-group reduction in MRI disease activity compared with each group's prestudy baseline, a consistent dose response is observed: 29%, 41%, 69%, and 73% lesion reduction in the placebo, 120 mg/d, 360 mg/d, and 720 mg/d groups, respectively. BG-12 was tolerated relatively well, with 91% of patients completing the fully blinded first 24 weeks, and 97% completing the dose-blinded, 24-week safety extension. As seen with Fumaderm, the most common BG-12 associated adverse effects were skin flushing and gastrointestinal events.

Phase III Trials of BG-12 in Multiple Sclerosis

Based upon these encouraging phase II trial results, two phase III trials were conducted: Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (DEFINE; ClinicalTrials.gov identifier: NCT00420212)[53] and Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (CONFIRM; ClinicalTrials.gov identifier: NCT00451451).[52] Both DEFINE and CONFIRM were 2-year, randomized, placebo-controlled trials, evaluating clinical relapses, progressive disability, and (in a subset of patients) MRI disease activity. Two doses of BG-12 were evaluated—240 mg three times per day (720 mg/d), and 240 mg twice a day (480 mg/d with placebo given for the midday dose)—and were compared with placebo given three times per day. The CONFIRM trial also included glatiramer acetate (GA) as an open-label (but still randomized and evaluator-blinded) treatment arm, as required by the European Medicines Agency, to provide a risk–benefit comparison to a standard therapy. Because of potential partial treatment unblinding due to skin flushing and gastrointestinal side effects, several steps were taken to ensure study validity: blinded examining neurologists were unaware of either treatment assignment (oral therapy vs. GA) or patient; patients were instructed to not take study medication within 4 hours of each study visit to reduce potential unblinding of study investigators; an independent, blinded adjudication committee confirmed all relapses; and image analysis was conducted blinded to all study information. Enrollments of DEFINE and CONFIRM studies started in 2007, and the last patient completed follow-up in 2011. The DEFINE study enrolled and dosed 1,234 patients; the CONFIRM study enrolled and dosed 1,417 (including the additional GA arm). Both studies enrolled patients from North and Central America, Europe, and Asia. Of note, these trials were one of the first to enroll MS patients in India. Seventy-seven percent of the study participants in the DEFINE study completed the study (68% on originally assigned study medication), and 80% of the study patients in the CONFIRM study completed the study (71% on originally assigned study medication).

Efficacy

In the DEFINE and CONFIRM studies, both dosing regimens of BG-12 reduced the annualized relapse rate (ARR; the primary outcome in the CONFIRM study) by 44 to 53% ($p < 0.001$ for all; ←**Table 2**).[52,53] Various sensitivity analyses in both studies showed consistent results. Similarly, the risk of relapse (the primary outcome in the DEFINE study) was also reduced by 34 to 50% in both dosing regimens ($p < 0.001$; ←**Table 2**). BG-12 reduced the risk of sustained progression of disability by 34 to 38% in the DEFINE study ($p < 0.05$), and 21 to 24% in the CONFIRM study, which was not significant. In the CONFIRM

Table 2 Key outcomes in BG-12 phase III studies

Reduction in:	Define[53]		Confirm[52]		GA (%)
	bid (%)	tid (%)	bid (%)	tid (%)	
Annualized relapse rate	53[a]	48[a]	44[a]	51[a]	29[b]
Risk of relapse	49[a]	50[a]	34[b]	45[a]	29[b]
Risk of sustained progression of disability	38[b]	34[c]	21[d]	24[d]	7[d]
New or enlarging T2 lesions	85[a]	74[a]	71[a]	73[a]	54[a]
New T1-hypointense lesions	72[a]	63[a]	57[a]	65[a]	41[b]
New gadolinium-enhancing lesions	90[a]	73[a]	74[a]	65[a]	61[a]

Abbreviations: BID, twice daily dosing; GA, glatiramer acetate; TID, three times daily dosing.
Note: Main clinical and MRI outcomes from the DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing Remitting Multiple Sclerosis) and CONFIRM (Comparator and an Oral Fumarate in Relapsing Remitting Multiple Sclerosis) phase III clinical trials.
[a] $p < 0.001$.
[b] $p \leq 0.01$.
[c] $p < 0.05$.
[d] Not significant.

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