

## Fingolimod is not effective in primary progressive multiple sclerosis

### **BACKGROUND:**

No treatments have been approved for primary progressive multiple sclerosis. Fingolimod, an oral sphingosine 1-phosphate receptor modulator, is effective in relapse-onset multiple sclerosis, but has not been assessed in primary progressive multiple sclerosis. We assessed the safety and efficacy of fingolimod in patients with primary progressive multiple sclerosis.

### **METHODS:**

In INFORMS, a multicentre, double-blind, placebo-controlled parallel-group study, patients with primary progressive multiple sclerosis recruited across 148 centres in 18 countries were randomly allocated (1:1) with computer-generated blocks to receive oral fingolimod or placebo for at least 36 months and a maximum of 5 years. Patients were initially assigned to fingolimod 1.25 mg per day or placebo (cohort 1); however, after a protocol amendment on Nov 19, 2009, patients were switched in a masked manner to fingolimod 0.5 mg, whereas those on placebo continued on matching placebo. From then onwards, patients were assigned to receive fingolimod 0.5 mg/day or placebo (cohort 2). Key inclusion criteria were age 25-65 years, clinical diagnosis of primary progressive multiple sclerosis, 1 year or more of disease progression, and two of the following criteria: positive brain MRI; positive spinal cord MRI; or positive cerebrospinal fluid. Additional eligibility criteria included disease duration of 2-10 years and objective evidence of disability progression in the previous 2 years. Patients and study investigators were masked to group assignment. We used a novel primary composite endpoint based on change from baseline in Expanded Disability Status Scale (EDSS), 25' Timed-Walk Test, or Nine-Hole Peg Test to assess time to 3-month confirmed disability progression in study participants treated for at least 3 years. All randomised patients took at least one dose of study drug. The primary efficacy analysis included all patients in cohort 2 and those assigned to placebo in cohort 1. The safety analysis included all patients in cohorts 1 and 2. This study is registered with ClinicalTrials.gov, number NCT00731692. The study is now closed.

### **FINDINGS:**

970 patients were randomly assigned between Sept 3, 2008, and Aug 30, 2011 (147 to fingolimod 1.25 mg and 133 to placebo in cohort 1; 336 to fingolimod 0.5 mg and 354 to placebo in cohort 2). The efficacy analysis set (n=823) consisted of 336 patients randomly allocated to fingolimod 0.5 mg and 487 to placebo. Baseline characteristics were similar across groups and representative of a primary progressive multiple sclerosis population (48% women, mean age 48.5 years [SD 8.4], mean EDSS 4.67 [SD 1.03], 87% free of gadolinium-enhancing lesions). By end of study, 3-month confirmed disability progression had occurred in 232 and 338 patients in the fingolimod and placebo groups, respectively, resulting in Kaplan-Meier estimates of 77.2% (95% CI 71.87-82.51) of patients in the fingolimod group versus 80.3% (73.31-87.25) of patients in the placebo group (risk reduction 5.05%; hazard ratio 0.95, 95% CI 0.80-1.12; p=0.544). Safety results were generally consistent with those of studies of fingolimod in patients with relapse-onset multiple sclerosis. Lymphopenia occurred in 19 (6%) patients in the fingolimod group versus none in the placebo group, bradycardia in five (1%) versus one (<1%), and first-degree atrioventricular block in three (1%) versus six (1%). Serious adverse events occurred in 84

(25%) patients in the fingolimod group and 117 (24%) in the placebo group, including macular oedema in six (2%) versus six (1%), and basal-cell carcinoma in 14 (4%) versus nine (2%).

**INTERPRETATION:**

The anti-inflammatory effects of fingolimod did not slow disease progression in primary progressive multiple sclerosis. Therapeutic strategies for primary progressive multiple sclerosis might need different approaches to those used for relapse-onset multiple sclerosis