Fingolimod first-dose effects in the PREFERMS real-world study of patients with relapsing–remitting multiple sclerosis

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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; Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor (S1PR) modulator approved for the treatment of relapsing multiple sclerosis (MS)[a]
- Approximately 114,000 patients have been treated with fingolimod in both the clinical trial and post-marketing settings; total patient exposure now exceeds 195,000 patient-years[b]
- 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[1–5]
- PREFERMS (Prospective, Randomized, active-controlled, open-label study to Evaluate patient retention of Fingolimod versus approved first-line disease-modifying thErapies in adults with Relapsing–remitting Multiple Sclerosis [RRMS]) is a 12-month, phase 4, open-label, active-controlled, randomized, multicenter study. The study enrolled 881 patients, mostly in the early stages of RRMS, who were treatment-naïve or had been treated with one class of injectable disease-modifying therapy (iDMT; interferon β or glatiramer acetate) or dimethyl fumarate (<2-month exposure)
  - The primary endpoint is the rate of retention of patients on randomized treatment

[a]The approved indication may vary from country to country. In the United States, fingolimod is approved for the treatment of patients with relapsing forms of MS. In the EU, it is approved for the treatment of patients with highly active relapsing–remitting MS.
[b]Data as of November 30, 2014; Q4 Novartis Pharmaceuticals Interim Financial Report, January 2015

OBJECTIVE

- 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, pivotal, phase 3 clinical studies

METHODS

Study designs and participants

- PREFERMS study recruited male and female patients aged 18–65 years, diagnosed with RRMS defined by the 2010 revised McDonald criteria,[6] with an Expanded Disability Status Scale (EDSS) score ≤6
  - Patients who were either treatment-naïve or previously treated with no more than one class of DMT (interferon β, glatiramer acetate or dimethyl fumarate [<2-month exposure]) were randomized 1:1 to receive fingolimod 0.5 mg or iDMT for 1 year
  - The PREFERMS analysis group comprised 637 patients treated with fingolimod who underwent first-dose observation after initial randomization or switch to fingolimod during the study and represented the interim analysis group
- The pooled phase 3 study population included patients aged 18–55 years with a diagnosis of RRMS defined using the 2005 revised McDonald criteria,[7] who experienced at least one confirmed relapse in the previous year (or at least two in the previous 2 years) and who had an EDSS score of 0–5.5
  - Patients were randomized to receive:
    - Fingolimod 0.5 mg or 1.25 mg once daily versus placebo for 2 years in the FREEDOMS or FREEDOMS II studies[1,3]
    - Fingolimod 0.5 mg or 1.25 mg once daily versus intramuscular interferon β-1a for 1 year in the TRANSFORMS study[2]
  - Here, results are reported only for the approved fingolimod 0.5 mg dose
- In both the PREFERMS group and the pooled phase 3 study population, patients randomized to fingolimod 0.5 mg underwent ECG monitoring at baseline and 6 hours after first dose, with vital signs (sitting HR and blood pressure) recorded hourly
- Patients were either discharged after 6 hours or were required to undergo extended observation as follows:
  - Patients who developed a HR lower than 45 bpm or a new-onset second-degree or higher AV block were monitored until resolution of the finding
  - Patients who developed QTc interval of 500 ms or more at the 6-hour ECG were monitored overnight
  - Patients with their lowest post-dose HR at the end of the observation period were monitored until HR started to increase
  - Patients who experienced symptomatic bradycardia for which treatment was required stayed overnight with continuous ECG monitoring and returned to the clinic on day 2 for 6-hour monitoring for the second dose of study drug

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 from the PREFERMS population and the pooled phase 3 study safety population
- Differences between the PREFERMS group and the pooled phase 3 study population are descriptive only and no statistical comparisons are presented. Direct comparison across studies is not possible because of differences in factors such as study design, patient population criteria, control groups, outcome definitions and geographic dispersion of study sites

RESULTS

Study population

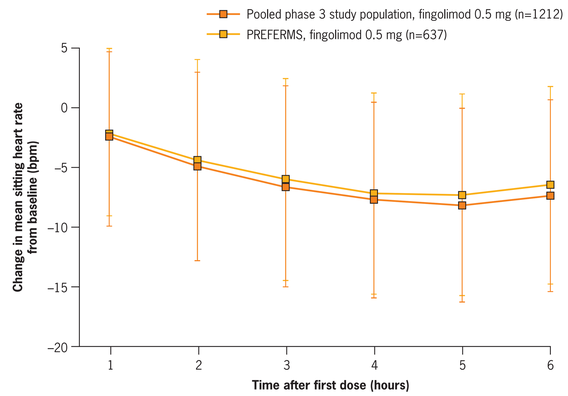
- Baseline demographics in PREFERMS (N=637) were generally consistent with those in the pooled phase 3 study population (N=1214) (**Table 1**)
  - Minor differences between the PREFERMS and pooled phase 3 study population groups were evident: in PREFERMS, patients were older (41.3 versus 37.8 years), a greater proportion were female (72.7% versus 70.3%) and a greater proportion were Black (15.1% versus 2.4%) (**Table 1**)
  - A higher proportion of patients in PREFERMS had existing hypertension compared with the pooled phase 3 study population (15.7% versus 7.8%; safety populations: n=637 and n=1212) (**Table 1**)
- In the PREFERMS and pooled phase 3 study population groups, few patients were receiving calcium-channel blocker (0.2%, both groups) or beta-blocker (1.6% and 2.3%, respectively) therapy, although over one-fifth (21.0%) of patients in the PREFERMS group were receiving selective serotonin-reuptake inhibitor therapy, which was twice as many as in the pooled phase 3 study population (9.3%) (**Table 1**)

Table 1. Baseline patient demographic characteristics and relevant medical history

	PREFERMS (N=637)	Pooled phase 3 study population (N=1214)
Sex, n (%)		
Female	463 (72.7)	853 (70.3)
Male	174 (27.3)	361 (29.7)
Age (years), mean (SD)	41.3 (10.72)	37.8 (8.85)
Age group (years), n (%)		
≤30	122 (19.2)	280 (23.1)
31–40	186 (29.2)	432 (35.6)
≥41	329 (51.6)	502 (41.4)
Race, n (%)		
Caucasian	526 (82.6)	1129 (93.0)
Black	96 (15.1)	29 (2.4)
Asian	1 (0.2)	10 (0.8)
Native American	1 (0.2)	3 (0.2)
Pacific Islander	1 (0.2)	0
Other	12 (1.9)	43 (3.5)
Weight (kg), mean (SD)	82.7 (20.57)	73.5 (16.72)
Body mass index (kg/m^2), mean (SD)	29.3 (7.10)	25.8 (5.30)
Safety population, n	**637**	**1212**
Hypertension, n (%)	100 (15.7)	95 (7.8)
Concomitant medication on day 1, n (%)		
Calcium-channel blocker	1 (0.2)	2 (0.2)
Beta-blocker	10 (1.6)	28 (2.3)
SSRI	134 (21.0)	113 (9.3)
Sitting HR (bpm), mean (SD)	73.5 (11.12)	73.0 (9.66)

No statistical comparisons are made. Direct comparison across studies is not possible because of differences in factors such as study design, patient population criteria, control groups, outcome definitions and geographic dispersion of study sites
bpm, beats per minute; HR, heart rate; SD, standard deviation; SSRI, selective serotonin-reuptake inhibitor

Figure 1. Mean sitting heart rate in the 6 hours following first dose



Data points represent change from baseline in sitting pulse (bpm), mean and standard deviation
No statistical comparisons are made. Direct comparison across studies is not possible because of differences in factors such as study design, patient population criteria, control groups, outcome definitions and geographic dispersion of study sites
bpm, beats per minute

Change in HR after first dose of fingolimod

- Pre-dose assessment mean (standard deviation) sitting HR was similar in both the PREFERMS group and the pooled phase 3 study population (73.5 [11.12] and 73.0 [9.66] bpm, respectively) (**Table 1**)
- Consistent with findings from the pooled phase 3 study population, HR following first-dose administration in the PREFERMS group reached a nadir of 66.1 (9.84) bpm at 5 hours (mean change from baseline, –7.3 bpm) and began to recover by 6 hours (**Figure 1**)

Clinical experience after first-dose administration

- Fingolimod at first-dose observation was generally well tolerated in the real-world setting (**Table 2**)
- 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 were discharged at 6 hours post-dose (**Table 2**)
- Few patients in PREFERMS required:
  - Extended observation after 6 hours (8.3% in the PREFERMS group; 12.9% in the pooled phase 3 study population)
  - Day-2 monitoring in the clinic (1.6% in the PREFERMS group; 2.6% in the pooled phase 3 study population)
  - Hospitalization (0.3% in the PREFERMS group; 1.2% in the pooled phase 3 study population)
    - A total of two patients were hospitalized in the PREFERMS group: one patient had new-onset Mobitz type I second-degree AV block and one patient showed 2:1 AV block. The events did not require treatment
- In both groups, most patients who underwent extended observation were asymptomatic and were discharged the same day (**Table 2**)
  - A single patient (0.2%) exhibited symptomatic bradycardia (light-headedness) in the PREFERMS group that did not require treatment; a similarly low rate was reported in patients in the pooled phase 3 study population (0.6%)
- No patients in the PREFERMS group permanently discontinued study drug on day 1; one patient discontinued in the pooled phase 3 study population (**Table 2**)

ECG findings at 6 hours post-dose

- Similar proportions of patients experienced first-degree AV block in the PREFERMS group and the pooled phase 3 study population (5.6% and 4.7%, respectively), and the incidence of Mobitz type I second-degree AV block was low in both groups (0.3% and 0.2%, respectively) (**Table 3**)
- 2:1 AV block was recorded only in the PREFERMS group, and in a single patient (0.2%) (**Table 3**)

Table 2. Clinical experience during initiation of fingolimod treatment

	PREFERMS (n=637)	Pooled phase 3 study population (n=1212)
Discharged at 6 hours	575 (90.3)	1006 (83.0)
Required extended monitoring after 6 hours	53 (8.3)	157 (12.9)
Required monitoring on day 2	10 (1.6)	32 (2.6)
Hospitalized	2 (0.3)	15 (1.2)
Study drug permanently discontinued on day 1	0	1 (0.1)
Bradycardia symptoms		
All	1 (0.2)	7 (0.6)
Mild	1 (0.2)	5 (0.4)
Moderate	0	2 (0.2)
Severe	0	0
Medication for bradycardia received during treatment initiation		
All	0	1 (0.1)
Isoprenaline	0	1 (0.1)
Atropine	0	0
Other	0	0

Data are n (%)
No statistical comparisons are made. Direct comparison across studies is not possible because of differences in factors such as study design, patient population criteria, control groups, outcome definitions and geographic dispersion of study sites

Table 3. AV conduction abnormalities of specific interest at 6 hours following first dose using 12-lead ECG

	PREFERMS (n=637)	Pooled phase 3 study population (n=1212)
ECG recordings	611	1190
First-degree AV block	34 (5.6)	56 (4.7)
Mobitz type I (Wenckebach) second-degree AV block	2 (0.3)	2 (0.2)
2:1 second-degree AV block	1 (0.2)	0
Mobitz type II second-degree AV block	0	0

Data are number of patients with ECG recordings (%)
Note: ambulatory ECG was only conducted in FREEDOMS II, not PREFERMS or the other phase 3 trials, and therefore are not included here
No statistical comparisons are made. Direct comparison across studies is not possible because of differences in factors such as study design, patient population criteria, control groups, outcome definitions and geographic dispersion of study sites
AV, atrioventricular; ECG, electrocardiogram

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Disclosures

N Tenenbaum, **X Meng**, **L Schofield** and **K Hawke**r are employees and stock holders of Novartis Pharmaceuticals Corporation.

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