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Proposed title: Oral fingolimod versus placebo in primary progressive multiple sclerosis: results of a large phase III, randomised trial

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Abstract

Background: There is no approved treatment for primary progressive multiple sclerosis (PPMS). Fingolimod, an oral sphingosine 1-phosphate receptor modulator, has significant benefits in relapsing MS (RMS), but has not been assessed in PPMS.

Methods: This randomised, double-blind trial (ClinicalTrials.gov, NCT00731692) evaluated fingolimod 0.5 mg versus placebo on disability progression in patients with PPMS treated for at least 3 years. Key inclusion criteria: clinical diagnosis of PPMS; disease duration 2–10 years and objective evidence of disability progression in the previous 2 years. A novel primary composite endpoint, based on change from baseline in Expanded Disability Status Scale (EDSS), 25' Timed-Walk Test or 9-Hole Peg Test, was used to assess time to 3-month confirmed disability progression (3M-CDP). Key secondary endpoints: disability progression assessed by EDSS and percent brain volume change (PBVC).

Findings: The efficacy analysis set (N=823) comprised 336 and 487 patients randomised to fingolimod 0.5 mg and placebo, respectively. Baseline characteristics were similar across groups and representative of a progressive population (48.4% women; mean age 48.5±8.4 years, mean EDSS=4.67±1.03, 87% free of Gadolinium-enhancing lesions). By end of the study, 3M-CDP (composite primary endpoint; Kaplan-Meier estimate, 95% confidence interval) occurred in 77.2% (71.87%; 82.51%) versus 80.3% (73.31%; 87.25%) of fingolimod versus placebo patients. Neither the primary composite (risk reduction [RR] 5.05%; p=0.544), nor EDSS (RR 11.99%; p=0.217) endpoints were met. PBVC was not different between the fingolimod and placebo groups (–1.49 and –1.53; p=0.673). There were fewer Gd+ and new T2 lesions in the fingolimod arm (78% and 73% reduction; both p<0.001), although overall MRI lesion activity was low. Safety results were generally consistent with fingolimod RMS trials.

Interpretation: The anti-inflammatory effects of fingolimod did not slow disease progression or brain volume loss in PPMS. Therapeutic strategies for PPMS may require different approaches than utilised for RMS.

Funding: Novartis Pharma AG **(Word count: 300 [limit 300])**

Panel: Research in context

Systematic review

We searched PubMed on July 8, 2015, with no restriction on language or publication date, using the search term “primary progressive multiple sclerosis”. We identified 324 articles, of which 4 were primary reports of results from randomised, blinded, placebo-controlled clinical trials. Of these, 2 were large-scale, phase III trials: the PROMiSE trial, in which the active comparator was glatiramer acetate, was designed as a 3-year trial, but was terminated early; and the 2-year OLYMPUS trial in which rituximab was the active comparator. Both studies used the EDSS as the primary outcome measure and were negative in terms of a treatment benefit on disability progression and BVL, despite effects on some MRI parameters. Subsequent discussion on these studies included the influence of the patient populations recruited, the duration,[30] and the endpoints used on the ability of PPMS trials to detect treatment differences.

*Interpretatio*n

INFORMS addressed the important limitations of previous studies in PPMS. INFORMS was adequately designed with a novel composite endpoint and patients were exposed to study drug for at least 3 years. Furthermore, the study was powered to 90% for the detection of a clinically meaningful treatment effect on disability progression. INFORMS successfully recruited a primary progressive MS population with very low inflammatory activity (few relapses and low number of Gd-enhancing lesions at baseline and throughout the study). Despite the adequate design and a worsening trial population, INFORMS did not show a benefit for fingolimod versus placebo in terms of disability progression or BVL in patients with PPMS. Furthermore, the finding that the pharmacodynamic effects of fingolimod did not impact disability progression or BVL, despite effects on MRI-detected inflammatory lesion activity that were consistent with results in RMS, add to the important discussion on the pathophysiology of progressive phase MS and will guide future research**.**

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS).[1] While relapsing MS (RMS, encompassing relapsing-remitting and secondary progressive MS) is the most frequent form, 10–15% of MS patients exhibit a progressive disability from onset with no, or very infrequent superimposed relapses and remissions (primary progressive MS or PPMS).[2,3]

Although part of the MS disease spectrum,[4] PPMS differs from RMS in several ways. The inflammatory component, as measured by the development of gadolinium (Gd)-enhancing MRI lesions, is less prominent than in RMS.[2,5]-Men and women are equally affected, in contrast to the higher frequency of women in RMS.[3,6] Patients with PPMS are generally about 10 years older at diagnosis compared with RMS patients (mean age around 40 years for PPMS versus 30 years for RMS).[2,6] Moreover, disability progresses more rapidly in PPMS such that the severity of disability according to age is similar to that in RMS.[7]

Despite the range of effective options available for RMS, to date, no treatment has been shown to change the disease course in PPMS. [8,9] Fingolimod (FTY720; GILENYA™, Novartis Pharma AG, Basel, Switzerland) is an oral sphingosine 1-phosphate (S1P) receptor modulator that, by downregulation of the $S1P_1$ receptor subtype, prevents lymphocyte egress from lymphoid tissues into the circulation. In RMS, fingolimod reduces the frequency of relapses, delays disability progression and reduces magnetic resonance imaging (MRI) lesion activity versus placebo; and decreases the frequency of relapses and active MRI lesions versus interferon (IFN) β-1a IM.[10-12] Furthermore, fingolimod significantly limits brain volume loss (BVL) in RMS compared with both placebo and IFN-β1a IM[12,13], a measure that correlates with disability progression.[14,15]

In addition to preventing lymphocyte egress from lymphoid tissues, fingolimod can cross the blood–brain barrier and bind to S1P1, S1P3, and S1P5 receptors located on neural cells.[16] Therefore, part of its therapeutic action may be independent of its effect on peripheral macrophages. It is known that S1P1 and S1P3 receptors are strongly expressed within MS lesions and this expression has been associated with astrogliosis, a key pathological feature of MS lesions.[17] In vitro and in vivo data suggest that fingolimod can directly inhibit neurodegeneration. Fingolimod treatment of isolated human astrocytes desensitised the S1P receptor-mediated neuroinflammatory pathways resulting in reduced astrogliosis and neurodegeneration.[17] Animal models of MS have demonstrated that fingolimod treatment can result in reduced neuroinflammatory disease and improved CNS tissue integrity.[18,19] This ability of fingolimod to reduce inflammatory infiltrates into the CNS, coupled with the potential effects on intrinsic mechanisms within the brain resulting in reduced neurodegeneration, provided the rationale for the **IN**vestigating **F**TY720 **OR**al in Primary Progressive **MS** (INFORMS) trial (NCT00731692). In this study, a novel composite endpoint was devised, including the 25' Timed Walk Test (25'TWT)[20] and the Nine-Hole Peg Test (9-HPT)[20,21] as additional components to the expanded disability status scale (EDSS),[22] to provide a more sensitive and comprehensive assessment of disability than the EDSS alone.

Methods

Study Design

This multicentre, double-blind, placebo-controlled, parallel-group study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[23] and the Declaration of Helsinki.[24] The protocol was approved by each site's institutional review board; patients gave written informed consent. A Steering Committee (for membership see the Supplementary Appendix) oversaw the study.

Randomization and masking

The randomization sequence was automatically generated by a validated system under the responsibility of Novartis Drug Supply Management. The randomization occurred in blocks of 4 within centre in a 1:1 ratio to fingolimod or placebo. All randomised drug assignments remained blinded for the entire double-blind treatment period. Treatment codes were accessible only to members of the data and safety monitoring board (DSMB) which was independent of Novartis and not otherwise involved in the conduct of the study. Masking (blinding) was achieved by using identical packaging, and identical capsule colour and size for active treatment and placebo.

Patients were initially randomised to receive fingolimod 1.25 mg/day or matching placebo in a 1:1 ratio. Following a 2009 protocol amendment after the decision to select the 0.5 mg dose of fingolimod for submission to regulatory authorities for RMS and to discontinue development of fingolimod 1.25 mg randomization into this initial cohort of patients was stopped. Patients randomised up to the release of this amendment were labelled as 'Cohort 1' with those originally randomised to fingolimod 1.25 mg switched in a blinded fashion to fingolimod 0.5 mg and those on placebo continued on matching placebo.

From this time point in 2009 onwards, patients were randomised into a new cohort ('Cohort 2'), which included patients who were recruited after the release of the amendment and were randomised in a 1:1 ratio to receive fingolimod 0.5 mg/day or placebo.

Heart rate reduction is a known pharmacologic effect of fingolimod that can potentially unblind study participants. To maintain blinding, an independent first dose administrator performed pulse rate monitoring after the first dose of study drug. Employees of the sponsor who were independent of the study team monitored first dose safety in a blinded fashion.

Patients

Key eligibility criteria were age of 25–65 years with a clinical diagnosis of PPMS according to the 2005 revised McDonald criteria.[25] Patients had to have demonstrated ≥1 year of disease progression plus two of the following three criteria: positive brain MRI; positive spinal cord MRI and/or positive cerebrospinal fluid (CSF). Central review to confirm that the diagnostic criteria for PPMS were met was required for all patients prior to randomization.

Additional inclusion criteria included time from first reported symptoms of 2–10 years prior to study entry; evidence of disability progression documented by an increase in the EDSS score ≥0.5 points in the past 2 years; objective evidence of disability measured by EDSS score of 3.5–6; pyramidal functional system score ≥2; and a 25'TWT <30 seconds was required. Exclusion criteria were similar to previous RMS trials (for complete details, see Supplementary Appendix).[10-12]

Study Procedures

Clinical assessments were performed at screening and at randomization (baseline) and at study visits that included safety assessments at 2 weeks and 1, 2, 3, 6, 9, 12 months during the first year after randomization and then every 3 months until month 36.

All efficacy assessments were performed by an independent specially trained and certified[26] evaluating physician. MRI scans were analysed at a central MRI centre by trained staff blinded to the study-group assignments. EDSS assessments were scheduled at screening, baseline and then every 3 months during the double-blind treatment period, at the end of treatment and at the 3-month follow-up visit. In the case of MS relapse, EDSS assessment by the independent physician was required at an unscheduled visit to confirm relapse. The 25'TWT and 9-HPT were assessed at baseline and every 3 months throughout the double-blind treatment period, at the end of treatment and at the 3-month follow-up visit.

Specifications of the adverse event (AE) monitoring procedure, as defined in the study protocol, are detailed in the Supplementary Appendix, which also provides other methodologic details, the list of members of the independent DSMB, and the members of the independent diagnosis adjudication board.

Objectives and End Points

The primary objective was to evaluate the effect of fingolimod versus placebo on delaying the time to confirmed disability progression (CDP). CDP was defined as the first occurrence of a progression according to at least one of the following 3 criteria: increase from baseline in the EDSS score by 1 point in patients with baseline EDSS score ≤5.0 or 0.5 point in patients with baseline EDSS score ≥5.5; increase of at least 20% from baseline in the 25'TWT; increase of at least 20% from baseline in time taken to complete the 9-HPT. Progression in at least one of the three components had to be sustained and confirmed at least 3 months later at a scheduled visit.

Protocol-defined key secondary objectives: 1) effect of fingolimod 0.5 mg versus placebo on delaying the time to 3-month CDP as measured by the EDSS; 2) effect of fingolimod 0.5 mg versus placebo on percent brain volume change (PBVC) as a measure of BVL. PBVC was measured using SIENA applied to T1-weighted images.[27]

Statistical Analysis

The study was powered to 90% to detect a reduction between fingolimod and placebo in the time to 3-month CDP based on the composite endpoint in a log-rank test at a two-sided significance level of 5%: a sample size of 654 patients (327 in each group) was needed to detect a 3-year event rate reduction in the fingolimod 0.5 mg group of 25% (50% event rate on placebo versus 37.5% on fingolimod).

The primary efficacy analysis population comprised all patients randomised to fingolimod 0.5 mg or placebo (Cohort 2) and all patients randomised to placebo in Cohort 1. Patients had to have taken at

least one dose of study drug to be included (modified ITT principle). The decision to use the placebo patients from Cohort 1 in the primary analysis population was made after a blinded review of the baseline data that revealed no apparent differences between patients in Cohort 1 and 2. Cohort 1 and 2 were also analysed separately (see Supplementary Appendix). All efficacy results, unless otherwise specified, are based on the primary efficacy analysis set. The safety analysis population comprised all patients from Cohorts 1 and 2.

The primary analysis used a Cox proportional hazards model to test for differences between fingolimod and placebo in the time to 3-month CDP based on the composite endpoint, with region, age, baseline EDSS, baseline 25'TWT and baseline 9-HPT as covariates.

The key secondary analysis of time to 3-month CDP based on EDSS was performed as for the primary efficacy endpoint, but only disability progressions based on the EDSS were analysed and baseline 25'TWT and baseline 9-HPT were not included as covariates in the Cox proportional hazards model. PBVC was analysed using a random coefficients model including treatment and region as fixed effects, and time, number of Gd-enhancing lesions at baseline, baseline T2 lesion volume and normalised brain volume at baseline as continuous covariates.

To control the type-I error rate, the primary and key secondary efficacy hypotheses were tested in sequential order in a hierarchical step down procedure.

Role of the funding source

The study sponsor participated in the design of the study, conduct of the study, data collection, data management, data analysis and interpretation, and preparation, review and approval of the paper. All authors had access to the data. All authors, including those employed by Novartis, were involved in manuscript preparation and had control over the content, for which they take full responsibility and

have given final approval for submission for publication.

Results

Enrolment was between July 2008 and August 2011. Patients were accrued across 148 centres in 18 countries (see the Supplementary Appendix for a list of the centres and principal investigators). In total, 1520 patients were screened with 970 randomised (280 patients were randomised (1:1) to fingolimod 1.25 mg or placebo in Cohort 1 and 690 patients were randomised (1:1) to receive either fingolimod 0.5 mg or placebo in Cohort 2).

Patient disposition is summarised in Figure 1. Table 1 presents the baseline characteristics of the efficacy analysis set, which were similar across treatment groups (Supplementary Appendix presents the baseline characteristics for the entire INFORMS patient population [Cohorts 1 and 2]).

The composite primary efficacy endpoint was not met (Table 2, Figure 2A): fingolimod demonstrated no difference compared with placebo (p=0.544) in the time to 3-month CDP. There was also no difference in the time to 3-month CDP based on EDSS alone (Table 2, Figure 2B). Efficacy by Cohort is presented in the Supplementary Appendix. No significant treatment effect was observed in either cohort.

A similar analysis for 6-month CDP was conducted and the conclusions were consistent with that of the primary endpoint (data not shown). Subgroup analyses by sex, age (≤40 vs. 41–55 vs. >55 years), EDSS at baseline (≤5 vs. >5), Gd lesion status at baseline and age/Gd status at baseline (≤50 and Gd+ ≥1 vs. >50 and Gd+ < 1) yielded similar results and did not alter the conclusion of a lack of efficacy of fingolimod in patients with PPMS (data not shown).

PBVC was also similar in patients treated with fingolimod 0.5 mg compared with placebo (Table 2). However, fingolimod reduced the number of new/newly enlarging T2 lesions by 73% and of Gd-enhancing T1 lesions by 78% (Table 2). A majority of patients remained free of new/newly enlarging

T2 lesions through the end of the study in both treatment arms (mean number of new/newly enlarging T2 lesions of 0.5 versus 0.13 lesions per year in the placebo and fingolimod arms, respectively; Table 2).

Confirmed relapses were reported for 6 (1.8%) and 41 (8.4%) patients in the fingolimod 0.5 mg and placebo groups, respectively.

As shown in Table 3, the incidence of AEs in the efficacy analysis set was generally comparable between groups (Supplementary Appendix provides a summary of AEs for the entire safety analysis set) and the overall AE profile was similar to trials of fingolimod for RMS.[10,12] The events were mild or moderate in severity in 74.1% of those receiving fingolimod versus 75.2% for placebo.

AEs that led to discontinuation of the study medication (including abnormal laboratory test results) were more common with fingolimod than with placebo (Table 3). Serious AEs were reported for 25.0% in patients receiving fingolimod and 24.0% for placebo.

Five deaths occurred during the study. Two in the group originally randomised to fingolimod 1.25 mg (1.4%; single cases of respiratory tract infection and aspiration pneumonia); 1 (0.3%) randomised to fingolimod 0.5 mg in the efficacy analysis set (metastatic lung cancer); and 2 (0.4%) in the combined placebo group (single cases of convulsion and pulmonary embolism).

AEs of special interest, such as cardiac conduction abnormalities, macular oedema, infections and neoplasms were in keeping with previous observations from RMS trials.

Discussion

In PPMS patients, fingolimod treatment did not decrease the risk of progression of disability versus placebo. There was also no difference between fingolimod and placebo on BVL. In both treatment groups, BVL was approximately 0.5% per year and the majority of patients progressed in their disability status, irrespective of treatment. The effects of fingolimod on MRI measures of lesion activity and clinical relapses (although very few in number) were consistent with results from RMS studies.[10-12]

INFORMS is the first large, prospective MS study that used a composite of three major domains of MS-associated disability as the primary endpoint. This composite endpoint yielded more progression events than its components of which the highest event rate was recorded for the 25'TWT. The outcomes of all measures included were consistent, supporting the potential usefulness of the composite endpoint in future PPMS trials.

Despite the inclusion of patients with a higher age and more advanced disability, the safety and tolerability results for fingolimod 0.5 mg in INFORMS were in keeping with RMS trials, including the rates of AEs of special interest such as cardiac conduction at first dose and infections.

Based on the event rates of both the composite primary disability endpoint and its components, including the traditional EDSS endpoint, the study was adequately powered to detect a treatment effect. The trial recruited a large, well-defined worsening population of PPMS patients who progressed substantially during the course of the study. A total of 80% of placebo treated patients demonstrated CDP according to the primary composite and 59% according to the EDSS endpoint. Event rates according to the EDSS were higher than those observed in the placebo arms of two other large phase III trials. In PROMiSe,[9] in which the active comparator was glatiramer acetate, the placebo arm event rate was 45.2%, while in the OLYMPUS rituximab trial,[8] the placebo rate was 38.5%. Interestingly more than 30% of the CDP events by the primary outcome occurred within the first 26 weeks after randomization. In

line with most previous PPMS cohorts,[8,9] the INFORMS population showed a low rate of active inflammatory MRI lesions (<15% positive for Gd-enhancing lesions at baseline) and a moderate T2 lesion burden. Together, these data suggest that the inclusion criteria of INFORMS succeeded in recruiting a characteristic progressing PPMS population.[4]

The rate of discontinuations in INFORMS was in line with previous PPMS trials,[8,9] which were of shorter duration, and also consistent with fingolimod trials in RMS where an approximate attrition rate of 10% per annum was observed.[10-12] Indeed, this rate of attrition was factored into the sample size calculations to ensure an ability to detect a treatment difference at the end of the trial.

As with RMS, the rate of BVL in these PPMS patients substantially exceeded that observed in individuals without MS.[28] In RMS, fingolimod showed a consistent and robust effect on BVL [12,13] that was not seen in this PPMS trial. In RMS the effect of fingolimod on BVL is associated with a reduction in inflammatory Gd-enhancing and new/enlarging T2 lesions, [15,29] but has also been attributed to additional actions independent of its anti-inflammatory effects. In PPMS, the effect of fingolimod on lesion activity (Gd-enhancing and new/enlarging T2 lesions) was consistent with that seen in RMS, although relatively fewer PPMS patients had lesion activity (Gd-enhancing or new/newly enlarging T2 lesions). These observations suggest that although fingolimod has an impact on inflammatory disease activity, it had little effect on the process that leads to BVL and disability progression in PPMS. Similarly, in the PROMiSe and the OLYMPUS trial, there was no effect of the active compound on BVL despite an effect on Gd-enhancing activity and T2 lesion burden at some timepoints.[8,9]

Unlike RMS, the inflammatory infiltrate within the CNS is not only less prominent in PPMS but also differs in its cellular composition.[2,5] It is probable that the pathophysiologic mechanisms that drive BVL differ, at least partially, in these two MS phenotypes and neurodegenerative processes may play a more prominent role in PPMS. The results of INFORMS suggest that anti-neuroinflammatory strategies

currently applied in RMS are unlikely to be beneficial in PPMS, and that novel approaches may be required to treat patients with PPMS.

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Contributors

All of the authors contributed to data interpretation, co-wrote the first draft, and reviewed and edited subsequent drafts. FL, DHM, MSF, BACC, JSW, HW, CL, H-PH, XM, BMJU, MM, BL, NP, DAH, and LK were members of the Steering Committee and contributed to study design. DAH and BL were the study statisticians. Editorial support was provided by Katy Demery (Novartis employee) and Paul Coyle (Western Edge Medical Communications Ltd.). Editorial support was funded by Novartis.

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References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *The New England journal of medicine* 2000; **343**(13): 938-52.
2. Antel J, Antel S, Caramanos Z, Arnold DL, Kuhlmann T. Primary progressive multiple sclerosis: part of the MS disease spectrum or separate disease entity? *Acta neuropathologica* 2012; **123**(5): 627-38.
3. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of primary progressive multiple sclerosis. *Neurology* 2009; **73**(23): 1996-2002.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; **83**(3): 278-86.
5. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. *The Lancet Neurology* 2015; **14**(2): 183-93.
6. Tremlett H, Paty D, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. *Neurology* 2005; **65**(12): 1919-23.
7. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain : a journal of neurology* 2006; **129**(Pt 3): 595-605.
8. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Annals of neurology* 2009; **66**(4): 460-71.
9. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Annals of neurology* 2007; **61**(1): 14-24.
10. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *The New England journal of medicine* 2010; **362**(5): 402-15.
11. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Neurology* 2014; **13**(6): 545-56.
12. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *The New England journal of medicine* 2010; **362**(5): 387-401.
13. Barkhof F, de Jong R, Sfikas N, et al. The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. *Multiple sclerosis* 2014; **20**(13): 1704-13.
14. Jacobsen C, Hagemeier J, Myhr KM, et al. Brain atrophy and disability progression in multiple sclerosis patients: a 10-year follow-up study. *Journal of neurology, neurosurgery, and psychiatry* 2014; **85**(10): 1109-15.
15. Radue EW, Barkhof F, Kappos L, et al. Correlation between brain volume loss and clinical and MRI outcomes in multiple sclerosis. *Neurology* 2015; **84**(8): 784-93.
16. Miron VE, Ludwin SK, Darlington PJ, et al. Fingolimod (FTY720) enhances remyelination following demyelination of organotypic cerebellar slices. *The American journal of pathology* 2010; **176**(6): 2682-94.
17. Colombo E, Di Dario M, Capitolo E, et al. Fingolimod may support neuroprotection via blockade of astrocyte nitric oxide. *Annals of neurology* 2014; **76**(3): 325-37.
18. Choi JW, Gardell SE, Herr DR, et al. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proceedings of the National Academy of Sciences of the United States of America* 2011; **108**(2): 751-6.
19. Foster CA, Mechtcheriakova D, Storch MK, et al. FTY720 rescue therapy in the dark agouti rat model of experimental autoimmune encephalomyelitis: expression of central nervous system genes and reversal of blood-brain-barrier damage. *Brain pathology* 2009; **19**(2): 254-66.
20. Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD. Quantitative functional measures in MS: what is a reliable change? *Neurology* 2002; **58**(8): 1294-6.

21. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association* 1985; **39**(6): 386-91.
22. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33**(11): 1444-52.
23. ICH harmonised tripartite guideline — guideline for good clinical practice: E6(R1). Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, June 10, 1996. http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html Accessed Octobe 5, 2014.
24. Declaration of Helsinki: ethical principles for medical research involving human subjects. http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed August 21, 2015.
25. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of neurology* 2005; **58**(6): 840-6.
26. Neurostatus training and documentation DVD for a standardized neurological examination and assessment of Kurtzke's functional systems and Expanded Disability Status Scale for MS patients. Basel, Switzerland: Neurostatus, 2007. (Available at: http://www.neurostatus.net).
27. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *NeuroImage* 2002; **17**(1): 479-89.
28. Hedman AM, van Haren NE, Schnack HG, Kahn RS, Hulshoff Pol HE. Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. *Human brain mapping* 2012; **33**(8): 1987-2002.
29. Sormani M, De Stefano N, Francis G, et al. Fingolimod effect on brain volume loss independently contributes to its effect on disability. *Multiple sclerosis* 2015; **21**(7): 916-24.
30. Hartung HP, Aktas O. Bleak prospects for primary progressive multiple sclerosis therapy: downs and downs, but a glimmer of hope. *Annals of neurology 2*009;**66**(4):429-32.

Table 1. Baseline characteristics of the patients, according to study group

Characteristic	Fingolimod 0.5 mg (N=336)	Placebo (N=487)	Total (N=823)
Demographics			
Sex, n (%)			
Male	173 (51.5%)	252 (51.7%)	425 (51.6%)
Female	163 (48.5%)	235 (48.3%)	398 (48.4%)
Age (years)			
Median (range)	49.0 (24, 65)	49.0 (27, 65)	49.0 (24, 65)
Mean (SD)	48.5 (8.6)	48.5 (8.3)	48.5 (8.4)
Age distribution (years), n (%)			
18–30	6 (1.8%)	4 (0.8%)	10 (1.2%)
31–40	60 (17.9%)	90 (18.5%)	150 (18.2%)
41–50	127 (37.8%)	194 (39.8%)	321 (39.0%)
>50	143 (42.6%)	199 (40.9%)	342 (41.6%)
Race, n (%)			
Caucasian	324 (96.4%)	467 (95.9%)	791 (96.1%)
Black	7 (2.1%)	6 (1.2%)	13 (1.6%)
Asian	0 (0%)	4 (0.8%)	4 (0.5%)
Other	5 (1.5%)	10 (2.1%)	15 (1.8%)

Clinical characteristics			
Disease duration since diagnosis, years			
Mean (SD)	2.80 (2.6)	2.91 (2.3)	2.87 (2.4)
Median (range)	1.98 (0.1, 20.1)	2.35 (0.1, 10.4)	2.14 (0.1, 20.1)
Disease duration since onset of symptoms , years			
Mean (SD)	5.8 (2.5)	5.9 (2.4)	5.8 (2.4)
Median (range)	5.4 (1, 20)	5.7 (2, 15)	5.6 (1, 20)
EDSS score			
Mean (SD)	4.70 (1.03)	4.66 (1.03)	4.67 (1.03)
Median (range)	4.50 (2.0, 6.5)	4.50 (2.0, 6.5)	4.50 (2.0, 6.5)
25'TWT score (seconds)			
Mean (SD)	9.05 (5.61)	9.09 (7.62)	9.08 (6.87)
Median (range)	7.23 (3.7, 41.0)	6.90 (3.1, 117.7)	7.05 (3.1, 117.7)
*9-HPT score *(seconds*)			
Mean (SD)	28.44 (11.47)	28.79 (16.45)	28.65 (14.62)
Median (range)	25.26 (17.2, 115.8)	25.33 (13.9, 218.3)	25.28 (13.9, 218.3)
PASAT 3 score			
Mean (SD)	44.3 (13.0)	45.0 (12.5)	

Median (range)	48.0 (4, 60)	48.0 (0, 60)	
History of DMT use, n (%)			
Treatment naïve	272 (81.0%)	372 (76.4%)	644 (78.3%)
Any IFN β	36 (10.7%)	66 (13.6%)	102 (12.4%)
Natalizumab	3 (0.9%)	2 (0.4%)	5 (0.6%)
Glatiramer acetate	26 (7.7%)	33 (6.8%)	59 (7.2%)
Other MS medicines	19 (5.7%)	36 (7.4%)	54 (6.7%)
MRI characteristics			
Number of Gd-enhancing lesions			
N	336	484	820
Mean (SD)	0.3 (1.10)	0.3 (1.03)	0.3 (1.06)
Median (range)	0 (0, 10)	0 (0, 14)	0 (0, 14)
n, (%) free of Gd+	290 (86.3)	423 (87.4)	713 (87.0)
Total volume of T2 lesions (mm^3)			
N	336	485	821
Mean (SD)	9442.7 (10179.7)	10038.2 (13030.9)	9794.5 (11943.5)
Median (range)	6109.5 (145, 52484)	5271.0 (44, 91964)	5705.0 (44, 91964)

Normalised brain volume (cm^3)			
N	335	483	818
Mean (SD)	1490.9 (86.5)	1491.7 (84.9)	1491.4 (85.5)
Median (range)	1491.0 (1243, 1725)	1498.0 (1206, 1725)	1493.0 (1206, 1725)

*Dominant hand

Table 2. Efficacy analysis for primary and secondary endpoints

Primary endpoint: 3-month confirmed disability progression (composite)				
	% progression (95% CI)*	**% risk reduction**	**Hazard ratio (95% CI)†**	**p-value**
Fingolimod 0.5 mg (n=336)	77.2% (71.87, 82.51)	5.05%	0.95 (0.80, 1.12)	0.544
Placebo (n=487)	80.3% (73.31, 87.25)			
3-month confirmed disability progression (EDSS)				
	% progression (95% CI)*	**% risk reduction**	**Hazard ratio (95% CI)†**	**p-value**
Fingolimod 0.5 mg (n=336)	54.3% (47.16, 61.45)	11.99%	0.88 (0.72, 1.08)	0.217
Placebo (n=487)	58.7% (53.30, 64.18)			
3-month confirmed disability progression (9-HPT)				
	% progression (95% CI)*	**% risk reduction**	**Hazard ratio (95% CI)†**	**p-value**
Fingolimod 0.5 mg (n=336)	33.6% (26.11, 41.08)	6.94%	0.93 (0.71, 1.22)	0.607
Placebo (n=487)	41.3% (32.10, 50.55)			

***3-month confirmed disability progression (25'TWT*)**

	% progression (95% CI)*	**% risk reduction**	**Hazard ratio (95% CI)†**	**p-value**
Fingolimod 0.5 mg (n=336)	62.9% (57.10, 68.62)	5.59%	0.94 (0.78, 1.14)	0.546
Placebo (n=487)	70.0% (61.78, 78.21)			

Percent change in brain volume to Month 36

	Adjusted mean (95% CI)	**Adjusted mean difference (95% CI) ‡**	**p-value**
Fingolimod 0.5 mg (n=293)	–1.49 (–1.64, –1.35)	0.04 (–0.15, 0.23)	0.673
Placebo (n=421)	–1.53 (–1.65, –1.41)		

Number of new/newly enlarged T2 lesions to Month 36

	Adjusted mean (95% CI)§	**Rate reduction (%)**	**Rate ratio (95% CI)§**	**p-value**
Fingolimod 0.5 mg (n=298)	0.13/year (0.10, 0.18)	73.3	0.267 (0.185, 0.386)	<0.001
Placebo	0.50/year			

(n=431)	(0.40, 0.61)			

Proportion of patients free of new/newly enlarging T2 lesions to end of study

	Proportion	**Odds ratio (95% CI)[††]**	**p-value**
Fingolimod 0.5 mg (n=298)	79.9%	2.79 (1.95, 4.00)	<0.001
Placebo (n=431)	60.3%		

Number of Gd-enhancing T1 lesions at Month 36

	Adjusted mean (95% CI)§	**Rate reduction (%)**	**Rate ratio (95% CI)§**	**p-value**
Fingolimod 0.5 mg (n=223)	0.05 (0.02, 0.09)	78.3%	0.217 (0.102, 0.463)	<0.001
Placebo (n=320)	0.21 (0.15, 0.30)			

Proportion of patients free of Gd-enhancing T1 lesions to end of study

	Proportion	**Odds ratio (95% CI)[¶]**	**p-value**
Fingolimod 0.5 mg (n=299)	87.0%	2.15 (1.39, 3.33)	<0.001
Placebo (n=432)	77.5%		

CI: confidence interval; n=total number of patients included in the analysis.
*Estimated from Kaplan-Meier analysis (for the end of study).
†Time to event using a Cox regression model adjusted for treatment, region, baseline EDSS, baseline 25'TWT, baseline 9-HPT for the composite endpoint (baseline EDSS, baseline 9-HPT and baseline 25'TWT for these respective parameters) and age.

‡ Obtained from fitting a random coefficients model with treatment and region as fixed effects; and time, baseline number of Gd-enhancing T1 lesions, baseline T2 volume, and baseline normalised brain volume as continuous covariates.
§Obtained from fitting a negative binomial regression model adjusted for treatment, region, baseline number of Gd-enhanced T1 lesions, and age.
††Obtained from fitting a logistic regression model adjusted for treatment, region, baseline number of Gd-enhanced T1 lesions and age.
¶Obtained from fitting a logistic regression model adjusted for treatment, region, and age.

Table 3. Adverse events, according to study group.

Event	Fingolimod 0.5 mg (N=336)	Placebo (N=487)
All events, n (%)		
At least one adverse event	324 (96.4%)	463 (95.1%)
Any adverse event leading to discontinuation of study drug*	52 (15.5%)	36 (7.4%)
Any serious adverse event	84 (25.0%)	117 (24.0%)
Abnormal laboratory value leading to discontinuation of study drug	27 (8.0%)	6 (1.2%)
Death	1 (0.3%)	2 (0.4%)
Most common AEs (≥5% in any group, preferred term), n (%)		
Nasopharyngitis	78 (23.2%)	135 (27.7%)
Headache	56 (16.7%)	77 (15.8%)
Urinary tract infection	50 (14.9%)	79 (16.2%)
Fall	47 (14.0%)	94 (19.3%)
Hypertension	43 (12.8%)	28 (5.7%)
Alanine aminotransferase increased	39 (11.6%)	9 (1.8%)
Back pain	37 (11.0%)	75 (15.4%)
Upper respiratory tract infection	37 (11.0%)	58 (11.9%)

Gamma-glutamyltransferase increased	31 (9.2%)	3 (0.6%)
Arthralgia	30 (8.9%)	49 (10.1%)
Constipation	29 (8.6%)	36 (7.4%)
Influenza	29 (8.6%)	43 (8.8%)
Cough	28 (8.3%)	34 (7.0%)
Fatigue	25 (7.4%)	44 (9.0%)
Nausea	21 (6.3%)	19 (3.9%)
Pain in extremity	21 (6.3%)	36 (7.4%)
Dizziness	19 (5.7%)	29 (6.0%)
Lymphopenia	19 (5.7%)	0 (0.0%)
Pyrexia	18 (5.4%)	21 (4.3%)
Abdominal pain upper	17 (5.1%)	12 (2.5%)
Melanocytic naevus	16 (4.8%)	31 (6.4%)
Depression	15 (4.5%)	39 (8.0%)
Insomnia	12 (3.6%)	29 (6.0%)
Adverse events of special interest, n (%)		
Cardiovascular disorders		
Bradycardia	5 (1.5%)	1 (0.2%)
Sinus Bradycardia	0	0
AV block first degree	3 (0.9%)	6 (1.2%)
AV block second degree	1 (0.3%)	0
Myocardial infarction	1 (0.3%)	0

Myocardial ischemia	1 (0.3%)	0
Angina pectoris	1 (0.3%)	3 (0.6%)
Hypertensive crisis	0	1 (0.2%)
Secondary hypertension	1 (0.3%)	0
Hypotension	2 (0.6%)	5 (1.0%)
Syncope / Presyncope	7 (2.1%)	9 (1.8%)
Macular Oedema		
Macular Oedema	6 (1.8%)	6 (1.2%)
Cystoid ME	1 (0.3%)	1 (0.2%)
Infection and Infestations		
Bronchitis	16 (4.8%)	21 (4.3%)
Cystitis/*bacterial*	9 (2.7%)	19 (3.9%)
Tinea versicolour	6 (1.8%)	8 (1.6%)
Pneumonia/Bronchopneumonia	6 (1.8%)	8 (1.6%)
Rare Infection and Infestations		
Meningitis	0	1 (0.2%)
Systemic mycosis	1 (0.3%)	0
Pulmonary sepsis	0	1 (0.2%)
Urosepsis	0	2 (0.4%)
Serratia sepsis	0	1 (0.2%)
Herpes zoster/VZV		
Herpes Zoster	10 (3.0%)	9 (1.8%)
Herpes Zoster meningomyelitis	1 (0.3%)	0
Herpes zoster *neurological*	0	1 (0.2%)

Herpes Zoster oticus/ophthalmic	0	1 (0.2%)
Hepatobiliary disorders		
Hepatocellular injury	2 (0.6%)	0
Hepatic function abnormal	1 (0.3%)	1 (0.2%)
Hyperbilirubinaemia	1 (0.3%)	0
Skin cancer		
Basal cell carcinoma	14 (4.2%)	9 (1.8%)
Squamous cell carcinoma/*of skin (comb.)*	6 (1.8%)	1 (0.2%)
Malignant melanoma/ *in situ (comb.)*	1 (0.3%)	0
Other malignancies		
Breast cancer	1 (0.3%)	0
Invasive lobular breast carcinoma	0	1 (0.2%)
Non-Hodgkin‘s lymphoma	1 (0.3%)	0
Lung neoplasm malignant	1 (0.3%)	0
Ovarian cancer	1 (0.3%)	0
Prostate cancer	1 (0.3%)	1 (0.2%)
Respiratory		
Dyspnoea	14 (4.2%)	16 (3.3%)
(exertional)	0	5 (1.0%)
Seizures/Convulsions		
Convulsion	2 (0.6%)	2 (0.4%)
Epilepsy	1 (0.3%)	0
Status epilepticus	0	1 (0.2%)

Investigations		
Blood cholesterol increased	15 (4.5%)	16 (3.3%)
Blood triglycerides increased	9 (2.7%)	9 (1.8%)
Low density lipoprotein increased	7 (2.1%)	3 (0.6%)
Weight increased	5 (1.5%)	1 (0.2%)
Carbon monoxide diffusing capacity decreased	7 (2.1%)	8 (1.6%)

*Any adverse event leading to discontinuation of the study drug includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings).

Figure legends

Figure 1. Enrolment, randomization, and follow-up

AE, adverse event

Figure 2. Time to 3-month confirmed disability progression: (A) primary composite endpoint; (B) EDSS (key secondary endpoint)

HR: hazard ratio; CI: confidence interval