**CONCLUSIONS**

- The first-dose effects of fingolimod 0.5 mg on heart rate and atrioventricular conduction in patients with relapsing MS in this real-world study were consistent with those found in completed controlled trials.
- Most patients were discharged at 6 hours, and few patients required extended cardiac monitoring after 6 hours.
- First-dose administration of fingolimod in the real-world setting is well tolerated.

**INTRODUCTION**

- Once-daily fingolimod 0.5 mg (FTY720, Galapagos, Novartis Pharma AG) is a sphingosine 1-phosphate receptor 1 (S1PR1) receptor modulator approved for the treatment of relapsing multiple sclerosis (MS).
- Approximately 1,140 patients have been treated with fingolimod in both the clinical trial and postmarketing settings; total patient exposure now exceeds 195,000 patient-years.
- In the phase 2 and 3 core and extension studies in patients with relapsing MS, fingolimod was generally well tolerated.
- A transient decrease in heart rate (HR) and asymptomatic atrioventricular (AV) conduction delays in a small number of patients are well-characterized pharmacological effects of fingolimod treatment initiation.

**PREFERMS (Prospective, Randomized, Active-controlled, open-label) study**

- To examine the first-dose effects of fingolimod in a real-world group of US patients with RRMS in the context of findings from controlled, post-treatment trials.

**METHODS**

- Study designs and participants:
  - **PREFERMS** study recruited male and female patients aged 18–65 years, diagnosed with RRMS meeting the 2010 revised McDonald criteria (EDSS ≤6) with at least one relapse in the previous year (or at least two in the previous 2 years) and who had an EDSS of 0–5.5.
  - Patients were randomized to receive fingolimod 0.5 mg or placebo at 6 months after first-dose treatment assignment in the PREFERMS study.

- **Results:**
  - 637 patients treated with fingolimod and 1,212 patients treated with placebo.
  - Average age, mean (SD) 41.3 (10.7) years
  - Male: 72.7% (909/1,212)
  - Female: 27.3% (323/1,212)
  - Hypertension: 100 (15.7%) vs. 95 (7.8%)
  - Diabetes: 57 (9.1%) vs. 57 (4.7%)
  - CHF: 32 (5.2%) vs. 28 (2.3%)
  - Asthma: 17 (2.8%) vs. 18 (1.5%)
  - Severe: 0 (0.0%) vs. 0 (0.0%)

- **Objectives:**
  - Evaluate the first-dose effects of fingolimod on heart rate and AV conduction in patients with relapsing MS in this real-world study.
  - Consistency of findings from completed controlled trials.
  - Contextualize findings from completed studies.

- **Analyses:**
  - These analyses are based on change from baseline sitting HR and incidence of newly occurring abnormal ECG during first-dose observation.
  - The analysis groups included all randomized patients in the PREFERMS population and the pooled phase 3 study population.

- **RESULTS:**

  **Changes in HR after first-dose fingolimod administration:**
  - Patients who experienced symptomatic bradycardia for which treatment was required: 0.3% (1/361) PREFERMS, 2.4% (30/1231) phase 3 study.
  - Patients who discontinued treatment due to symptomatic bradycardia: 0.3% (1/361) PREFERMS, 0.2% (2/1212) phase 3 study.

- **Medications used for prevention of symptomatic bradycardia in the first 6 hours:**
  - Calcium-channel blocker: 0.2% (7/361) PREFERMS, 0.2% (2/1212) phase 3 study.
  - Beta-blocker: 0.8% (3/361) PREFERMS, 0.4% (5/1212) phase 3 study.

- **Safety analyses:**
  - No deaths in either group.

- **Conclusion:**
  - Fingolimod at first-dose observation was generally well tolerated in the real-world setting.
  - Overall, 90.3% (n=575/637) of patients in the PREFERMS group, and 83.0% (1006/1212) of patients in the pooled phase 3 study population criteria, control groups, outcome definitions and geographic dispersion of studies.

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