Categorical change in T2 lesion volume and clinical outcomes in the phase 3 FREEDOMS and extension study, evaluating fingolimod in patients with relapsing–remitting multiple sclerosis

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CONCLUSIONS

- **In the FREEDOMS trial in patients with RRMS, change in T2 lesion volume at 2 years was related to disability at both 2 years and 4 years**
- **Compared with patients with stable or decreased T2 lesion volume, patients with increased T2 lesion volume appeared to be more at risk of long-term disease progression, based on worsening disability scores and increased rates of confirmed disability progression**
- **Fewer patients receiving fingolimod than placebo had increased T2 lesion volume at 2 years, demonstrating the ability of fingolimod to slow the accumulation of focal MRI disease, which in turn may be associated with a reduction in long-term disability progression**

INTRODUCTION

- Burden of disease in multiple sclerosis (MS) is generally assessed using magnetic resonance imaging (MRI) measurements of T2 lesion volume (T2LV)
  - Increases in T2LV of approximately 5–15% per year are typically seen on the MRI scans of untreated patients with relapsing–remitting MS (RRMS) enrolled in clinical trials[1,2]
- Cross-sectional and longitudinal studies suggest an association between the burden of focal damage, as assessed by T2LV, and measures of disability progression[3–6]
- Once-daily fingolimod 0.5 mg (FTY720; Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor (S1PR) modulator approved for the treatment of relapsing MS[a]
- Approximately 114,000 patients have been treated with fingolimod in both the clinical trial and post-marketing settings; total patient exposure now exceeds 195,000 patient-years[b]
- Compared with placebo at 24 months in the phase 3, placebo-controlled FREEDOMS and FREEDOMS II trials, fingolimod treatment had beneficial effects on disability endpoints, including 3- and 6-month confirmed disability progression (CDP), Expanded Disability Status Scale (EDSS) scores and MS Functional Composite (MSFC) z-scores[7,8]
  - Coinciding with this clinical improvement, median T2LV also decreased between baseline and 24 months in patients receiving fingolimod (respective median percentage change from baseline in FREEDOMS and FREEDOMS II: fingolimod 1.25 mg, –3.10 and –10.08; fingolimod 0.5 mg, –1.69 and –7.10), but increased among patients on placebo (8.61 and 0.83)[7,8]
- In this *post hoc* analysis of the FREEDOMS trial[7] and its extension (up to 48 months),[9] we categorized changes in T2LV at 24 months as 'increased', 'stable' or 'decreased'.
- In the overall population and by treatment group, we then examined possible associations between T2LV categories and disability progression at 24 months and at 48 months

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

[b]Data as of November 30, 2014; Q4 Novartis Pharmaceuticals Interim Financial Report, January 2015

OBJECTIVE

- To investigate disability outcomes at months 24 and 48 in the FREEDOMS study and its extension in relation to categorical changes in T2LV from baseline to month 24

METHODS

- FREEDOMS was a 24-month, double-blind, randomized, multicenter, placebo-controlled, parallel group study comparing the effect of once-daily fingolimod (0.5 mg and 1.25 mg doses) with that of placebo. In the study extension, patients continued on the fingolimod dose assigned in the core phase (0.5 mg or 1.25 mg) or were re-randomized 1:1 from placebo to fingolimod (0.5 mg or 1.25 mg)
- Patient eligibility criteria and methods of clinical and MRI measurements have been reported previously[7]
- *Post hoc* analyses were confined to patients evaluated for T2LV at baseline and month 24, and are presented for the fingolimod 0.5 mg group, the placebo group and the full analysis set (FAS; all patients in the placebo, fingolimod 0.5 mg and fingolimod 1.25 mg groups)
- Patients were assigned to different T2LV categories depending on their recorded change in T2LV from baseline to month 24. Categories were:
  - Increased T2LV, an increase from baseline of more than 500 mm^3
  - Stable T2LV, an increase or a decrease of no more than 500 mm^3
  - Decreased T2LV, a decrease of more than 500 mm^3
- Clinical outcomes included 3- and 6-month CDP,[7] change in EDSS score and change in MSFC z-score
- Additional analyses assessed the relationship between T2LV category and disability endpoints at month 48

RESULTS

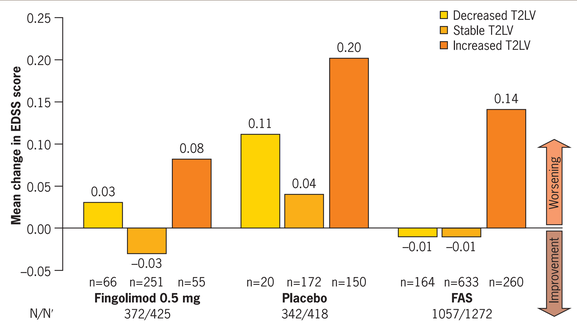
- Change in T2LV at month 24 was available for 1057 of the 1272 patients randomized in FREEDOMS (the FAS), which included 372 of the 425 patients randomized to fingolimod 0.5 mg and 342 of the 418 patients randomized to placebo
- A summary of baseline characteristics by T2LV category is presented in **Table 1**
  - Baseline characteristics were mostly similar across the treatment groups and T2LV categories
  - Compared with patients in other T2LV categories, those whose T2LV had decreased at month 24 had generally had MS for longer when enrolled, and those whose T2LV had increased at month 24 had enrolled with greater levels of disability (higher EDSS scores)
- At month 24, 85.2% of patients in the fingolimod 0.5 mg group showed stable or decreased T2LV (67.5% and 17.7%, respectively) compared with 56.1% of patients in the placebo group (stable: 50.3%; decreased: 5.8%)
- Mean changes in EDSS scores from baseline to month 24 are presented in **Figure 1**. In all analysis groups, worsening disability (increasing EDSS score) was greatest among the group of patients with increased T2LV, the greatest increase in mean EDSS score being in the placebo group
- Similarly, in all analysis groups, worsening disability based on decreases in MSFC z-score was generally greatest among those patients with increased T2LV (**Figure 2**)
- A similar trend was evident when considering 3- and 6-month CDP in the FAS. Proportionately more patients experienced disability progression in the increased T2LV category than in the other categories, and this association was seen both at month 24 and at month 48 (**Figure 3**)
- The changes from baseline to month 48 in mean EDSS scores (**Figure 4**) and in mean MSFC z-scores (**Figure 5**) also suggested an ongoing association between disability progression and changes in T2LV observed at month 24
- Among patients treated with fingolimod 0.5 mg, the slight improvements in mean EDSS and mean MSFC scores in the decreased and stable T2LV groups suggest that preventing increases in T2LV prevents accrual of disability

Table 1. Baseline characteristics

Baseline characteristic	Fingolimod 0.5 mg (N=372)			Placebo (N=342)			Full analysis set (N=1057)		
	Decreased T2LV (n=66, 17.7%)	Stable T2LV (n=251, 67.5%)	Increased T2LV (n=55, 14.8%)	Decreased T2LV (n=20, 5.9%)	Stable T2LV (n=172, 50.3%)	Increased T2LV (n=150, 43.9%)	Decreased T2LV (n=164, 15.5%)	Stable T2LV (n=633, 59.9%)	Increased T2LV (n=260, 24.6%)
Age (years)	36.6 (8.4)	36.7 (8.4)	35.1 (9.1)	36.4 (8.0)	38.3 (8.7)	36.5 (8.5)	36.3 (8.7)	37.6 (8.6)	36.4 (8.8)
Duration of MS (years)	5.5 (5.3)	4.4 (4.6)	4.0 (4.7)	5.8 (6.7)	5.2 (5.4)	5.2 (5.3)	5.8 (5.8)	4.7 (5.1)	5.1 (5.2)
Relapses in previous year (n)	1.6 (0.9)	1.4 (0.7)	1.5 (0.8)	1.8 (0.9)	1.4 (0.6)	1.5 (0.8)	1.6 (1.0)	1.4 (0.7)	1.5 (0.8)
Relapses in previous 2 years (n)	2.4 (1.7)	2.0 (1.0)	2.2 (1.1)	2.2 (0.9)	2.1 (1.1)	2.3 (1.3)	2.3 (1.5)	2.0 (1.0)	2.3 (1.4)
EDSS score	2.3 (1.2)	2.2 (1.2)	2.5 (1.3)	2.3 (1.2)	2.4 (1.2)	2.5 (1.3)	2.4 (1.4)	2.3 (1.2)	2.5 (1.3)
MSFC z-score	0.0 (0.6)	0.2 (0.5)	–0.1 (0.6)	–0.1 (0.7)	0.1 (0.6)	–0.1 (0.6)	–0.1 (0.8)	0.1 (0.6)	–0.1 (0.6)

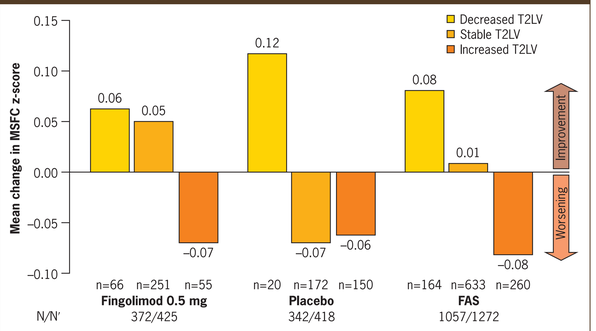
Data are mean (standard deviation)
Full analysis set comprises the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
N=number of patients with T2LV data available at month 24
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; T2LV, T2 lesion volume

Figure 1. Mean changes in EDSS scores from baseline to month 24



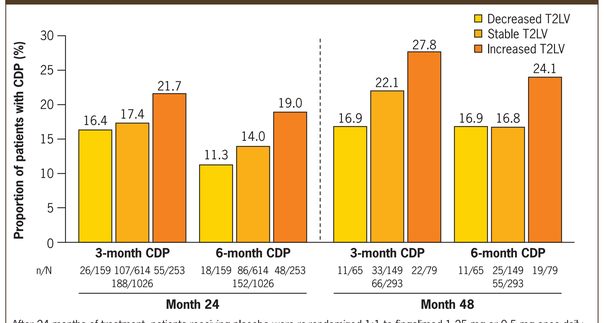
FAS comprised the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
n=number of patients with EDSS data available; N=number of patients with change in T2LV data available; N'=total number of patients randomized
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
EDSS, Expanded Disability Status Scale; FAS, full analysis set; T2LV, T2 lesion volume

Figure 2. Mean changes in MSFC z-scores from baseline to month 24



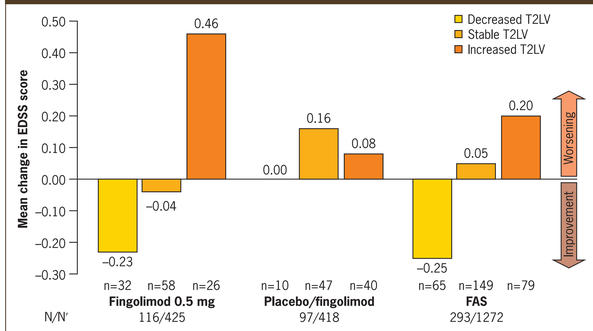
FAS comprised the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
n=number of patients with MSFC data available; N=number of patients with change in T2LV data available; N'=total number of patients randomized
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
FAS, full analysis set; MSFC, Multiple Sclerosis Functional Composite; T2LV, T2 lesion volume

Figure 3. Proportion of patients with 3-month or 6-month CDP at month 24 and month 48 (FAS)



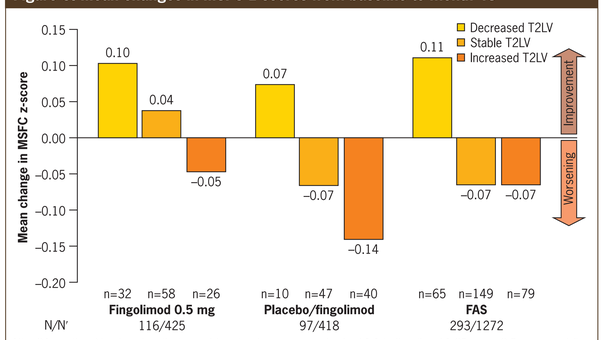
After 24 months of treatment, patients receiving placebo were re-randomized 1:1 to fingolimod 1.25 mg or 0.5 mg once daily
FAS comprised the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
n=number of patients with 3- or 6-month CDP by T2LV category; N=total number of patients by T2LV category
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
CDP, confirmed disability progression; FAS, full analysis set; T2LV, T2 lesion volume

Figure 4. Mean changes in EDSS scores from baseline to month 48



After 24 months of treatment, patients receiving placebo were re-randomized 1:1 to fingolimod 1.25 mg or 0.5 mg once daily
FAS comprised the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
n=number of patients with EDSS data available; N=number of patients with change in T2LV data available; N'=total number of patients randomized
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
EDSS, Expanded Disability Status Scale; FAS, full analysis set; T2LV, T2 lesion volume

Figure 5. Mean changes in MSFC z-scores from baseline to month 48



After 24 months of treatment, patients receiving placebo were re-randomized 1:1 to fingolimod 1.25 mg or 0.5 mg once daily
FAS comprised the fingolimod 0.5 mg and 1.25 mg dose groups and the placebo group
n=number of patients with MSFC data available; N=number of patients with change in T2LV data available; N'=total number of patients randomized
T2LV categories at month 24: increased T2LV was an increase from baseline of more than 500 mm^3; stable T2LV was an increase or a decrease of no more than 500 mm^3; decreased T2LV was a decrease of more than 500 mm^3
FAS, full analysis set; MSFC, multiple sclerosis functional composite; T2LV, T2 lesion volume

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