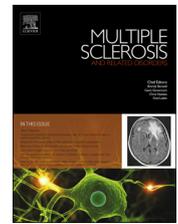


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Fingolimod in relapsing multiple sclerosis: An integrated analysis of safety findings

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Abstract

Background: Fingolimod 0.5 mg once daily is the first approved oral therapy for relapsing multiple sclerosis (MS).

Objective: To report integrated long-term safety data from phase 2/3 fingolimod studies.

Methods: Descriptive safety data are reported from the FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS) study, a 24-month, randomized, double-blind study comparing fingolimod 0.5 mg and 1.25 mg with placebo, and an All Studies group (patients who received fingolimod 0.5 mg ($n=1640$) or 1.25–0.5 mg ($n=1776$) in phase 2/3 studies and associated extensions). Relevant post-marketing experience, up to December 2011, is included.

Results: The incidence of adverse events (AEs) and serious AEs (SAEs) was similar with fingolimod and placebo in FREEDOMS. In the All Studies group, fingolimod 0.5 mg was associated with transient, rarely symptomatic (0.5%), bradycardia and second-degree atrioventricular block on treatment initiation, minor blood pressure increases, frequent (9%) but generally asymptomatic liver enzyme elevations, and macular oedema (0.4%). The incidences of infections (including serious and herpes infections), malignancies, SAEs and treatment discontinuations due to AEs were similar with fingolimod 0.5 mg and placebo.

Abbreviations: AV, atrioventricular; FREEDOMS, FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; HPS, haemophagocytic syndrome; LRTI, lower respiratory tract infection; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; S1PR, sphingosine 1-phosphate receptor; TRANSFORMS, Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis; ULN, upper limit of normal

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Conclusion: The safety profile of fingolimod has been well characterized in this large combined trial population. Although infrequent SAEs can occur, there is no increased risk of infections, malignancies or serious cardiovascular events versus placebo.

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1. Introduction

Fingolimod (FTY720; Gilenya[®], Novartis Pharma AG, Basel, Switzerland) is the first of a new class of therapeutic compounds - the sphingosine 1-phosphate receptor (S1PR) modulators (Brinkmann et al., 2010; Chun and Hartung, 2010). It is approved as a once-daily oral therapy at 0.5 mg for the treatment of relapsing forms of multiple sclerosis (MS) in many countries (European Medicines Agency, 2011; US Food and Drug Administration, 2010). S1PRs are expressed in many tissues, including cells of the immune, cardiovascular and central nervous systems (Brinkmann, 2007). In the immune system, modulation of S1PRs by fingolimod results in the retention of circulating lymphocytes in the lymph nodes, with a reversible reduction of peripheral blood lymphocyte counts to approximately 30% of pre-treatment values, which is postulated to reduce recirculation of autoreactive lymphocytes and to prevent infiltration into the central nervous system (Brinkmann et al., 2010; Chun and Hartung, 2010). Fingolimod treatment specifically retains naïve T cells and central memory T cells in the lymph nodes, while largely sparing effector memory T cells (Mehling et al., 2008; Pham et al., 2008), which are important in immune surveillance (Lanzavecchia and Sallusto, 2000).

Fingolimod has demonstrated superior efficacy to placebo as well as to the approved first-line therapy, intramuscular (IM) interferon beta-1a (Avonex[®], Biogen Idec, Weston, MA, USA) in a phase 2 study and three phase 3 studies: FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS), FREEDOMS II and Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) in relapsing MS (Calabresi et al., in press; Cohen et al., 2010; Comi et al., 2010; Kappos et al., 2006, 2010; Khatri et al., 2011).

Here, we report safety data from an integrated analysis of FREEDOMS, FREEDOMS II, TRANSFORMS, the single MS phase 2 study and their extensions. In addition, we report deaths from the clinical development programme and post-marketing setting from May 2003 to December 2011, as well as other post-marketing safety cases of particular interest.

2. Materials and methods

2.1. Analysis groups

Results are reported from the following two analysis groups: the FREEDOMS group, which included all patients enrolled in the 2-year core phase of FREEDOMS (Kappos et al., 2010) (ClinicalTrials.gov identifier NCT00289978), and the All Studies group, which was an integrated analysis of safety data from all patients who received once-daily fingolimod in the 6-month, placebo-controlled, phase 2 core study

(1.25 mg or 5.0 mg; ClinicalTrials.gov identifier NCT00333138), the 2-year phase 3 core studies (FREEDOMS, FREEDOMS II [0.5 mg or 1.25 mg; ClinicalTrials.gov identifier NCT00355134]) and the 1-year phase 3 core study TRANSFORMS (0.5 mg or 1.25 mg; ClinicalTrials.gov identifier NCT00340834), and their completed long-term extensions.

Following approval of fingolimod 0.5 mg, all patients receiving fingolimod 1.25 mg in study extensions were switched to fingolimod 0.5 mg (this group was referred to in the All Studies analysis as fingolimod 1.25-0.5 mg). Patients remained in study extensions until 31 March 2011 (database lock) or until the cut-off for the ongoing FREEDOMS II extension (Figure 1). Patients were then transferred to the ongoing, long-term observational safety study 2399 (ClinicalTrials.gov identifier NCT01281657).

Study methodologies for FREEDOMS, FREEDOMS II, TRANSFORMS and the phase 2 study have been previously reported in accordance with CONSORT guidelines (Cohen et al., 2010; Kappos et al., 2006, 2010; Khatri et al., 2011). The study design and entry criteria for FREEDOMS II closely match those of FREEDOMS. The FREEDOMS group provides a 24-month, placebo-controlled comparison with fingolimod, and the All Studies group provides fingolimod safety data from a larger population with longer follow-up. Data describing cardiovascular effects following treatment initiation come only from the phase 3 studies because data on these effects were not collected in a compatible manner during the phase 2 core study. All deaths are reported for patients exposed to fingolimod during May 2003-December 2011, including clinical trials and post-marketing data.

2.1.1. Outcome measures and analyses

Results are reported for the safety population, comprising all patients who received at least one dose of study drug. Safety analyses were summarized by means of descriptive statistics; numerical (not statistical) differences are described. The proportions of patients experiencing adverse events (AEs) and serious AEs (SAEs) are reported for the FREEDOMS group and the All Studies group (with a focus on the fingolimod 1.25-0.5 mg and 0.5 mg groups). Also reported in more detail are the following AEs of special interest: treatment initiation effects (pooled data from phase 3 studies only), infections, hypertension and notable increases in blood pressure, macular oedema, malignancies, liver enzyme effects and lymphopenia (FREEDOMS group; All Studies group). Patients were required to interrupt dosing if lymphocyte counts fell below a threshold ($<0.1 \times 10^9/L$ initially, later increased to $<0.2 \times 10^9/L$ at the request of the regulatory agency, but not due to any safety signal). Dosing could resume once lymphocyte counts reached $0.6 \times 10^9/L$. Due to a potential risk for teratogenesis, as seen in animals, fingolimod is not recommended for use in women who are, or want to become, pregnant. Full details of pregnancy outcomes and pregnancy risks are reported elsewhere

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