Long-Term Safety and Tolerability of Fingolimod in Relapsing-Remitting MS

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CONCLUSION

- **With long-term dosing of up to 7 years, fingolimod was well tolerated with no new safety concerns in patients with relapsing MS.**

INTRODUCTION

- Fingolimod, a first-in-class sphingosine 1-phosphate receptor modulator, was the first oral therapy approved in the United States and more than 60 countries for treatment of relapsing multiple sclerosis (MS).[a]
- In clinical trials, fingolimod has demonstrated superior efficacy to placebo[1,2] and interferon β-1a (IFNβ-1a) intramuscular[3] (IM) and was generally well tolerated in patients with relapsing or relapsing-remitting MS.

OBJECTIVE

- To evaluate the long-term safety and tolerability of fingolimod using data from extension phases of the phase 2 study,[1] the pivotal phase 3 Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study,[2] and the Trial Assessing Injectable Interferon vs Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS)[3]

METHODS

Study Designs

- Phase 2 study
  - Patients with relapsing MS were randomized to receive once-daily fingolimod 1.25 or 5.0 mg or placebo for 6 months **(Figure 1)**.
  - In the long-term extension phase (up to 6.5 years), patients receiving placebo were re-randomized to once-daily, dose-blind fingolimod 1.25 or 5.0 mg; patients receiving fingolimod continued with their assigned dose (1.25 or 5.0 mg).
  - During study visits in months 15–24, all patients receiving fingolimod 5.0 mg were switched to open-label 1.25 mg. Subsequently (during visits in months 60–69), all patients were switched to fingolimod 0.5 mg until the end of the study.
- FREEDOMS
  - Patients with relapsing-remitting MS were randomized to receive once-daily fingolimod 0.5 or 1.25 mg or placebo for 2 years **(Figure 2).**
  - In the extension phase (up to 2 years), patients continued to receive the fingolimod dose assigned in the core phase (0.5 or 1.25 mg once daily) or were re-randomized (1:1) from placebo to fingolimod 0.5 or 1.25 mg once daily.
  - Subsequently, all patients receiving the 1.25-mg dose were switched to open-label fingolimod 0.5 mg following discontinuation of the 1.25-mg dose from further clinical development.
- TRANSFORMS
  - Patients with relapsing-remitting MS were randomized to receive once-daily fingolimod 0.5 or 1.25 mg or IFNβ-1a IM (30 µg once weekly) for 1 year **(Figure 3)**.
  - In the extension phase (up to 3.5 years), patients receiving fingolimod continued on their original dose and patients receiving IFNβ-1a IM were randomized to once-daily fingolimod 0.5 or 1.25 mg.
  - Subsequently, all patients were switched to open-label fingolimod 0.5 mg after approximately 2.8 years.

[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.*

Figure 1. Study design of phase 2 study

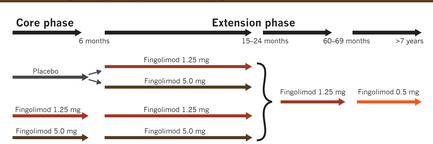

Figure 2. Study design of FREEDOMS

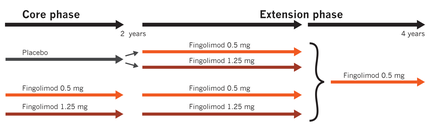

Figure 3. Study design of TRANSFORMS

IFNβ-1a=interferon β-1a.

Safety Assessments

- Safety data were assessed using descriptive statistics and included
  - Adverse events (AEs) and serious AEs (SAEs)
  - Physical examinations, electrocardiography, and vital signs
  - Laboratory evaluations: hematology, blood chemistry
  - High-resolution computed tomography, pulmonary function tests
  - Ophthalmologic assessment (eg, ophthalmologic examination, optical coherence tomography)
  - Dermatologic examinations

RESULTS

Phase 2 Extension

- 255 of 281 (90.7%) patients completed the phase 2 study, and 122 of 281 (43.4%) completed the phase 2 extension and entered the long-term follow-up study; 133/281 (47.3%) patients completed at least 6 years of treatment, and 94/281 (33.5%) patients completed at least 7 years.
- AEs were reported in similar proportions of patients across treatment groups **(Table 1)**.

Table 1. Phase 2 study: AEs and SAEs

Event, n (%)	Placebo to fingolimod* n=93	Fingolimod 1.25 mg* n=94	Fingolimod 5 mg* n=94
Any AE	89 (95.7)	92 (97.9)	93 (98.9)
Any SAE	25 (26.9)	19 (20.2)	32 (34.0)
AE resulting in discontinuation	22 (23.7)	27 (28.7)	26 (27.7)
Most commonly reported AEs†			
Nasopharyngitis	34 (36.6)	39 (41.5)	42 (44.7)
Headache	28 (30.1)	35 (37.2)	25 (26.6)
Fatigue	22 (23.7)	23 (24.5)	16 (17.0)
Influenza	16 (17.2)	23 (24.5)	22 (23.4)
Back pain	22 (23.7)	16 (17.0)	19 (20.2)
Upper respiratory tract infection	19 (20.4)	19 (20.2)	18 (19.1)
Lymphopenia	13 (14.0)	18 (19.1)	18 (19.1)
Pain in extremity	18 (19.4)	15 (16.0)	15 (16.0)
Cough	12 (12.9)	16 (17.0)	19 (20.2)
ALT increased	18 (19.4)	12 (12.8)	15 (16.0)
Diarrhea	12 (12.9)	18 (19.1)	15 (16.0)
Arthralgia	17 (18.3)	14 (14.9)	12 (12.8)
Hypertension	13 (14.0)	19 (20.2)	11 (11.7)

AE=adverse event; ALT=alanine aminotransferase; SAE=serious adverse event.
**All patients were switched to fingolimod 0.5 mg after approximately 5 years.*
†AEs reported in ≥15% of patients in any treatment group.

- The most common AEs were nasopharyngitis, headache, and fatigue.
- Incidence of AEs leading to discontinuation was 23.7%–28.7% and incidence of SAEs was 20.2%–34.0% across treatment groups.
- 16 (5.7%) cases of herpes zoster infection and 14 (5.0%) cases of skin malignancies were reported.
- No chronic effects of fingolimod on heart rate or atrioventricular conduction were observed over 7 years of treatment.

FREEDOMS

- 920 of 1272 (72%) patients completed the core study and entered the long-term extension; 773 (84%) of these completed the study.
- AEs were reported in similar proportions of patients across treatment groups **(Table 2)**.

Table 2. FREEDOMS: AEs and SAEs

Event, n (%)	Placebo to fingolimod 0.5 mg n=155	Placebo to fingolimod 1.25 mg* n=145	Fingolimod 0.5 mg n=331	Fingolimod 1.25 mg* n=289
Any AE	148 (95.5)	133 (91.7)	314 (94.9)	272 (94.1)
Any SAE	11 (7.1)	17 (11.7)	31 (9.4)	31 (10.7)
AE resulting in discontinuation	14 (9.0)	14 (9.7)	15 (4.5)	16 (5.5)
Most commonly reported AEs†				
Nasopharyngitis	44 (28.4)	39 (26.9)	84 (25.4)	82 (28.4)
Lymphopenia	17 (11.0)	19 (13.1)	52 (15.7)	52 (18.0)
Upper respiratory tract infection	24 (15.5)	23 (15.9)	58 (17.5)	39 (13.5)
Influenza	12 (7.7)	9 (6.2)	33 (10.0)	30 (10.4)
Headache	26 (16.8)	18 (12.4)	41 (12.4)	27 (9.3)
Lymphocyte count decreased	14 (9.0)	12 (8.3)	16 (4.8)	29 (10.0)
ALT increased	9 (5.8)	16 (11.0)	11 (3.3)	10 (3.5)
Most commonly reported SAEs‡				
Cholelithiasis	0	0	0	2 (0.7)
Appendicitis	0	0	2 (0.6)	1 (0.3)
Basal cell carcinoma	0	2 (1.4)	3 (0.9)	2 (0.7)
Uterine leiomyoma	0	0	2 (0.6)	0
MS relapse	0	0	0	3 (1.0)
Epilepsy	0	0	2 (0.6)	0
Depression	0	2 (1.4)	0	0

AE=adverse event; ALT=alanine aminotransferase; MS=multiple sclerosis; SAE=serious adverse event.
**All patients receiving fingolimod 1.25 mg were switched to fingolimod 0.5 mg after the fingolimod 1.25-mg dose was discontinued from all MS clinical studies.*
†AEs reported in ≥10% of patients in any treatment group during the extension phase.
‡SAEs reported in ≥2 patients in any organ system class in any treatment group.

- The most common AEs were nasopharyngitis, lymphopenia, and upper respiratory tract infection.
- Incidence of AEs leading to discontinuation was 4.5%–9.7% and SAE incidence was low (7.1%–11.7%) and similar across treatment groups.
- Basal cell carcinoma was reported in 7 (0%–1.4%) patients and elevated alanine aminotransferase was reported in 46 (3.3%–11.0%) patients.

TRANSFORMS

- 1030 of 1292 (79.7%) patients completed the core study and entered the long-term extension; 772 (75.2%) of these completed the study.
- AEs were reported in similar proportions of patients across treatment groups **(Table 3)**.
- Nasopharyngitis, lymphopenia, and headache were most common AEs reported and were comparable across all treatment groups.
- Incidence of AEs leading to discontinuation was 7.8%–16.7% and SAE incidence was 12.1%–21.3%.
- There were 35 total cases (2.7%–4.8% across treatment groups) of herpes zoster infection; 5 cases were reported as serious AEs. Macular edema occurred in 3 patients; breast cancer occurred in 3 patients.

Table 3. TRANSFORMS: AEs and SAEs

Event, n (%)	IFNβ-1a to fingolimod 0.5 mg n=167	IFNβ-1a to fingolimod 1.25 mg* n=174	Fingolimod 0.5 mg n=356	Fingolimod 1.25 mg* n=330
Any AE	154 (92.2)	168 (96.6)	337 (94.7)	312 (94.5)
Any SAE	21 (12.6)	37 (21.3)	55 (15.4)	40 (12.1)
AE resulting in discontinuation	13 (7.8)	29 (16.7)	30 (8.4)	32 (9.7)
Most commonly reported AEs†				
Nasopharyngitis	51 (30.5)	53 (30.5)	112 (31.5)	105 (31.8)
Lymphopenia	26 (15.6)	39 (22.4)	52 (14.6)	71 (21.5)
Headache	38 (22.8)	36 (20.7)	69 (19.4)	51 (15.5)
Upper respiratory tract infection	21 (12.6)	28 (16.1)	38 (10.7)	47 (14.2)
Lymphocyte count decreased	16 (9.6)	27 (15.5)	26 (7.3)	46 (13.9)
Back pain	18 (10.8)	18 (10.3)	35 (9.8)	43 (13.0)
Urinary tract infection	18 (10.8)	10 (5.7)	40 (11.2)	40 (12.1)
Melanocytic nevus	16 (9.6)	16 (9.2)	35 (9.8)	37 (11.2)
Cough	20 (12.0)	22 (12.6)	33 (9.3)	32 (9.7)
Diarrhea	15 (9.0)	20 (11.5)	35 (9.8)	28 (8.5)
Influenza	17 (10.2)	17 (9.8)	36 (10.1)	27 (8.2)
ALT increased	15 (9.0)	19 (10.9)	19 (5.3)	25 (7.6)
Most commonly reported SAEs‡				
Lymphopenia	0	2 (1.1)	1 (0.3)	1 (0.3)
Bradycardia	1 (0.6)	3 (1.7)	0	1 (0.3)
Second-degree AV block	0	2 (1.1)	0	0
Vertigo	0	2 (1.1)	0	2 (0.6)
Macular edema	1 (0.6)	2 (1.1)	0	0
Cholelithiasis	0	0	4 (1.1)	0
Herpes zoster	1 (0.6)	1 (0.6)	0	3 (0.9)
Pneumonia	0	0	1 (0.3)	3 (0.9)
Cystitis	0	0	2 (0.6)	0
Lower limb fracture	0	0	2 (0.6)	0
Road traffic accident	0	0	2 (0.6)	0
Basal cell carcinoma	1 (0.6)	2 (1.1)	6 (1.7)	2 (0.6)
Breast cancer	0	1 (0.6)	2 (0.6)	0
MS relapse	2 (1.2)	0	4 (1.1)	4 (1.2)
Spontaneous abortion	0	0	2 (0.6)	1 (0.3)
Menorrhagia	0	2 (1.1)	0	0
Dyspnea	0	0	0	2 (0.6)

AE=adverse event; ALT=alanine aminotransferase; AV=atrioventricular; MS=multiple sclerosis; SAE=serious adverse event.
**All patients receiving fingolimod 1.25 mg were switched to fingolimod 0.5 mg.*
†AEs reported in ≥10% of patients in any treatment group.
‡SAEs reported in ≥2 patients in any organ system class in any treatment group.

References

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Disclosures

X. Meng, R. Hashmonay, and N. Tenenbaum are employees and stockholders of Novartis Pharmaceuticals Corporation.

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