BG00012 – A Novel Oral Therapy in Development for the Treatment of Multiple Sclerosis

a report by

Robert J Fox

Staff Neurologist and Medical Director, Mellen Center for Multiple Sclerosis, Cleveland Clinic

DOI:10.17925/ENR.2008.03.01.99

Multiple sclerosis (MS) is an inflammatory disease of the brain and spinal cord characterised by focal areas of demyelination and neuronal destruction. Historically, disease-modifying therapies used to treat MS have been administered by injection, exerting their effects through generalised immunomodulatory and anti-inflammatory mechanisms.[1] These injection therapies are only moderately effective in reducing relapses and disability progression,[2–5] and many patients discontinue therapy due to tolerability concerns, fear and/or inconvenience of frequent injections.[6,7] Thus, there is an unmet medical need in MS for safe and effective oral therapies with novel mechanisms of action.

Similar to MS, psoriasis is an autoimmune-mediated disorder. Fumaric acid esters (FAEs) have been used for the treatment of psoriasis in Europe for over 20 years, and a formulation of FAEs – dimethyl fumarate and ethylhydrogen fumarate (Fumaderm®) – has been approved for the treatment of severe chronic plaque psoriasis in Germany since 1994.[8–12] BG00012 is an oral formulation of dimethyl fumarate that may exert a combination of anti-inflammatory and neuroprotective biological effects. Pilot and phase II clinical studies of Fumaderm and BG00012, respectively, in patients with MS have shown positive results, and BG00012 holds promise to be one of the first oral therapies available for the treatment of relapsing MS.

This article discusses the potential mechanisms of action of BG00012 and reviews the available clinical data of its efficacy and safety in patients with MS. In addition, two phase III clinical trials of BG00012 in patients with relapsing–remitting MS that are currently recruiting patients are described.

Potential Mechanisms of Action in Multiple Sclerosis

MS is an autoimmune-mediated disorder characterised by inflammation, destruction of myelin, loss of oligodendrocytes, axonal damage and subsequent neuronal loss in the central nervous system (CNS).[13–16] Although the pathogenesis of MS is not completely understood, blood–brain barrier (BBB) breakdown has been postulated as an early event in the disease process.[17] It is believed that interactions between adhesion molecules on activated leukocytes and their complementary receptors on endothelial cells of the vessel wall promote leukocyte migration across the BBB.[18] In the CNS, immune cells initiate a series of events that lead to upregulation of the expression of endothelial adhesion molecules, recruitment of additional lymphocytes and monocytes and production of inflammatory cytokines.[19,20] In addition, there is accumulating scientific evidence that oxidative stress may play a major role in the neuronal damage that occurs in MS.[21] For example, activated macrophages and microglial cells may degrade myelin and damage oligodendrocytes by generating oxygen or nitrogen free radicals, producing excitatory amino acids and releasing proteolytic and lipolytic enzymes.[22]

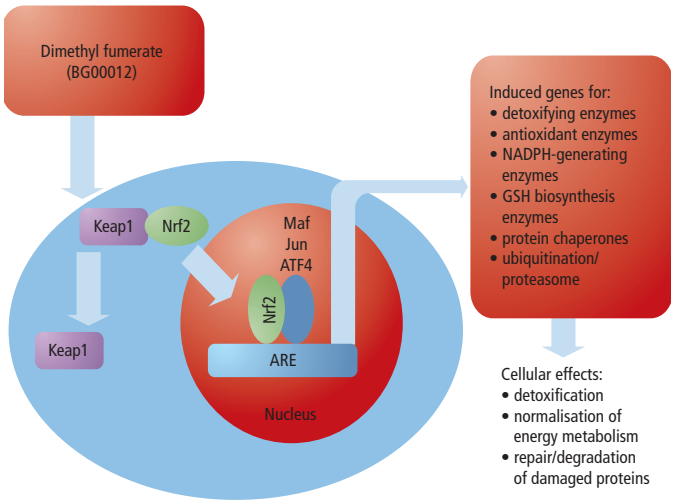
FAEs have been shown to affect aspects of the inflammatory cascade thought to be involved in MS. Data from *in vitro* studies showed that dimethyl fumarate and related FAEs increase the production and induce the expression of anti-inflammatory cytokines, such as interleukin (IL)-10, IL-4 and IL-5.[23–26] Other *in vitro* studies demonstrated that dimethyl fumarate and its primary metabolite, monomethyl fumarate, can both inhibit expression of pro-inflammatory cytokines such as IL-6, IL-1β and tumour necrosis factor (TNF)-α and inhibit the secondary effects of inflammatory cytokines such as IL-1β and TNF-α.[25,27–31] Hence, it is thought that dimethyl fumarate can induce a shift from a T helper (Th)-1 (pro-inflammatory) to a Th-2 (anti-inflammatory) T-cell response.[32]

In addition to exerting anti-inflammatory effects, BG00012 may modulate metabolic homeostasis and cellular response to oxidative stress, a possible cause of cell and tissue damage in persistent inflammation (see *Figure 1*). Dimethyl fumarate is a well-known inducer of phase II detoxification genes, and treatment of cultured astroglia and microglia with FAEs has been shown to upregulate the Phase II detoxification enzyme NAD(P)H:quinone oxidoreductase-1 (NQO-1).[30] The NQO-1 gene is a prototypical transcriptional target for the nuclear factor E2-related factor 2 (Nrf2), a transcription factor that controls Phase II detoxifying gene expression and is critical for oxidative stress response and immune homeostasis.[31,33,34] Recent studies have demonstrated that BG00012 and monomethyl fumarate can activate Nrf2 *in vitro*.[35] The Nrf2 pathway has been implicated as a mediator of a range of neuroprotective effects in the CNS, including inhibition of oxidative and excitotoxic neuronal damage,[36–40] protection of the BBB[41] and regulation of myelin maintenance.[42] Hence, the current body of experimental evidence suggests that BG00012 may provide a dual neuroprotective and anti-inflammatory

Robert J Fox is a Staff Neurologist and Medical Director at the Mellen Center for Multiple Sclerosis at the Cleveland Clinic, Ohio. He serves as an advisory committee member and principal site investigator for many clinical trials, including as co-ordinating principal investigator for a phase III clinical trial of fumarate (BG00012) in relapsing–remitting multiple sclerosis (MS). His research interests focus on innovative magnetic resonance imaging (MRI) techniques to evaluate MS treatments and tissue recovery after injury, in which he is principal investigator and co-investigator on grants funded by the National Institutes of Health (NIH) and the National MS Society. He is a member of various advisory and review committees for the National MS Society and the General Advisory Council for the Cleveland Clinic General Clinical Research Center, and a consultant to the pharmaceutical industry regarding the development of new treatments for MS. Dr Fox recieved his medical degree from the Johns Hopkins University, completed neurology residency training at the University of Pennsylvania and recieved his masters degree in clinical research from the Case Western Reserve University.

E: foxr@ccf.org

Figure 1: BG00012 May Induce Detoxification and Cellular Protection



BG00012 inhibits sequestration of the transcription factor Nrf2 (nuclear factor E2-related factor 2) by its regulatory protein Keap1 (kelch-like ECH-associated protein 1). This allows Nrf2 to accumulate in the nucleus and through the antioxidant response element (ARE) induce expression of Phase II genes that promote cellular detoxification and normalisation of energy metabolism.

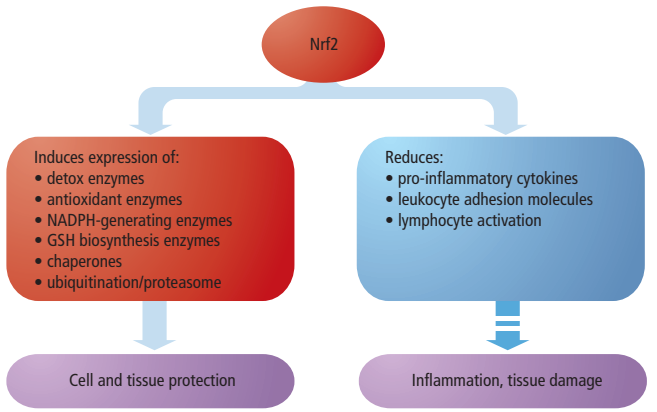
therapeutic effect not targeted by contemporary MS therapies (see *Figure 2*).

Clinical Efficacy and Safety

A pilot study by Schimrigk et al. investigated the safety and efficacy of Fumaderm in MS patients.[26] This was a prospective, open-label, baseline-controlled study conducted in 10 patients with relapsing–remitting MS. The study comprised four phases: a six-week baseline phase, an 18-week treatment phase (weeks 0–18), a four-week washout phase (weeks 19–22), followed by a second 48-week treatment phase (weeks 23–70). At the beginning of each treatment phase, the dose of FAE treatment was titrated over nine weeks up to a dose of 240mg (120mg tablets) three times/day (TID), administered by mouth (PO) during the first treatment phase, and up to 120mg TID PO during the second treatment phase. Safety was assessed by the incidence and severity of adverse events, physical examination, neurological examination, blood chemistry/haematology, electrocardiogram, and urinalysis. The primary efficacy end-point was the number and volume of gadolinium-enhanced (Gd+) lesions on T1-weighted images on magnetic resonance imaging (MRI) scans. Clinical outcomes included the Expanded Disability Status Scale (EDSS) score, the ambulation index (AI) and the nine-hole peg test (9-HPT).[26]

The most common adverse events were gastrointestinal symptoms (diarrhoea, cramps, nausea) and flushing, which were experienced by almost all patients. These events decreased after the first six weeks of the treatment phase. FAEs significantly reduced the mean number of Gd+ lesions after 22 and 70 weeks of treatment: the mean number of Gd+ lesions decreased from 11.28 (range 2–39) at baseline to 0.57 (range 0–3) at week 22 and to 0.28 (range 0–1) at week 70 (both $p<0.02$). Similarly, Gd+ lesion volume was significantly reduced with FAE from 244.5mm^3 at baseline to 8.6mm^3 at 22 weeks and 2.14mm^3 at week 70 ($p<0.018$). Six of the 10 patients who completed the study had either stable or non-significant improvements on EDSS, HPT and AI scores over the course of the study.[26]

Figure 2: Nuclear Factor E2-related Factor 2 Pathway May Induce a Neuroprotective Response and Modulate the Inflammatory Response



In addition to neuroprotection, BG00012 may also have an anti-inflammatory effect.[43,44]

Based on its efficacy in psoriasis and the positive results of the pilot study conducted by Schimrigk et al.,[26] a phase IIb study was conducted to further explore the efficacy and safety of BG00012 in patients with relapsing–remitting MS.[45] This was a double-blind, placebo-controlled, dose-ranging, multinational study of BG00012 involving 257 MS patients. Patients were randomised on a 1:1:1:1 ratio to receive BG00012 120mg PO once daily, BG00012 120mg PO TID, BG00012 240mg PO TID or placebo for 24 weeks.

The study comprised a 24-week blinded, placebo-controlled treatment period (part 1) followed by a 24-week dose-blinded safety extension period (part 2) during which all patients received BG00012. During the safety extension, patients who received BG00012 during the treatment period were maintained on the same BG00012 dose and patients who received placebo were treated with BG00012 240mg TID. The primary end-point was the total number of new Gd+ lesions on MRI scans at weeks 12, 16, 20 and 24. Additional end-points included the cumulative number of new Gd+ lesions (weeks 4–24), new T2-hyperintense and T1-hypointense lesions at week 24 and annualised relapse rate. Safety and tolerability were also assessed.[45]

The results of this study showed that BG00012 240mg TID met the primary end-point and significantly reduced the total number of Gd+ lesions by 69% compared with placebo ($p<0.001$). In addition, BG00012 240mg TID significantly reduced the number of new or enlarging T2-hyperintense lesions ($p<0.001$) and the number of new T1-hypointense lesions ($p<0.014$) compared with placebo.[45] The results of this study also suggest that BG00012 has a favourable safety profile. Of 257 enrolled patients, 176 (92%) BG00012 patients and 59 (91%) placebo patients completed the 24-week treatment phase. The most common adverse events were flushing, headache, nasopharyngitis and nausea. The incidence of infection was similar between BG00012- and placebo-treated patients.[46] BG00012 continued to be safe and well tolerated during the 24-week safety extension phase, with a reduction in the incidence of common adverse events observed in patients who received BG00012 treatment over the entire study.[47] The favourable efficacy and safety profiles of BG00012 observed in the phase IIb study led to the initiation of two phase III registration studies.

Figure 3: Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (DEFINE) Study

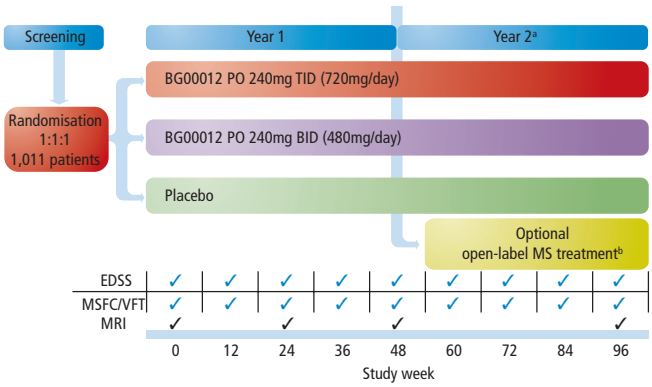
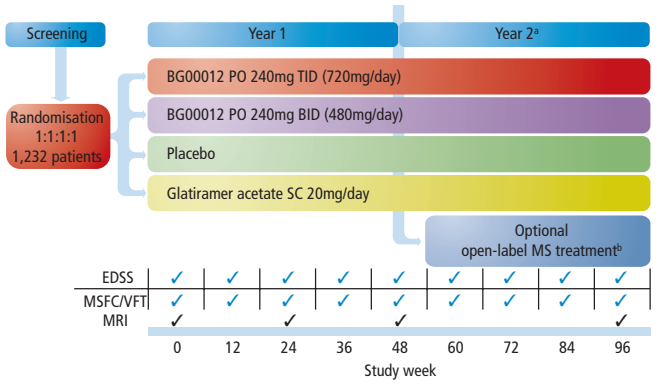


Figure 4: Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) Study



a. 30-day, post-last dose of blinded study treatment safety assessments will be conducted at week 100 (visit 25).
b. Any patient may switch to open-label multiple sclerosis (MS) treatment after 1) sustained progression of disability at any time, or 2) one confirmed relapse after 24 weeks (DEFINE study) or two confirmed relapses (CONFIRM study) and having completed 48 weeks of therapy.
BID = two times daily; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; MSFC = Multiple Sclerosis Functional Composite; PO = orally; SC = subcutaneous; TID = three times daily; VFT = visual function test.

Ongoing Phase III Studies

Two phase III studies, the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-remitting Multiple Sclerosis (DEFINE) study and the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) study, are being conducted to confirm and further evaluate the efficacy and safety of BG00012 in patients with relapsing MS (see *Figures 3* and *4*). DEFINE and CONFIRM are placebo-controlled studies, which are the most effective type of study for determining the efficacy and safety of a therapy, minimising confounding variables. However, in both studies potential ethical concerns of placebo-controlled studies are addressed by obtaining full informed consent regarding available treatment options at study entry and upon signs of confirmed disease activity, and by giving patients the option of switching to rescue MS therapy following signs of confirmed disease activity. Hence, these studies address concerns surrounding the increased risk of disease progression with delayed treatment.[48,49] These studies are currently enrolling patients.

Study Designs

DEFINE and CONFIRM are multicentre, parallel-group, randomised, placebo-controlled, dose-comparison, phase III clinical studies. In the double-blind DEFINE study, patients are randomised in a 1:1:1 ratio to receive oral BG00012 240mg TID, BG00012 240mg BID or placebo (see *Figure 4*). In the CONFIRM study, patients are equally randomised to receive oral BG00012 240mg TID, BG00012 240mg BID, placebo or subcutaneous glatiramer acetate (GA) 20mg once daily (see *Figure 4*). CONFIRM is rater-blinded for all four treatment groups and double-blinded for BG00012 and placebo. The duration of both studies is 100 weeks.

In both DEFINE and CONFIRM, patients may switch to open-label rescue MS therapy if they experience one of the following: one confirmed relapse at >24 weeks (DEFINE) or two confirmed relapses at any time (CONFIRM), and have completed at least 48 weeks of blinded treatment, or significant protocol-defined disability progression (≥1.0-point increase in the EDSS score from a baseline score of ≥1.0, or ≥1.5-point increase from a baseline EDSS score of 0, sustained for 12 weeks) at any time. Patients are provided with informed consent regarding available treatment options at study entry and upon confirmed disease activity. They may choose any MS therapy as optional open-label rescue therapy. If a patient chooses intramuscular interferon beta-1a, it will be provided.

Patients

Approximately 1,000 patients across 27 countries are being enrolled in the DEFINE study, and approximately 1,200 patients across 24 countries are being enrolled in CONFIRM. In general, suitable participants in these trials are persons who are 18–55 years of age with a confirmed diagnosis of relapsing–remitting MS and EDSS 0–5.0 and who experienced at least one relapse in the past 12 months or a Gd+ lesion on recent MRI. More detailed inclusion and exclusion criteria of eligible patients are summarised in *Table 1*.

End-points

In DEFINE, the primary end-point is the proportion of patients relapsing at two years. Secondary end-points include the number of new or enlarging T2-hyperintense lesions over two years, the number of Gd+ lesions at two years, the rate of clinical relapse at one year, and the rate of disability progression at two years. Progression is defined as a ≥1.0-point increase in EDSS score from baseline EDSS ≥1.0 sustained for 12 weeks, or a ≥1.5-point increase in EDSS score from baseline EDSS = 0 sustained for 12 weeks.

In CONFIRM, the primary end-point is the rate of clinical relapse at two years. Secondary end-points include the number of new or enlarging T2-hyperintense lesions over two years, the number of new T1-hypointense lesions at two years, the proportion of patients relapsing at two years, and the rate of disability progression at two years. In addition, the benefit–risk profile at two years of BG00012 versus placebo compared with GA versus placebo will be evaluated. Exploratory comparisons for the primary, secondary and tertiary efficacy end-points will be made between GA and placebo. The comparison between BG00012 and GA will be made by comparing the relative effect of each active treatment against placebo.

The safety and tolerability of BG00012 are assessed in both studies.

Table 1: Key Inclusion and Exclusion Criteria for Patient Enrolment in the DEFINE and CONFIRM Studies

Inclusion Criteria	Exclusion Criteria
Demographics	Disease characteristics
• Men and women 18–55 years of age, inclusive	• Progressive forms of MS • MS relapse within 50 days of randomisation or lack of stabilisation from a previous relapse
Disease characteristics	General medical history
• Diagnosis of RRMS (McDonald criteria)[50] • Baseline EDSS score between 0 and 5 • Disease activity as evidenced by one of the following: ≥1 relapse within 12 months of randomisation or Evidence of Gd+ lesion activity on MRI scan performed within six weeks of randomisation	• History of severe allergic or anaphylactic reactions or known drug hypersensitivity • Abnormal blood or laboratory test at screening: ALT, AST, or GGT ≥2 times the upper limit of normal; leukocytes <3,500 cells/mm^3; or eosinophils >0.7GI/l • Abnormal urine test at screening i.e. proteinuria, haematuria, or glycosuria of unknown aetiology, confirmed by a second test two weeks later Treatment history • BG00012 or Fumaderm or GA* at any time • Mitoxantrone or cyclophosphamide within 12 months of randomisation • Cyclosporine, azathioprine, methotrexate, natalizumab, IVIG, plasmapheresis or cytopheresis within six months of randomisation • IFN-α, IFN-β or SC/oral GA† within three months of randomisation • IV/oral corticosteroids or 4-aminopyridine or related products within 30 days of randomisation

** CONFIRM only; † DEFINE only.*
ALT = alanine transaminase; AST = aspartate transaminase; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; GGT = gamma-glutamyl-transaminase; IFN = interferon; IVIG = intravenous immunoglobulin; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; SC = subcutaneous.

DEFINE and CONFIRM are also assessing the potential neuroprotective effects of BG00012 on MRI measures. In a subset of patients in both studies, conventional MRI measures will include Gd+ lesions, T2 lesions and T1 holes at baseline, six months, one year and two years. Additional imaging studies will evaluate the effect of BG00012 on magnetisation transfer ratio (MTR) and brain atrophy at six months, one year and two years. MTR in normal-appearing tissue will indicate the effects of BG00012 on reducing tissue damage, particularly myelin loss, and MTR within lesions will measure the effects of BG00012 on tissue recovery, including re-myelination. Brain atrophy will assess the ability of BG00012 to reduce permanent tissue damage and neurodegeneration.

Schedule of Assessments

In both DEFINE and CONFIRM, study visits are scheduled every four weeks from baseline (visit 0) to week 100 (visit 25) for assessment of relapses and monitoring of safety. Relapses are also assessed at unscheduled visits as necessary and confirmed by an independent panel of blinded neurologists. This independent panel will help ensure unbiased assessment of relapse events for all treatment arms, allowing consistent and objective evaluations and preserving the integrity of the primary end-points. As shown in *Figures 3* and *4*, disability progression as measured by EDSS and the Multiple Sclerosis Functional Composite (MSFC) is assessed at baseline and every 12 weeks thereafter. Brain MRI scans are performed in a subset of patients (approximately 400 patients in DEFINE and 550 patients in CONFIRM) at baseline and weeks 24, 48 and 96. Safety assessments include the following: blood chemistry (monthly), including tests of liver and renal function; parathyroid hormone and vitamin D levels (annually); haematology (monthly for three months, then quarterly); lipid profiles (monthly for six months, then quarterly); urinalysis (monthly), including microalbumin and b2-microglobulin (quarterly); and electrocardiogram (every six months).

Summary

Preliminary clinical data suggest that BG00012 is a promising oral therapy for the treatment of MS, with a mechanism not currently targeted by other therapies; BG00012 activates the Nrf2 pathway, which may have a dual neuroprotective and anti-inflammatory therapeutic effect. The phase III registration studies of BG00012 in patients with relapsing–remitting MS (DEFINE and CONFIRM) are currently enrolling patients. The objective of these studies is to confirm the efficacy and safety results of the phase IIb study of BG00012 in MS patients. The DEFINE and CONFIRM studies are uniquely designed to address the ethical dilemma posed by the use of placebo controls in clinical trials in the era of effective disease-modifying therapies. Furthermore, the uncomplicated monitoring schedule and criteria for rescue therapy of the BG00012 phase III studies should result in their straightforward implementation while ensuring patient safety. ■

Acknowledgement

The author thanks Nancy M Bormann for providing editorial assistance.

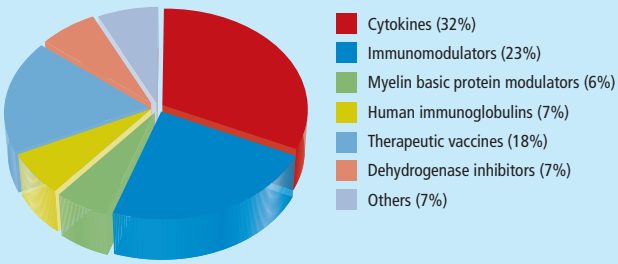
1. Yong VW, Differential mechanisms of action of interferon-β and glatiramer acetate in MS, *Neurology*, 2002;59:802–8.
2. IFNB Multiple Sclerosis Study Group, Interferon beta-1a is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial, *Neurology*, 1993;43:655–61.
3. Jacobs LD, Cookfair DL, Rudick RA, et al., Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis, *Ann Neurol*, 1996;39:285–94.
4. PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group, Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis, *Lancet*, 1998;352: 1498–1504.
5. Johnson KP, Brooks BR, Cohen JA, et al., Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial, *Neurology*, 1995;45:1268–76.
6. Mohr DC, Boudewyn AC, Likosky W, et al., Injectable medication for the treatment of multiple sclerosis: the influence of self-efficacy expectations and injection anxiety on adherence and ability to self-inject, *Ann Behav Med*, 2001;23:125–32.
7. O'Rourke KET, Hutchinson M, Stopping beta-interferon therapy in multiple sclerosis: an analysis of stopping patterns, *Mult Scler*, 2005;11:46–50.
8. Bayard W, Hunziker T, Krebs A, et al., Peroral long-term treatment of psoriasis using fumaric acid derivatives, *Hautarzt*, 1987;38:279–85.
9. Kolbach DN, Nieboer C, Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment, *J Am Acad*

Dermatol, 1992;27:769–71.
10. Altmeyer PJ, Matthes U, Pawlak F, et al., Antipsoriatic effect of fumaric acid derivates. Results of a multicenter double-blind study in 100 patients, *J Am Acad Dermatol*, 1994;30:977–81.
11. Mrowietz U, Christophers E, Altmeyer P, Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study, *Br J Dermatol*, 1998;138:456–60.
12. Prinz JC, The role of T cells in psoriasis, *J Eur Acad Dermatol Venereol*, 2003;17:257–70.
13. De Stefano N, Naroyoanan S, Matthews PM, et al., *In vivo* evidence for axonal dysfunction remote from focal cerebral demyelination of the type seen in multiple sclerosis, *Brain*, 1999; 122:1933–9.
14. Ferguson B, Matyszak MK, Esivi MM, Axonal damage in acute multiple sclerosis lesions, *Brain*, 1997;120:393–9.
15. Silber E, Sharief MK, Axonal degeneration in the pathogenesis of multiple sclerosis, *J Neurol Sci*, 1999;170:11–18.
16. Trapp BD, Peterson J, Ransohoff RM, et al., Axonal transaction in the lesions of multiple sclerosis, *N Engl J Med*, 1998;338:278–85.
17. Kermode AG, Thompson AJ, Tofts P, et al., Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis, *Brain*, 1990;113:1477–89.
18. Kraus J, Oschmann P, The impact of interferon-beta treatment on the blood-brain barrier, *Drug Discov Today*, 2006;11:755–62.
19. Raine CS, The Dale E McFarlin Memorial Lecture: the immunology of the multiple sclerosis lesion, *Ann Neurol*, 1994;36:S61–S72.
20. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG, Multiple sclerosis, *N Engl J Med*, 2000;343:938–52.
21. Gilgun-Sherki Y, Melamed E, Offen D, The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy, *J Neurol*, 2004;251:261–8.
22. Imitola J, Chitnis T, Khoury SJ, Insights into the molecular pathogenesis of progression in multiple sclerosis: potential implications for future therapies, *Arch Neurol*, 2006;63:25–33.
23. Asadullah K, Schmid H, Friedrich M, et al., Influence of monomethylfumarate on monocytic cytokine formation–eplanation for adverse and therapeutic effects in psoriasis? *Arch Dermatol Res*, 1997;289;623–30.
24. de Jong R, Bezemer AC, Zomerdijk TP, et al., Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate, *Eur J Immunol*, 1996;26:2067–74.
25. Schilling S, Goelz S, Linker R, et al., Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration, *Clin Exp Immunol*, 2006; 145:101–7.
26. Schimrigk S, Brune N, Hellwig K, et al., Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-contrilled pilot study, *Eur J Neurol*, 2006;13:604–10.
27. Litjens NH Rademaker M, Ravensbergen B, et al., Monotheyl-fumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses, *Eur J Immunol*, 2004;34:565–75.
28. Loewe R, Holnthoner W, Groger M, et al., Dimethylfumarate inhibits TNF-induced nuclear entry of NF-kappa B/p65 in human endothelial cells, *J Immunol*, 2002;168:4781–7.
29. Loewe R, Pillinger M, de Martin R, et al., Dimethylfumarate inhibits tumor-necrosis-factor-induced CD62E expression in an NF-κB-dependent manner, *J Invest Dermatol*, 2001;117:1363–8.
30. Wierinckx A, Breve J, Mercier D, et al., Detoxification enzyme inducers modify cytokine production in rat mixed glial cells, *J Neuroimmunol*, 2005;166:132–43.
31. Chen XL, Dodd G, Thomas S, et al., Activation of Nrf2/ARE pathway protects endothelial cells from oxidant injury and inhibits inflammatory gene expression, *Am J Physiol Heart Circ Physiol*, 2006;290:H1862–H1870.
32. Ockenfels HM, Schultewolter T, Ockenfels G, et al., The antipsoriatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network, *Br J Dermatol*, 1998;139:390–95.
33. Itoh K, Chiba T, Takahashi S, et al., An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements, *Biochem Biophys Res Commun*, 1997;236:313–22.
34. Venugopal R, Jaiswal AK, Nrf2 and Nrf1 in association with Jun proteins regulate antioxidant response element-mediated expression and coordinated induction of genes encoding detoxifying enzymes, *Oncogene*, 1998;17:3145–56.
35. Lukashev M, Zeng W, Ryan S, et al., Activation of Nrf2 and modulation of disease progression in EAE models by BG00012 (Dimethyl Fumarate) suggests a novel mechanism of action combining anti-inflammatory and neuroprotective modalities. Presented at: 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, Prague, October 12, 2007.
36. Calabrese V, Ravagna A, Colombrita C, et al., Acetylcarnitine induces heme oxygenase in rat astrocytes and protects against oxidative stress: involvement of the transcription factor Nrf2, *J Neurosci Res*, 2005;79:509–21.
37. Li J, Johnson D, Calkins M, et al., Stabilization of Nrf2 by tBHQ confers protection against oxidative stress-induced cell death in human neural stem cells, *Toxicol Sci*, 2005;83:313–28.
38. Satoh T, Okamato SI, Cui J, et al., Activation of the Keap1/Nrf2 pathway for neuroprotection by electrophillic phase II inducers, *Proc Natl Acad Sci*, 2006;103:768–73.
39. Shih AY, Li P, Murphy TH, A small-molecule-inducible Nrf2-mediated antioxidant response provides effective prophylaxis against cerebral ischemia *in vivo*, *J Neurosci*, 2005;25:10321–35.
40. Vargas MR, Pehar M, Cassina P, et al., Fibroblast growth factor-1 induces heme oxygenase-1 via nuclear factor erythroid 2-related factor 2 (Nrf2) in spinal cord astrocytes: consequences for motor neuron survival, *J Biol Chem*, 2005;27:25571–9.
41. Zhao C, Zawadzka M, Roulois AJ, et al., Promoting remyelination in multiple sclerosis by endogenous adult neural stem/precursor cells: Defining cellular targets, *J Neurol Sci*, 2007; epub ahead of print.
42. Hubbs AF, Benkovic SA, Miller DB, et al., Vacuolar leukoence-phalopathy with widespread astrogliosis in mice lacking transcription factor Nrf2, *Am J Pathol*, 2007;170:2068–76.
43. Thimmulappa RK, Lee H, Rangasamy T, et al. Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. *J Clin Invest* 2006;116:984–995.
44. Ma Q, Battelli L, Hubbs AF. Multiorgan autoimmune inflammation, enhanced lymphoproliferation, and impaired homeostasis of reactive oxygen species in mice lacking the antioxidant-activated transcription factor Nrf2. *Am J Pathol* 2006;168:1960–1974.
45. Kappos L, Miller DH, MacManus DG, et al., BG00012, a novel oral fumarate, is effective in patients with relapsing-remitting multiple sclerosis, *Mult Scler*, 2006;12(Suppl. 1):S85.
46. Gold R, Havrdova E, Kappos L, et al., Safety of a noval oral single-agent fumarate, BG00012, in patients with relapsing-remitting multiple sclerosis: results of a phase 2b study, *J Neurol*, 2006; 253(Suppl. 2):ii144–ii145.
47. Kappos L, Safety and tolerability results of a phase 2b extension study of the novel oral fumarate BG00012 for the treatment of relapsing-remitting multiple sclerosis, *Neurology*, 2007;68 (Suppl. 1):A276.
48. Rudick RA, Baier M, Cutter G, et al., Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients, *Mult Scler*, 2005;11:626–34.
49. Johnson KP, Brooks BR, Ford CC, et al., Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial, *Mult Scler*, 2003;9: 585–91.
50. McDonald WI, Compston A, Edan G, et al., Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis, *Ann Neurol*, 2001;50:121–7.

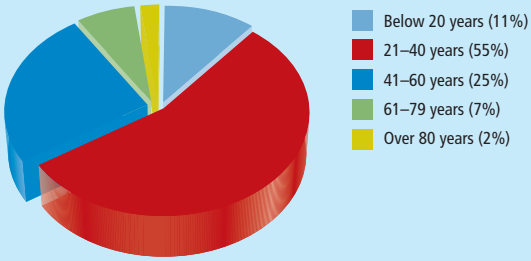
Multiple Sclerosis in Europe

- 'Sclérose en plaques' – the inflammatory, demyelinating disease of the central nervous system – was first described by the French neurologist Charcot in 1868.
- In Europe multiple sclerosis (MS) is the most common cause of neurological disability in young adults, affecting one in 800 of the population, with an estimated 350,000 suffers in Western Europe alone.
- The National Multiple Sclerosis Society recommends disease-modifying drugs to counteract the myelin destruction: Avonex®, Betaseron®, Copaxone®, Rebif® or Tysabri®. These can reduce exacerbations, slow the progression of physical disability and temper severity of attacks.
- The World Health Organization (WHO) calculates a total cost of approximately US$51,000 per patient.
- MS occurs more often in geographical latitudes above 40°.
- The prevalence of the disease varies considerably by geography, with rates significantly higher in northern European than in Mediterranean countries. The Orkney and Shetland Islands (UK) have the highest rates in the world.
- At present there is no generally accepted means of preventing MS.

Late-stage Multiple Sclerosis Drug Pipeline, 2007



Age at First Multple Sclerosis Episode



Source: Touch Briefings, The Lundbeck Institute, The National Multiple Sclerosis Society, World Health Organisation.