ORAL FINGOLIMOD TREATMENT FOR MS

Ariel Miller
Multiple Sclerosis & Brain Research Center, Carmel Medical Center, Haifa, Israel

Introduction: Oral fingolimod a sphingosine 1-phosphate receptor modulator – is the lead compound in a novel class of drugs for the treatment of MS It targets MS via actions in both the immune system and CNS. Fingolimod gained FDA for the treatment of relapsing forms of multiple sclerosis last year and more recently EMA approval for active multiple sclerosis despite previous treatment or as first line for highly active MS**.**

MoA : There are five different subtypes of sphingosine 1-phosphate (S1P) receptor, S1P1 to S1P5, Fingolimod binds to S1P1, S1P3, S1P4 and S1P5 , with highest affinity to receptors expressed on lymphocytes and cells of the central nervous system. Normal lymphocytes circulate within the systemic immune compartment, including the secondary lymphoid organs egress from the lymph nodes requires sphingosine 1-phosphate 1 receptor signalling Fingolimod is a super-agonist of sphingosine 1-phosphate 1 (S1P1), which down-regulates expression of S1P1 and inhibits lymphocyte egress thus lymphocytes accumulate in the lymph node during fingolimod treatment, and absolute lymphocyte count decreases, Fingolimod reduces T cell mediated inflammation and tissue damage in the central nervous system . S1P1 receptors on glial cells and neurons in the central nervous system affect functions relevant to Multiple Sclerosis. . In the experimental autoimmune encephalomyelitis (EAE) model, benefits were observed with fingolimod, regardless of the stage of disease Fingolimod prevents development of any disease when used as prophylaxis in an EAE rat model Animals treated at the time of first relapse recovered completely and remained stable for up to 15 days, animals given rescue treatment with fingolimod, after 40 days of disease, showed a significant improvement in EAE score.

Efficacy data: Fingolimod was studied in 2 large scale phase III studies. **F**ingolimod **R**esearch **E**valuating **E**ffects of **D**aily **O**ral therapy in **MS** (FREEDOMS) is a Phase III study that was designed to demonstrate superiority of fingolimod to placebo for annualised relapse rate in patients with relapsing–remitting Multiple Sclerosis treated up to 24 months. Reductions in relapse rate of -54% were seen with oral fingolimod 0.5 vs placebo. Fingolimod treated patients achieved significant improvements in disability progression over 2 years. Fingolimod was significantly superior to placebo for both the number of new and enlarging T2 lesions over 24 months and for the number of T1 gadolinium-enhancing lesions at 6, 12 and 24 months.

TRial **A**ssessing injectable interfero**N** v**S** **F**ty720 **O**ral in **R**elapsing–remitting **MS** (TRANSFORMS) is a Phase III study comparing efficacy, safety and tolerability of oral fingolimod dosed at 0.5 and 1.25 mg/d with interferon (IFN) beta-1a. 30 µg I.M every week. Patients treated with 0.5 mg fingolimod achieved a 52% reduction in annualised relapse rate vs IFN beta-1a intramuscularly. Statistically significant reductions in annualised relapse rate vs placebo were achieved for both doses of oral fingolimod in both treatment-naïve and previously treated patients The proportion of patients who were relapse-free was statistically significantly greater ($p<0.001$) in the oral fingolimod treatment groups compared with the interferon (IFN) beta-1a group. Patients receiving oral fingolimod achieved statistically significant reductions in new/newly enlarged T2 lesions, and in the number of gadolinium-enhancing T1 lesions, as determined by magnetic resonance imaging, compared with interferon beta-1a at 12 months. In addition Patients receiving oral fingolimod had significantly ($p<0.001$) smaller reductions in brain volume over 12 months compared with those receiving interferon beta-1.

Safety profile: Fingolimod was generally well tolerated in these trials of up to 2 years' duration, with most adverse events being manageable and of mild to moderate severity; Transient, generally asymptomatic bradycardia and infrequent atrioventricular block were seen with the administration of the first dose. Macular oedema and serious infections occurred infrequently. Reversible, asymptomatic elevations of liver enzymes could also occur there were two deaths from opportunistic infections, albeit these occurred with fingolimod 1.25 mg/day (higher than the recommended dosage). Limited long-term data indicated that no new safety concerns had arisen after 5 years of fingolimod treatment**.**

Summary: fingolimod provides a novel treatment for MS with a new mechanism of action. During the clinical trial program, fingolimod treatment has demonstrated high efficacy with a relatively acceptable safety profile, As the first approved oral disease-modifying treatment, fingolimod offers patients a convenient alternative to regular self-injection for the treatment of relapsing forms of MS.