

DRAFT Appeal Letter – Tecfidera

TODAY's DATE

Health Plan Addressee Line 1

Health Plan Addressee Line 2

Dear Sir or Ms.:

I am requesting reconsideration of your (**denial, limit, etc.**) of Tecfidera (dimethyl fumarate) for my patient (**patient name**), who suffers from a relapsing form of multiple sclerosis.

Tecfidera, formerly known as BG-12, is approved by the FDA as an oral (self-administered) first-line therapy for adults with relapsing forms of MS

Tecfidera has been shown to be of benefit in relapsing multiple sclerosis in two Phase III clinical trials. In the DEFINE trial, the medication produced a 49% reduction in the proportion of people who experienced relapses over 2 years, and had a similar significant impact on disease activity detected on MRI. This resulted in a 38% reduction in the risk of confirmed progression of disability as measured by the Expanded Disability Status Scale (EDSS).ⁱ

In the CONFIRM trial, Tecfidera produced a significant 44% reduction in the average annual number of MS relapses (annualized relapse rate,) compared with the placebo group. An active reference group taking glatiramer acetate (Copaxone) was included in this study and reduced the annualized relapse rate by 29% compared to placebo. Significant reductions in disease activity on MRI and in the proportion of patients experiencing relapses over two years also favored the Tecfidera groups in this study.ⁱⁱ In both of these studies, Tecfidera was demonstrated to have an excellent safety profile with no increased incidence in infection rates or serious adverse events compared to placebo at the approved dose level.

Additional details about these studies, their endpoints and other information useful to healthcare professionals and payers is compiled for easy online access by The Multiple Sclerosis Emerging Therapies Collaborative (<http://www.ms-coalition.org/emergingtherapies/medications/disease-modifying/dimethyl-fumarate-formerly-called-bg-12-tecfidera>).

I am recommending Tecfidera (240mg bid) for my patient at this time based on its demonstrated potency in treating relapsing MS, its safety profile, and its tolerability advantages for my patient (insert name) with full knowledge of his/her diagnosis, medical history, past treatment and symptoms. (INSERT HERE your rationale, including chart notes and references to disease progression, symptoms, past treatment attempts and effects, etc.)

Sincerely,

John Smith, MD

ⁱ Gold R, Kappos L, Arnold DL, DEFINE Study Investigators. "Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis". [N Engl J Med. 2012 Sep 20;367\(12\):1098-107.](#)

ⁱ Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, Dawson KT; CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. [N Engl J Med. 2012 Sep 20;367\(12\):1087-97.](#)

Citation

N Engl J Med. 2012 Sep 20;367(12):1098-107

Title

Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis.

Authors

Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, Sweetser MT, Yang M, Sheikh SI, Dawson KT; DEFINE Study Investigators.

Collaborators (246)

Department of Neurology, St. Josef-Hospital/Ruhr-University Bochum, Bochum, Germany.
ralf.gold@ruhr-uni-bochum.de

Abstract

BACKGROUND: BG-12 (dimethyl fumarate) was shown to have antiinflammatory and cytoprotective properties in preclinical experiments and to result in significant reductions in disease activity on magnetic resonance imaging (MRI) in a phase 2, placebo-controlled study involving patients with relapsing-remitting multiple sclerosis.

METHODS: We conducted a randomized, double-blind, placebo-controlled phase 3 study involving patients with relapsing-remitting multiple sclerosis. Patients were randomly assigned to receive oral BG-12 at a dose of 240 mg twice daily, BG-12 at a dose of 240 mg three times daily, or placebo. The primary end point was the proportion of patients who had a relapse by 2 years. Other end points included the annualized relapse rate, the time to confirmed progression of disability, and findings on MRI.

RESULTS: The estimated proportion of patients who had a relapse was significantly lower in the two BG-12 groups than in the placebo group (27% with BG-12 twice daily and 26% with BG-12 thrice daily vs. 46% with placebo, $P < 0.001$ for both comparisons). The annualized relapse rate at 2 years was 0.17 in the twice-daily BG-12 group and 0.19 in the thrice-daily BG-12 group, as compared with 0.36 in the placebo group, representing relative reductions of 53% and 48% with the two BG-12 regimens, respectively ($P < 0.001$ for the comparison of each BG-12 regimen with placebo). The estimated proportion of patients with confirmed progression of disability was 16% in the twice-daily BG-12 group, 18% in the thrice-daily BG-12 group, and 27% in the placebo group, with significant relative risk reductions of 38% with BG-12

twice daily ($P=0.005$) and 34% with BG-12 thrice daily ($P=0.01$). BG-12 also significantly reduced the number of gadolinium-enhancing lesions and of new or enlarging T(2)-weighted hyperintense lesions ($P<0.001$ for the comparison of each BG-12 regimen with placebo). Adverse events associated with BG-12 included flushing and gastrointestinal events, such as diarrhea, nausea, and upper abdominal pain, as well as decreased lymphocyte counts and elevated liver aminotransferase levels.

CONCLUSIONS: In patients with relapsing-remitting multiple sclerosis, both BG-12 regimens, as compared with placebo, significantly reduced the proportion of patients who had a relapse, the annualized relapse rate, the rate of disability progression, and the number of lesions on MRI. (Funded by Biogen Idec; DEFINE ClinicalTrials.gov number, NCT00420212.).

Citation

N Engl J Med. 2012 Sep 20;367(12):1087-97.

Title

Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.

Authors

Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Vigiuetta V, Dawson KT; CONFIRM Study Investigators.

Collaborators (295)

SourceMellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH 44195, USA. foxr@ccf.org

Abstract

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

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

RESULTS: At 2 years, the annualized relapse rate was significantly lower with twice-daily BG-12 (0.22), thrice-daily BG-12 (0.20), and glatiramer acetate (0.29) than with placebo (0.40) (relative reductions: twice-daily BG-12, 44%, $P < 0.001$; thrice-daily BG-12, 51%, $P < 0.001$; glatiramer acetate, 29%, $P = 0.01$). Reductions in disability progression with twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate versus placebo (21%, 24%, and 7%, respectively) were not significant. As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the numbers of new or enlarging T(2)-weighted hyperintense lesions (all $P < 0.001$) and new T(1)-weighted hypointense lesions ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively). In post hoc comparisons of BG-12 versus glatiramer acetate, differences were not significant except for the annualized relapse rate (thrice-daily BG-12), new

or enlarging T(2)-weighted hyperintense lesions (both BG-12 doses), and new T(1)-weighted hypointense lesions (thrice-daily BG-12) (nominal $P < 0.05$ for each comparison). Adverse events occurring at a higher incidence with an active treatment than with placebo included flushing and gastrointestinal events (with BG-12) and injection-related events (with glatiramer acetate). There were no malignant neoplasms or opportunistic infections reported with BG-12. Lymphocyte counts decreased with BG-12.

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