

# Fingolimod for the treatment of multiple sclerosis: a review of the evidence from the FREEDOMS and TRANSFORMS studies

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Fingolimod (Gilenya®) is the first oral immunomodulating drug approved for relapsing–remitting multiple sclerosis. Its novel mechanism of action inhibits the egress of autoreactive B and T cells from lymph nodes, thus preventing them from crossing into the CNS. Two recent large Phase III clinical trials both met their primary end points clearing the way for approval by the US FDA in September 2010. Despite robust clinical efficacy, safety concerns arose in both trials, including, but not limited to, increased risk of infection, cardiac issues and a higher incidence of cancer. Further long-term data will clarify these safety issues to enable clinicians to feel comfortable when prescribing fingolimod on a routine basis. This article will review the clinical trial data from the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) and FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) studies.

**Keywords:** fingolimod • immunomodulating drug • lymphocyte • multiple sclerosis • neuroprotection • sphingosine 1-phosphate receptor

Multiple sclerosis (MS) is an autoimmune disease of the brain and spinal cord for which there is no cure. MS commonly begins between the ages of 20–50 years and is the most common cause of neurological disability in young adults. Over the past 17 years, seven therapeutic agents were approved for the treatment of relapsing–remitting MS. All of these immunomodulating drugs (IMDs) were shown to have a beneficial effect on disease outcome measures in controlled clinical trials, but unfortunately required parenteral administration. All of these IMDs had shortcomings that include, but are not limited to, injection fatigue, flu-like symptoms, noncompliance with injections, suboptimal response due to breakthrough disease, an increased risk in the development of a potentially fatal brain disease in the case of one drug (natalizumab) and cardiotoxicity/increased risk of leukemia in another (mitoxantrone). In short, an effective oral drug was sorely needed. Fingolimod (Gilenya®) represents the first oral IMD approved by the US FDA for the treatment of relapsing–remitting MS.

## Fingolimod overview

Although the putative cause of MS is unknown, it is believed that activated B and T cells play a crucial role in the pathogenesis of the disease. Fingolimod is a sphingosine 1-phosphate receptor modulator that prevents activated B and T cells from leaving the lymph system, thereby acting as a functional antagonist [1]. The molecule is derived from the fungus *Isaria sinclairii*, long thought to have immunomodulating properties. Fingolimod was originally studied in organ transplant patients as an anti-organ rejection drug, but failed to show superiority over standard immunosuppressive agents. At the 0.5 mg dose that was recently approved by the FDA, fingolimod

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causes a 73% reduction in the circulating lymphocyte count [1]. The lymphocyte reduction occurs within hours and reaches its nadir in 1 week. The half life of fingolimod is 6–9 days with a T<sub>max</sub> of 12–16 h [2]. Steady state is achieved in the circulation in 1–2 months [2]. In addition, fingolimod is highly lipophilic and binds to glial cells and the myelin sheath in the CNS. Of particular interest is the fact that animal studies have shown that remyelination occurs in the setting of fingolimod treatment, suggesting a potential neuroprotective effect. The mechanism by which this occurs is currently not well understood [3]. Recently, Th17 cells were discovered and appear to play a pivotal role in the pathogenesis of experimental autoimmune encephalomyelitis [4]. New evidence suggests fingolimod reduces this proinflammatory cell population [5].

### TRANSFORMS study

The Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis (TRANSFORMS) study was a 12-month double-blind, double-dummy comparator trial of 1292 patients at 172 clinical centers in 18 countries [1]. Patients were required to have an expanded disability status scale (EDSS) of 0–5.5. Inclusion criteria required the patients to have had one relapse in the past year or two relapses within the past 2 years. Patients were randomly assigned equally into three arms to receive:

- Intramuscular IFN-β1a weekly/placebo oral daily pill
- Fingolimod 1.25 mg daily/placebo intramuscular injection weekly
- Fingolimod 0.5 mg daily pill/placebo intramuscular injection weekly

The primary end point was the annualized relapse rate with secondary outcome measures that included new or enlarged T2 lesions and progression of disability sustained for at least 3 months.

### ■ Results

A total of 87% of patients finished the trial. The annualized relapse rate was significantly lower in both fingolimod groups compared with the IFN-β1a group. In the fingolimod 0.5 mg arm, there was a 52% reduction in the relapse rate and a 38% reduction in the fingolimod 1.25 mg arm ( $p < 0.0001$  vs  $p = 0.0004$ , respectively) [1]. Although more than 50% of patients had prior exposure to IMDs, there was no difference in the magnitude of the treatment effect between patients naive to treatment versus those with prior exposure [1]. MRI outcome measurements were statistically significant in favor of fingolimod at both doses in regards to new or enlarged T2 lesions, gadolinium-enhancing lesions, and mean percentage

reduction in brain volume at 12 months [1]. However, there was no change in T2 lesion volume over 1 year. There was no significant difference in the disability progression between the three groups after 12 months, which was not unexpected given the short duration of the trial.

### ■ Adverse events

Overall, there was no difference in adverse events reported in the three study groups. Serious adverse events leading to drug discontinuation were highest in the fingolimod 1.25 mg arm [1]. The most common reason for discontinuation was bradycardia or atrioventricular block with all events occurring after the first dose of fingolimod. There were no persistent abnormalities seen on electrocardiogram in patients who continued on fingolimod. There were two deaths in the clinical trial. Both occurred in the higher dose fingolimod arm. The first case was a patient who developed primary disseminated zoster after treatment with high-dose intravenous solumedrol therapy for an MS relapse. She returned to her job and was exposed to chicken pox [1]. Varicella zoster virus titer was negative prior to her enrollment in the clinical trial. The second case involved a man who developed herpes simplex encephalitis. Antiviral therapy was delayed as his symptoms were initially felt to be from an acute MS relapse. He also received high-dose intravenous solumedrol therapy as per study protocol [1]. Two other patients died after the trial was completed. One patient died of metastatic breast cancer 10 months after study drug discontinuation. The second patient died from progressive neurological deterioration 6 months after the study drug was stopped. The overall infection rate was similar across the three study arms [1]. The only serious infections that were reported in more than one patient were appendicitis and herpes infections. Macular edema was found in six patients during the trial, four in the 1.25 mg group and two in the 0.5 mg group [1]. Five of the six cases occurred within the first 4 months of therapy. The edema resolved within 3 months after discontinuation of fingolimod in four patients, was unchanged 1 month after discontinuation in one patient, and was reduced 8 months after discontinuation in one patient.

There were a total of 14 cancers reported during the trial, 12 of which occurred in the fingolimod arms (Table 1) [1]. There does not appear to be an increased risk of malignancy with increased exposure to fingolimod and the cases of skin cancer that were found were potentially related to increased screening and surveillance for such malignancies.

The TRANSFORMS extension study was a 1-year study with a primary outcome measure to determine the percentage of patients free from confirmed relapses [6]. All of the patients who were on IFN-β1a were switched to either fingolimod 0.5 or 1.25 mg in a 1:1 ratio. The

patients who were on fingolimod 0.5 or 1.25 mg during the core phase of TRANSFORMS were maintained on their dosing schedule. The percentage of patients who were relapse free at 2 years is as follows: 73% for the fingolimod 0.5 mg group, 71% for the fingolimod 1.25 mg group, and 60% for the IFN- $\beta$ 1a group who were switched to either 0.5 or 1.25 mg from months 12 to 24 ( $p < 0.001$ ) [6]. Patients started on IFN- $\beta$ 1a never 'caught up' to the patients in either fingolimod arm during the second year extension phase of the trial. Unique safety issues were seen during the extension phase in this subgroup. There was a higher incidence of herpes infections in both fingolimod arms, elevated liver enzymes and first-degree AV block (three cases in the fingolimod 1.25 mg group only) [6]. This may raise some practical clinical concerns about monitoring patients who switch from interferon products to fingolimod.

### FREEDOMS

The FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) trial was a 24-month randomized, double-blind study designed to determine the efficacy of lower dose fingolimod (0.5 mg) and higher dose fingolimod (1.25 mg) versus placebo [7]. A total of 1272 patients at 138 centers in 22 countries participated in the study. As was the case with the TRANSFORMS study, the primary outcome measure was the annualized relapse rate. Patients aged 18–55 years were enrolled if they met the inclusion criteria, one of which required having one relapse in the past year or two relapses in the past 2 years. An important secondary outcome measure was the absence of sustained disability progression at 3 and 6 months.

#### ■ Results

Both fingolimod groups did better than placebo in terms of annualized relapse rates: 54% for the 0.5 mg dose and 60% for the 1.25 mg dose ( $p < 0.001$ ) [7]. There was no statistical difference in relapse rates between the two fingolimod groups. A key secondary end point was the confirmed absence of disability progression. This was statistically significant at 3 and 6 months, respectively [7]. The EDSS was unchanged or improved slightly in both fingolimod groups but worsened in the placebo group. Patients on fingolimod demonstrated significantly less new gadolinium-enhancing lesions as well as new or enlarging T2 lesions [7]. The median volume of T2 lesions decreased over 24 months for patients taking fingolimod while the placebo patients had an increase in median T2 volume [7].

Adverse events in the FREEDOMS trial were similar to the TRANSFORMS study [7]. The rate of herpes infections was similar across all three groups. Macular edema was detected in seven patients on study drug, with

**Table 1. Adverse events in the TRANSFORMS study.**

| Event                                     | Fingolimod           |                     | IFN- $\beta$ 1a<br>(n = 431) |
|---|----------------------|---------------------|------------------------------|
|   | 1.25 mg<br>(n = 420) | 0.5 mg<br>(n = 429) |                              |
| Basal-cell carcinoma                      | 2 (0.5)              | 3 (0.7)             | 1 (0.2)                      |
| Melanoma (including <i>in situ</i> )      | 0                    | 3 (0.7)             | 0                            |
| Breast cancer (including <i>in situ</i> ) | 2 (0.5)              | 2 (0.5)             | 0                            |

five of the cases occurring in the first 3 months of therapy. All of the macular edema cases occurred in patients on the higher dose of fingolimod. A total of six patients had resolution of visual symptoms within 6 months of discontinuing study drug. Three patients died during the clinical trial, two in the placebo arm (pulmonary embolism and traffic accident) and one patient died in the higher dose fingolimod (suicide) [7]. There was no increased risk of cancer in the treatment group.

### Future perspective

Any new, effective therapy is welcomed by patients suffering from a chronic disease. MS is no different. Patients are tired of undertaking home injection therapies and wish for the ease and convenience of oral IMD therapies. Fingolimod is the first oral IMD therapy approved for use in relapsing–remitting MS. Clinicians have also wished for an improved treatment arsenal as the current available therapies often produce suboptimal results in patient outcomes. However, a number of questions arise with the advent of fingolimod.

- If a patient is stable clinically and radiographically on a current IMD therapy and is tolerating the drug well, does it make sense to switch therapies?
- Will patients on fingolimod have an increased risk of developing infections and/or cancer? Fingolimod is known to reduce the circulating lymphocyte count by approximately 70%. By definition, this is an immunosuppressive agent and as with other such drugs, one would expect to see an increased risk for impaired immune surveillance leading to a higher risk of cancer and infections;
- Will fingolimod help patients with secondary progressive or primary progressive MS? Certainly there is a large unmet treatment need in this population of patients. A study of fingolimod for the treatment of PPMS is currently ongoing;
- How much will fingolimod cost? Currently, patients are used to paying low copays for prescription medications at their pharmacies and may be surprised by the

cost of this daily oral pill as it appears the price will be higher than the current platform therapies available on the market.

- Finally, where fingolimod will be utilized in the clinician's armamentarium of MS therapeutics remains unclear at this time. For instance, there is a known increased risk of developing progressive multifocal leukoencephalopathy in patients on natalizumab who have received immunosuppressant drugs prior to the initiation of natalizumab therapy [8]. It is unknown if patients who receive fingolimod therapy and switch over to natalizumab will be at greater risk of developing PML. Despite these concerns, more than 90% of

patients in the FREEDOMS and TRANSFORMS studies tolerated fingolimod well enough to complete the trial.

### Financial & competing interests disclosure

*The authors participated in the TRANSFORMS study and did receive standard compensation for work done associated with the study. Bhupendra O Khatri receives a consulting fees from Novartis, Serono, Pfizer, Teva and Biogen Idec. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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## Executive summary

### Fingolimod (Gilenya®)

- Fingolimod represents the first oral IMD therapy for the treatment of relapsing MS. Its novel mechanism of action prevents the signaling of activated B and T cells from leaving the lymph nodes and thus prevents these cells from gaining access to the CNS.

### Clinical trial data

- In the TRANSFORMS study, fingolimod met its primary end point in that it was shown to be statistically more effective in reducing the relapse rate compared with intramuscular IFN-β1a.
- In the FREEDOMS study, fingolimod-treated patients had a statistically significant reduction in the risk of accumulating disability at 3 and 6 months versus placebo.

### Side effects

- Although the robust clinical data and ease of administration make fingolimod an attractive treatment option, long term safety issues related to impaired immune surveillance (infection and malignancy) and side effects (bradycardia, AV block and macular edema) need further investigation.
- Patients screened for the TRANSFORMS and FREEDOMS studies were excluded from these trials if they had hypertension, diabetes mellitus, asthma, macular edema or clinically significant systemic disease.

### Neuroprotection

- A hot button topic in the field of MS is neuroprotection. Fingolimod appears to have lipophilic properties allowing CNS penetration and may exhibit beneficial effects on microglia. Objective brain MRI measurements showed a statistically significant reduction in the rate of brain volume loss.

### Cost

- There has been a meteoric rise in the cost of the IMDs used to treat MS. MS clinicians will increasingly have to weigh the balance between cost and efficacy of the IMDs used in MS. This high cost will only strengthen the need for quality patient assistance programs to help defray the cost of these medications for patients who already run the risk of decreased earning potential in their employment due to physical and cognitive disability.

## Bibliography

- Cohen JA, Barkhof F, Comi G *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* 362, 402–415 (2010).
- Gilenya®, package insert. Novartis Pharmaceuticals Corporation. East Hanover, NJ, USA.
- Foster CA, Howard LM, Schweitzer A *et al.* Brain penetration of the oral immunomodulatory drug FTY720 and its phosphorylation in the central nervous system during experimental autoimmune encephalomyelitis: consequences for mode of action in multiple sclerosis. *J. Pharmacol. Exp. Ther.* 323, 469–476 (2007).
- Slavin AJ, Zamvil SS. FTY720 and central memory. *Neurology* 75, 388–389 (2010).
- Mehling M, Lindberg R, Raulf F *et al.* Th17 central memory cells are reduced by FTY720 in patients with multiple sclerosis. *Neurology* 75, 403–410 (2010).
- Khatri BO, Barkhof F, Comi G *et al.* Oral fingolimod (FTY720) reduces the rate of relapses that require steroid intervention or hospitalization compared with intramuscular interferon B-1a: results from a Phase III study (TRANSFORMS) in multiple sclerosis. Presented at: *Poster Session III: Multiple Sclerosis: Therapeutics*. AAN, Seattle, WA, USA, April 2009.
- Kappos L, Radue EW, O'Connor P *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* 463, 387–401 (2010).
- Tysabri®, package insert. Biogen Idec, Cambridge, MA, USA.