# Cardiac Effects of Fingolimod in Patients With Multiple Sclerosis



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## CONCLUSIONS

- **Results of this interim analysis of first-dose observation data in the EPOC study are consistent with previous studies.[1,2]**
  - **HR effects were transient and began to resolve approximately 6 hours after first-dose administration.**
  - **The incidence of symptomatic bradycardia in the EPOC study was low, and all cases resolved spontaneously.**
- **In patients with postdose ECG, no second-degree AV blocks were reported.**
- **According to fingolimod prescribing information, all patients should be observed and receive hourly pulse and BP measurements for at least 6 hours after first dose and undergo ECG predose and after the 6-hour observation.[4]**

## INTRODUCTION AND BACKGROUND

- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 other countries for treatment of relapsing multiple sclerosis (MS).[a]
- In phase 3 randomized, double-blind, clinical trials, fingolimod 0.5 mg has demonstrated efficacy in reducing the annualized relapse rate vs placebo (fingolimod, 0.18; placebo, 0.40; 54% reduction; $P<0.001$)[1] and intramuscular (IM) interferon (IFN) β-1a 30 µg once weekly (fingolimod, 0.16; IFNβ-1a, 0.33; 52% reduction; $P<0.001$).[2]
- At treatment initiation, fingolimod induces a transient and generally benign reduction in heart rate (HR) that is maximal by 4–6 hours after the first dose and normalizes over days to weeks with continued dosing.[1,2]
- This report presents first-dose cardiovascular effects after therapy initiation with fingolimod 0.5 mg following a switch from standard-of-care disease-modifying therapy (DMT) in the phase 4 study to Evaluate Patient Outcomes, Safety, and Tolerability of Fingolimod (EPOC; NCT01216072).

## METHODS

### *Study Design*

- EPOC was a 6-month, randomized, open-label, multicenter study conducted in the United States and Canada. Patients were randomized 3:1 to once-daily fingolimod 0.5 mg or standard-of-care DMT for 6 months.
  - There was no washout period between previous therapy and fingolimod treatment.
  - Patients randomized to DMT either remained on their prerandomization DMT or changed to another DMT based on the investigator's judgment.
  - Patients randomized to DMT who completed the study were eligible for 3 months of open-label treatment with fingolimod 0.5 mg; data presented here focus on patients initially randomized to fingolimod 0.5 mg.
- The protocol was amended following the US Food and Drug Administration approval of fingolimod to include an interim analysis of safety during the 6-hour first-dose observation period. This reflects the US prescribing information, which states that all patients initiating fingolimod 0.5 mg should be observed for signs and symptoms of bradycardia for 6 hours after the first dose and that a predose electrocardiogram (ECG) should be obtained for patients at higher risk of bradyarrhythmia.

### *Patients*

- Eligible patients were 18–65 years of age with relapsing forms of MS as defined by 2005 revised McDonald criteria[3] and an Expanded Disability Status Scale score of 0–5.5.
- Patients were required to be fingolimod-naive and to have received continual treatment for ≥6 months with a single standard-of-care DMT (IFNβ-1b subcutaneous [SC] 0.25 mg every other day, IFNβ-1a IM 30 µg once weekly, IFNβ-1a SC 22 or 44 µg 3 times weekly, or glatiramer acetate SC 20 mg once daily).
- Key exclusion criteria were significant cardiac history (eg, history of cardiac arrest, myocardial infarction, unstable ischemic heart disease, or coronary spasm within 6 months; cardiac failure [class III or IV] or any severe cardiac disease at screening; ECG evidence of Mobitz type II second-degree heart block, third-degree atrioventricular [AV] block [absent functional pacemaker], or increased QTc interval [>470 ms]; uncontrolled or poorly controlled hypertension [systolic/diastolic blood pressure (BP) >140/90 mmHg]); macular edema; active infection; treatment with natalizumab, immunosuppressants, immunoglobulins, or monoclonal antibodies ≤6 months before screening; any live or live attenuated vaccines ≤1 month before screening; treatment with cladribine, cyclophosphamide, or mitoxantrone at any time; and current treatment with class Ia or class III antiarrhythmic drugs.

[a]*The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.*

### *First-Dose Observation Assessments*

- A predose ECG was conducted, and predose and hourly postdose measurements of sitting HR were collected during the 6-hour first-dose observation period.
- In addition, an ECG at 6 hours following first dose was performed if clinically indicated.
- Data were analyzed descriptively.

## RESULTS

### *Patients*

- For the 6-month study, 790 patients were randomized to fingolimod treatment, and 783 received at least 1 dose of fingolimod; patients were mainly women (75.9%) and had a mean age of 46.0 years **(Table 1)**.

**Table 1. Patient demographics and clinical characteristics**

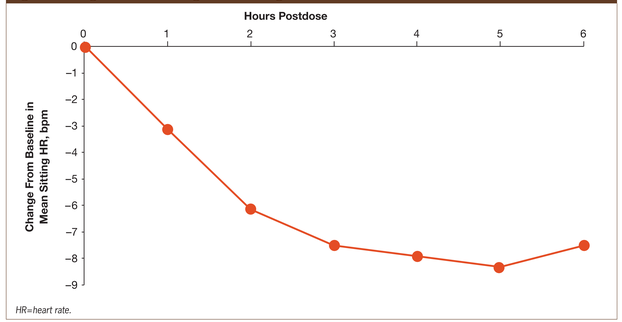
| Characteristic | Fingolimod 0.5 mg (n=783) |
|---|---|
| Mean (SD) age, y | 46.0 (9.82) |
| Women, n (%) | 594 (75.9) |
| Race, n (%) | |
| White | 639 (81.6) |
| Black | 111 (14.2) |
| Other | 33 (4.2) |
| Mean (SD) duration of MS symptoms, y | 12.1 (8.40) |
| Mean (SD) number of relapses | |
| Past year | 0.8 (1.20) |
| Past 2 years | 1.4 (2.05) |
| Mean (SD) EDSS score | 2.4 (1.32) |
| Range | 0.0–7.0 |
| Patients with previous MS treatments, n (%) | |
| Glatiramer acetate | 258 (33.0) |
| IFNβ-1a IM | 206 (26.3) |
| IFNβ-1a SC | 195 (24.9) |
| IFNβ-1b SC | 124 (15.8) |

*EDSS=Expanded Disability Status Scale; IFN=interferon; IM=intramuscular; MS=multiple sclerosis; SC=subcutaneous.*

### *Change in HR After First-Dose Fingolimod*

- At predose assessment, mean (SD) sitting HR was 74.1 (10.03) beats per minute (bpm), and following first-dose administration, HR reached a nadir of 65.6 (9.33) bpm at 5 hours (mean change from baseline, –8.3 bpm) and began to recover by 6 hours **(Figure)**.

**Figure. Change in mean sitting HR after fingolimod first-dose administration**




*HR=heart rate.*

### *Clinical Status After First-Dose Administration*

- The majority of patients (98.6% [n=772/783]) were discharged at 6 hours postdose.
  - 10 (1.3%) patients required extended observation after 6 hours.
  - 3 (0.4%) patients required a day-2 observation in the clinic; 2 of these patients had undergone extended observation on day 1.
    - 1 patient returned for day-2 observation to ensure safety, did not undergo postdose ECG, and was discharged with an HR of 53 bpm.
    - 1 patient with first-degree AV block and sinus bradycardia on day 1 returned for repeat ECG; no abnormalities were detected on day 2, and the patient was discharged with an HR of 60 bpm.
    - 1 patient with a left anterior hemiblock at screening, predose, and 6 hours postdose had the same abnormality in morning and afternoon ECG on day 2; the patient was discharged with an HR of 53 bpm.
- 12 patients had an adverse event of bradycardia during the first-dose observation period; 8 patients (1%) reported symptomatic bradycardia, and 4 patients reported asymptomatic bradycardia. No patient required treatment for bradycardia.

### *Symptomatic Bradycardia*

- Dizziness was the most common symptom of bradycardia observed following fingolimod first-dose administration and observation; all bradycardia symptoms were mild except for 1 report of dizziness of moderate severity **(Table 2)**.
- Mean ± SD HR maximally decreased to 53.6±8.53 (range, 38–64) bpm during bradycardia events and recovered to 62.6±9.46 (range, 52–80) bpm after resolution of bradycardia symptoms.

**Table 2. Symptoms of bradycardia occurring within 2 days after fingolimod first-dose administration (n=9*)**

| Symptom, n (%) | Fingolimod 0.5 mg (n=783) |
|---|---|
| Dizziness | 6 (0.8) |
| Gait disturbance | 1 (0.1) |
| Cardiac discomfort | 1 (0.1) |
| Dyspnea | 1 (0.1) |
| Palpitations | 1 (0.1) |
| Fatigue | 1 (0.1) |

**Includes 8 patients with bradycardia events on day 1 and 1 patient with bradycardia reported on day 2.*

### *ECG 6 Hours Postdose*

- 137/783 patients (17.5%) had a postdose ECG performed within 6 hours.
- There were 28 new ECG findings that differed from baseline ECGs. The most common new ECG findings included first-degree AV block (n=11 [8.0%]) and sinus bradycardia (n=10 [7.3%]) **(Table 3)**.
- No second-degree AV blocks were detected.

**Table 3. New ECG findings within 6 hours postdose***

| Abnormality, n (%) | Fingolimod 0.5 mg (n=137) |
|---|---|
| First-degree AV block | 11 (8.0) |
| Sinus bradycardia | 10 (7.3) |
| Left anterior hemiblock | 1 (0.7) |
| Atrial premature complex | 2 (1.5) |
| Biphasic T waves | 1 (0.7) |

*AV=atrioventricular; ECG=electrocardiogram.*
**3 additional abnormalities were detected at unscheduled post–first dose ECGs before hour 6: 1 AV Mobitz 1, 1 sinus bradycardia, and 1 first-degree AV block. All 3 abnormalities had resolved by the 6-hour postdose ECG.*

## References

1. Kappos L, et al. *N Engl J Med.* 2010;362:387-401.
2. Cohen JA, et al. *N Engl J Med.* 2010;362:402-415.
3. Polman CH, et al. *Ann Neurol.* 2005;58:840-846.
4. Gilenya® (fingolimod). Full Prescribing Information, Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2012.

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