DIMETHYL FUMARATE

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Dimethyl fumarate (BG 00012), licensed for the treatment of psoriasis, has been shown to provide positive effects in MS patients. The exact mechanism of action of BG00012 is unknown. Nonclinical studies have demonstrated that fumaric acid esters may modulate the immune system through enhancement of the Nrf2 signaling pathway. This leads to inhibition of expression of pro-inflammatory mediators such as Il-1ß, IL-6, TNF-α, and potentially provide cytoprotection effect. In vitro studies have shown that dimetyl fumarate can induce also the expression of anti-inflammatory cytokines such as IL-4, IL-5 or IL-10. Cell and tissue protection is connected with induction of detoxifying and antioxidant enzymes. In Phase II study 257 patients with relapsing remitting multiple sclerosis, aged 18-55 years, were randomized to receive BG00012 120 mg once daily (n=64), 120 mg three times daily (n=64), 240 mg three times daily (n=64) or placebo(n=65) for 24 weeks.

This was followed by a 24 week extension period for safety evaluation, during which patients receiving placebo were treated with BG00012 240 mg three times daily.

The primary end-point was the total number of new gadolinium enhancing (Gd+) lesions on MRI scans at weeks 12, 16, 20 and 24. Additional end-points included cumulative number of new Gd+ lesions (weeks 4-24), new or enlarging T2-hyperintense lesions and new T1-hypointense lesions at week 24 as well as annualized relapse rate.

BG00012 at the dose of 240 mg three times daily reduced the total number of new GD+ lesions accumulated from week 12 through week 24 by 69%. There was also reduction in studied group of T2 lesions by 48% and the reduction of T1 hipointense lesions by 53% compared with placebo.

Nonsignificant trend towards reduction in the annualized relapse rate has also been observed.

The safety profile was good. Of 257 enrolled patients 92% completed the 24 week treatment phase. The most common side effects of BG00012 included headache, nasopharyngitis, nauseas and flushing. The incidence of infection was similar between BG00012 and placebo –treated patients.

Currently Phase III studies are ongoing comparing BG00012 given in dose 480 mg and 720mg with placebo for 96 weeks (DEFINE) and comparing BG00012 at the same doses with placebo and glatiramer acetate given s.c. 20 mg/day (CONFIRM).