BG00012: AN EMERGING ORAL THERAPY FOR THE TREATMENT OF PATIENTS WITH MULTIPLE SCLEROSIS

N. Putzki
MS Center Essen, University Clinic Essen, Germany
MS Center, Cantonal Hospital, St. Gall, Switzerland

Multiple sclerosis (MS) is a central nervous system (CNS) disorder associated with myelin and axonal damage and degeneration as well as neuronal loss, all which may lead to progressive disability. Major causes of CNS injury in MS include inflammatory and oxidative stress, as well as excitotoxic damage to neurons and oligodendrocytes.

Traditional disease-modifying therapies (DMTs) for MS have pleiotropic effects on the disease pathophysiology including immunomodulation and control of cytokine production. These DMTs are associated with an approximately 30% reduction in annualized relapse rate and only some have been shown to delay disability progression. Adherence to the traditional DMTs is adversely affected by side effects, many of which are related to injection. Biologic therapies for MS, which are designed to target specific molecules implicated in disease pathophysiology, are generally associated with improved efficacy but can have greater safety risks. Therefore, there remains an unmet need for novel safe and effective MS DMTs with alternative routes of administration that address tolerability issues and side effects associated with current therapies, as well as degenerative aspects of MS.

BG00012 is an oral formulation of dimethyl fumarate (DMF) in development for the treatment of relapsing MS. In vitro, DMF and its primary metabolite, monomethyl fumarate (MMF), have been shown to activate the Nrf2 transcriptional pathway, a critical regulator of immune homeostasis and oxidative stress response. In animals with experimental autoimmune encephalomyelitis, treatment with DMF and MMF improved clinical scores, decreased inflammation, and reduced axonal and myelin loss without causing obvious changes in T-cell function or infiltration. Together, these data suggest that BG00012 may have a dual anti-inflammatory and neuroprotective mechanism of action.

In a pilot study of patients with relapsing MS, treatment with a fumarate-containing oral formulation significantly reduced the number and volume of gadolinium-enhancing (Gd+) lesions on magnetic resonance imaging (MRI) brain scans compared with baseline (P<0.018). Based on this finding, a randomized, double-blind, placebo-controlled, dose-ranging, phase 2b study of patients with relapsing MS was subsequently conducted to determine the efficacy and safety of BG00012. In this study, BG00012 240 mg three times daily (tid) significantly reduced the mean total number of Gd+ lesions from Weeks 12 to 24 by 69% compared with placebo (1.4 vs 4.5, P<0.0001). Treatment with BG00012 240 mg tid also significantly reduced the number of T2-hyperintense lesions by 48% and the number of T1-hypointense lesions by 53% at Week 24 compared with placebo (P=0.0006 and P=0.014, respectively), and was associated with a reduced likelihood of conversion of Gd+ lesions to T1 non-Gd+ lesions compared with placebo (P<0.0001). These data provide clinical evidence supporting the proposed anti-inflammatory and neuroprotective mechanism of action of BG00012. BG00012 was also associated with a nonsignificant trend toward reduction in relapse rate compared with placebo at Week 24 (0.44 vs 0.65, P=0.272) of the phase 2b study, and relapse rates continued to decrease with continued dose-blinded BG00012 treatment during Weeks 24 to 48.

BG00012 has demonstrated a favorable safety profile in clinical studies to date. In the phase 2b study, adverse events significantly more common in BG00012-treated than placebo patients were abdominal pain, flushing, and hot flush; these adverse events decreased in frequency over time, with a significant decrease apparent after the first month of treatment. In addition, serious adverse events and infections occurred at similar, low rates among BG00012 and placebo groups.

BG00012 is currently being evaluated in two phase 3 studies, DEFINE and CONFIRM which will further assess its clinical and MRI efficacy, and safety. In addition, MRI assessments, including magnetization transfer ratio, will be used to determine if BG00012 has a neuroprotective effect that is independent of its anti-inflammatory action. The results of DEFINE and CONFIRM, as well as ongoing preclinical studies assessing the proposed dual anti-inflammatory and neuroprotective mechanism of action of BG00012, will further define its role as an oral therapy for the treatment of MS.