Cardiac Effects of Fingolimod: First-Dose Observation

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CONCLUSIONS

- **Results from FIRST and FREEDOMS II confirm the transient and generally benign first-dose effect of fingolimod on HR and AV conduction.**
- **In the broader patient population of the postmarketing FIRST study, which was inclusive of patients with cardiac factors, the first-dose cardiac effects of fingolimod 0.5 mg were generally benign and consistent with observations in pivotal trials.**
- **The decrease in HR is well characterized, self-limited, and mostly asymptomatic.**
- **No Mobitz II or third-degree AV blocks were noted.**

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]
- Initiation of treatment with fingolimod is associated with a transient, self-limited, and mostly asymptomatic decrease in heart rate (HR) and slowing of atrioventricular (AV) conduction.[1,2]

OBJECTIVE

- To analyze the first-dose cardiovascular effects of fingolimod 0.5 mg in the FIRST and FREEDOMS II studies

METHODS

Study Designs

- FIRST was a 4-month, open-label, phase 3b study (N=2417) that evaluated the cardiac safety of fingolimod in a broader patient population with relapsing MS than those of previous phase 3 studies. Patients included those with controlled diabetes, chronic asthma, and cardiac factors (n=245), including β-blocker and/or calcium channel blocker use (n=120), resting HR of 45–54 beats per minute (bpm), Mobitz type I second-degree AV block, positive tilt test, or recurrent symptomatic bradycardia (NCT01127750).
- FREEDOMS II was a 2-year, double-blind, placebo-controlled, phase 3 study (N=1083) that evaluated the efficacy and safety of fingolimod in patients with relapsing-remitting MS (NCT00355134).

Assessments

- Day 1 assessments were made by an independent first-dose administrator to preserve blinding.
- For both studies, HR and blood pressure (BP) were recorded hourly for at least 6 hours following first-dose administration.
- Holter ambulatory electrocardiogram (AECG) monitoring was conducted for 24 hours predose and 6 hours postdose for 2415 patients in FIRST.
- Holter 24-hour AECG monitoring was conducted on day of first dose for 1057 patients enrolled in FREEDOMS II.

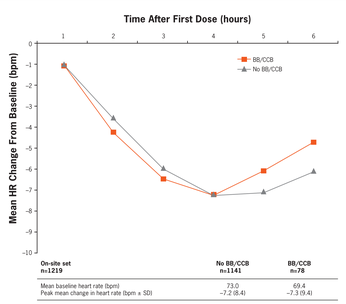
[a]*The approved indication may vary from country to country. In the United States, it is approved for the treatment of patients with relapsing forms of MS. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS.*

RESULTS

FIRST

- Nadir HR occurred 4–5 hours postdose, and mean decrease in HR was –7.4 and –6.5 bpm in patients without and with cardiac factors, respectively.
- Nadir HR occurred at 4 hours, and mean decrease in HR was –7.2 and –7.3 bpm in patients without and with concomitant β-blocker and/or calcium channel blocker use **(Figure 1)**.

Figure 1. FIRST study: mean change from baseline in heart rate by concomitant β-blocker/calcium channel blocker use



BB=β-blocker; CCB=calcium channel blocker; HR=heart rate.

- Postdose Holter AECG data showed that the overall study population incidence of Mobitz I and 2:1 second-degree AV block was 1.3% and 0.5%, respectively **(Table 1)**.

Table 1. FIRST study: incidence of AV blocks in 6-hour pretreatment vs 6-hour posttreatment with fingolimod 0.5 mg by cardiac factors and concomitant β-blocker and/or calcium channel blocker use

	Pretreatment Holter ECG		Post–first dose Holter ECG	
	Mobitz I AV block*	2:1 AV block	Mobitz I AV block*	2:1 AV block
No cardiac factors,† n=2120	2 (0.1)	0	18 (0.8)	6 (0.3)
Cardiac factors,† n=295	11 (3.7)	2 (0.7)	13 (4.4)	5 (1.7)
BB/CCB, n=120	0	0	0	0

Data are presented as number of patients (%); percentages are calculated using the safety population with AECG readings.
Study population incidence of Mobitz I = 1.3%; incidence of 2:1 AV block = 0.5%.
AV=atrioventricular; BB=β-blocker; CCB=calcium channel blocker.
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†Concomitant BB/CCB use, resting pulse 45–54 bpm, Mobitz I second-degree AV block, recurrent symptomatic bradycardia, or positive tilt test.

- Patients receiving β-blocker and/or calcium channel blocker treatment did not have any second-degree AV blocks recorded on Holter AECG within 6 hours of the first dose of fingolimod.
- No higher grade or complex AV block was observed.
- 1 patient had a >3-sec pause in both screening and postdose Holter AECG results, and 1 patient discontinued the study drug because of second-degree AV block.

FREEDOMS II

- The clinician-observed mean maximal decrease in HR was –8.5 bpm in the fingolimod 0.5-mg group.
  - This was consistent with a pooled analysis of first-dose observation data from three phase 3 studies.
- Holter 24-hour AECG data showed that the incidence of second-degree AV block with fingolimod vs placebo was 3.7% vs 2.0% (Mobitz I) and 2.0% vs 0% (2:1 AV block) **(Table 2)**.

Table 2. FREEDOMS II study: ambulatory ECG findings at screening and on day 1 (24 hours postdose)

	Screening		Day 1	
	Placebo (n=350)	Fingolimod 0.5 mg (n=354)	Placebo (n=346)	Fingolimod 0.5 mg (n=351)
Mobitz I AV block*	4 (1.1)	5 (1.4)	7 (2.0)	13 (3.7)
2:1 AV block	0	0	0	7 (2.0)
Mobitz II AV block	0	0	0	0

Data are presented as number of patients (%); percentages are calculated using the safety population with ambulatory ECG readings on screening, or day 1, respectively.
AV=atrioventricular.
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- Most first-occurrence second-degree AV blocks were observed <6 hours after first dose (Mobitz I: 2.6%; 2:1 AV block: 1.4%) vs 6–24 hours (Mobitz I: 1.1%; 2:1 AV block: 0.6%) **(Table 3)**.
- Mobitz II or higher degree AV blocks were not observed on day 1 of treatment.

Table 3. FREEDOMS II study: incidence of AV blocks by time interval postdose on day 1 (24 hours postdose)

	Placebo (n=346)	Fingolimod 0.5 mg (n=351)
Any second-degree or higher AV block		
0–6 hours postdose	0	11 (3.1)
>6–12 hours	0	1 (0.3)
>12 hours	7 (2.0)	2 (0.6)
Mobitz I second-degree AV block*		
0–6 hours postdose	0	9 (2.6)
>6–12 hours	0	2 (0.6)
>12 hours	7 (2.0)	2 (0.6)
2:1 AV block		
0–6 hours postdose	0	5 (1.4)
>6–12 hours	0	0
>12 hours	0	2 (0.6)

Data are presented as number of patients (%); percentages are calculated using the safety population with ambulatory ECG readings on day 1.
AV=atrioventricular.
** Wenckebach.*

References

1. Kappos L, et al. *N Engl J Med.* 2010;362(5):387-401.
2. Cohen JA, et al. *N Engl J Med.* 2010;362(5):402-415.

Disclosures

S. Randhawa, X. Meng, and R. Hashmonay are employees and stockholders of Novartis Pharmaceuticals Corporation.

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