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TRIAL WATCH

Phase III success for Biogen's oral multiple sclerosis therapy

Biogen Idec have announced that their fumaric acid ester, dimethyl fumarate (BG-12), has met the primary and secondary end points of a global Phase III trial — DEFINE — which was designed to assess the efficacy and safety of this novel oral agent in patients with relapsing–remitting multiple sclerosis (RRMS).

MS is a chronic disease of the central nervous system that causes inflammation and destruction of both the myelin sheath and neurons, with symptoms including cognitive impairment, muscle weakness and severe fatigue. Most patients are initially diagnosed with RRMS, which — as its name suggests — is characterized by temporary symptom exacerbations, followed by periods of partial or complete recovery. Within 10–15 years, secondary progressive MS usually develops, which is associated with a worsening of symptoms (mostly without relapses) that culminates in marked disability.

MS therapy involves the long-term use of disease-modifying injectable immunosuppressants or immunomodulators, which, in addition to causing unpleasant side effects and having variable efficacy, are inconvenient and painful, resulting in poor compliance. Although natalizumab is generally well tolerated and safe, it is associated with the rare but serious brain infection known as progressive multifocal leukoencephalopathy (PML). Oral agents have been long-awaited, and although the first of these — the sphingosine-1-phosphate receptor modulator fingolimod — has received US approval, it too has raised safety concerns that have limited its use as a first-line agent.

"First-line treatment for MS is composed of injectables — β-interferons and glatiramer acetate — but also oral fingolimod in the United States; with natalizumab and fingolimod being used for aggressive MS or second-line [treatment] both in the United States and the European Union," notes Professor Hans-Peter Hartung, Chair of Neurology, Heinrich Heine University, Düsseldorf, Germany. "Higher doses of fingolimod that were studied were associated with few but serious adverse events possibly related to the drug, including skin cancers and herpes infections, but these were not apparent when fingolimod was studied at the dose now approved (0.5 mg once daily). However, as with all strongly effective immunomodulators, the risk exists that immune surveillance may be compromised and allow emergence of opportunistic infections and malignancies," he explains. Professor Howard Weiner, Director of the Partners MS Center, Brigham And Women's Hospital, Boston, Massachusetts, USA, adds: "Unmet needs for MS are oral medications with a high degree of efficacy and a good safety profile."

Several oral agents aiming to address these needs are currently undergoing Phase III trials — these include BG-12, laquinimod (Teva Pharmaceuticals) and teriflunomide (Sanofi-Aventis). Another oral agent, cladribine (Merck), is in registration in the United States, but the US Food and Drug Administration recently requested additional safety data. "Considering the safety concerns of fingolimod there is room for other orals, but whether their safety profile will be necessarily better is unpredictable," says Hartung.

BG-12 acts by inhibiting translocation of nuclear factor-κB (NF-κB) and activation of downstream NF-κB-dependent pro-inflammatory pathways. It is also the first MS drug to activate the NRF2 transcriptional pathway, which maintains myelin integrity. Given that fumaric acid esters are currently used to treat psoriasis and their side-effect profile is therefore well characterized, it is anticipated that BG-12 will be safer than existing MS therapies.

Clinical data for BG-12 so far are promising. In the DEFINE trial, which involved over 1,200 patients, 240 mg of BG-12 administered orally twice daily reduced the proportion of patients who relapsed at 2 years by 49% and lowered the annual relapse rate by 53%, which compares favourably to current front-line agents and laquinimod. BG-12 decreased the progression of disability by 38%, as measured by the Expanded Disability Severity Scale, which are among the largest levels of reduction observed with current MS drugs. In addition, the agent reduced the number of new or newly enlarging T2 hyperintense lesions and gadolinium-enhancing lesions by 85% and 90%, respectively. BG-12 also demonstrated a favourable safety and tolerability profile, with the overall incidence of adverse events being similar to placebo.

Further analysis of data from the DEFINE trial is in progress and the results of a second Phase III trial — CONFIRM, which is evaluating BG-12 and an active reference comparator, glatiramer acetate — are expected later this year. A long-term safety trial is also ongoing.

"BG-12 compares favourably to fingolimod and laquinimod and may have advantages in terms of safety over fingolimod," says Weiner. "However, it is too early to make statements regarding efficacy until further Phase III trials are completed," he concludes.