DX08

The effect of fingolimod on four measures of disease activity in patients with relapsing – remitting multiple sclerosis: a meta-analysis of the phase 3 FREEDOMS trials

P Repovic,[1] G Karlsson,[2] M Merschhemke[2] and DA Häring[2]

[1]Multiple Sclerosis Center, Swedish Neuroscience Institute, Seattle, WA, USA

[2]Novartis Pharma AG, Basel, Switzerland

Friday, June 3, 2016, Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC), National Harbor, MD

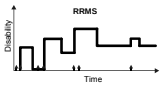
Disclosures

- Pavle Repovic has received honoraria or research support from Biogen, EMD Serono, Genzyme, Novartis, Pfizer and Teva
- Goeril Karlsson, Martin Merschhemke and Dieter A Häring are employees of Novartis Pharma AG

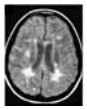
Disease activity in MS

- The four most important measures of disease activity or worsening in MS[1–4] are:

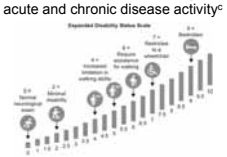
Relapse activity
Acute clinical disease activity[a]



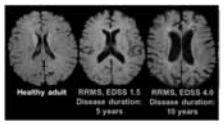
Lesion formation
MRI measure of focal inflammation/damage[b]



Disability progression
Functional impairment resulting from acute and chronic disease activity[c]



Brain volume loss
MRI measure of change in brain volume between two time points[d]



[a]Relapse activity graph adapted from Lublin *et al. Neurology* 2014;83:287–286; [b]MRI lesion image from Wattjes *et al. Nat. Rev. Neurol.* 2015;11:597–606. © 2015, with permission from Nature Publishing Group; [c]EDSS chart adapted from Kurtzke JF. *Neurology* 1983;33:1444–52. [d]MRI brain volume loss images from Bermel RA and Bakshi R. *Lancet Neurol* 2006;5: 158–70. © 2006, with permission from Elsevier. MRI, magnetic resonance imaging. 1. Bevan CJ, Cree BAC. *JAMA Neurol* 2014;71:269–70; 2. Havrdova E *et al. Lancet Neurol* 2009;8:254–60;3. Giovannoni G *et al. Lancet Neurol* 2011;10:329–37; 4. Banwell *B et al. Mult Scler Relat Disord* 2013;2:65–7

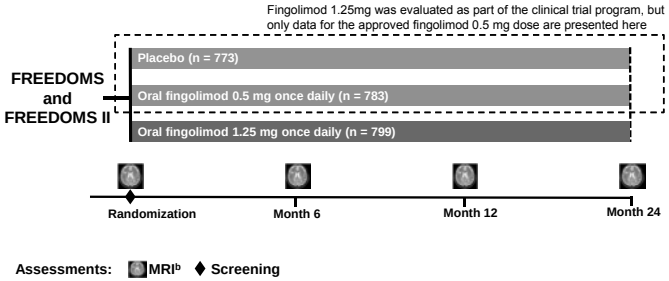
Objective

- To determine the consistency of the treatment effect of fingolimod 0.5 mg on four measures of disease activity across the 2-year randomized, placebo-controlled FREEDOMS and FREEDOMS II trials in patients with RRMS

RRMS, relapsing–remitting multiple sclerosis

Study design

- Disease activity was examined in patients with RRMS, pooled from the 2-year phase 3, randomized, double-blind FREEDOMS[1] and FREEDOMS II[2] trials[a]



[a]Key inclusion criteria: adults aged 18–55 years with RRMS, ≥ 1 relapse in the previous year (or ≥ 2 in the previous 2 years) and an EDSS score of 0–5.5
[b]MRI scans at screening were performed within 30 days of randomization
1. Kappos L *et al. N Engl J Med* 2010;362:387–401; 2. Calabresi PA *et al. Lancet Neurol* 2014;13:545–56

Baseline characteristics – individual studies

Mean ± SD unless otherwise stated	FREEDOMS		FREEDOMS II	
	Fingolimod 0.5 mg (N = 425)	Placebo (N = 418)	Fingolimod 0.5 mg (N = 358)	Placebo (N = 355)
Age, years	36.6 ± 8.8	37.2 ± 8.6	40.6 ± 8.4	40.1 ± 8.4
Women, n (%)	296 (69.6)	298 (71.3)	275 (76.8)	288 (81.1)
Time from onset, years	8.0 ± 6.6	8.1 ± 6.3	10.4 ± 8.0	10.7 ± 7.8
EDSS	2.3 ± 1.3	2.5 ± 1.3	2.4 ± 1.3	2.4 ± 1.3
Relapses within previous 2 years, n	2.1 ± 1.1	2.2 ± 1.2	2.2 ± 1.4	2.2 ± 1.5
Absence of Gd+ lesions, n (%)[a]	262 (62.1)	262 (63.1)	218 (61.1)	225 (63.6)
T2 lesion volume, cm^3	6.1 ± 7.6	6.1 ± 7.0	5.5 ± 8.0	5.5 ± 7.8
T1 hypointense lesion volume, cm^3	1.9 ± 2.9	1.9 ± 3.1	1.4 ± 3.0	1.4 ± 2.7
Normalized brain volume, cm^3	1521 ± 83	1512 ± 86	1522 ± 82	1526 ± 85

[a]Total number of patients with an evaluable MRI scan
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SD, standard deviation

Baseline characteristics – pooled population

Mean ± SD unless otherwise stated	Fingolimod 0.5 mg[a] (N = 783)	Placebo[a] (N = 773)
Age, years	38.4 ± 8.8	38.6 ± 8.6
Women, n (%)	571 (72.9)	586 (75.8)
Treatment-naïve, n (%)	338 (43.2)	345 (44.6)
Time from onset, years	9.1 ± 7.4	9.3 ± 7.2
EDSS	2.3 ± 1.3	2.5 ± 1.3
Relapses within previous 2 years, n	2.2 ± 1.3	2.2 ± 1.3
Absence of Gd+ lesions, n (%)[b]	480 (61.6)	487 (63.3)
T2 lesion volume, cm^3	5.8 ± 7.8	5.9 ± 7.4
T1 hypointense lesion volume, cm^3	1.7 ± 2.9	1.7 ± 2.9
Normalized brain volume, cm^3	1521 ± 83	1519 ± 86

[a]Patients pooled from FREEDOMS and FREEDOMS II
[b]Total number of patients with an evaluable MRI scan
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; SD, standard deviation

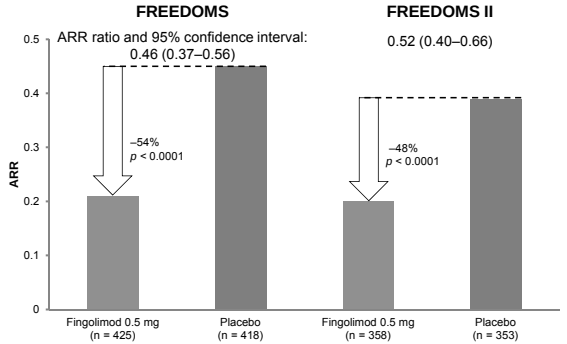
Methods

- Data from FREEDOMS (N = 843) and FREEDOMS II (N = 713) analyzed by study, and also in meta-analysis[a] of the combined data
  1. Annualized relapse rates[b] (ARR); negative binomial model
  2. New or enlarging T2 lesions; negative binomial model
  3. Brain volume loss; ANCOVA model
  4. Disability progression (6-month confirmed progression); Kaplan–Meier curves and Cox proportional hazards model

[a]Meta-analysis: an analysis of more than one study; statistical models included adjustments for treatment, study and a treatment-by-study interaction; the statistical test of the interaction term is a heterogeneity test; if the test is non-significant the result from the pooled analysis applies to both studies.
[b]New neurological symptoms present for at least 24 hours, in the absence of fever or infection, manifesting ≥ 30 days from onset of a preceding demyelinating event and confirmed by an independent evaluating physician in the 7 days following symptom onset and confirmation by EDSS; an increase in EDSS score of ≥ 1.5 if baseline (BL) score = 0, ≥ 1.0 if BL score = 0.5–5.0 and ≥ 0.5 otherwise sustained over at least 6 months and confirmed at the next scheduled visits
EDSS, Expanded Disability Status Scale

Annualized relapse rate – individual studies

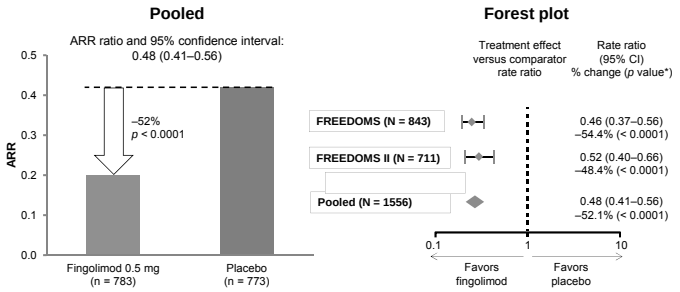
- Fingolimod 0.5 mg reduced the ARR compared with placebo in FREEDOMS and FREEDOMS II



Negative binomial regression of the number of confirmed relapses, with treatment as a factor, and baseline EDSS score and number of relapses in the past 2 years as covariates. Adjusted by the time on study, with ln(time) used as offset variable
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale

Annualized relapse rate – pooled population

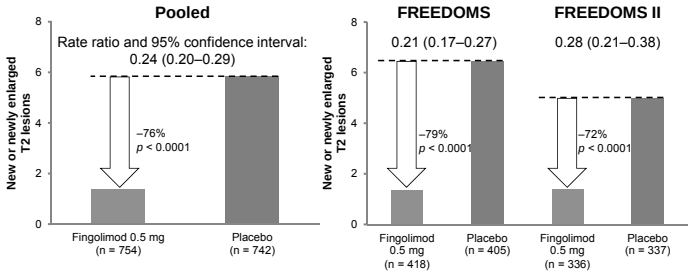
- Fingolimod 0.5 mg reduced the ARR by 52% compared with placebo
  - There was no evidence of treatment effect heterogeneity[a] between trials



[a]Statistical heterogeneity test : *p* value 0.393; if non-significant the treatment effect reported in the pooled analysis applies to both studies.
Negative binomial regression of the number of confirmed relapses, with treatment as a factor, and baseline EDSS score and number of relapses in the past 2 years as covariates. Adjusted by the time on study, with ln(time) used as offset variable
ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale

New or newly enlarged T2 lesions

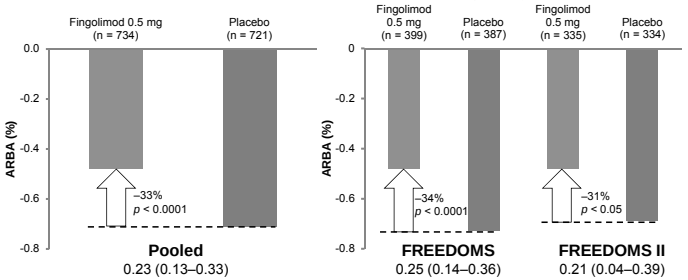
- Fingolimod 0.5 mg reduced new or newly enlarged T2 lesions by 76% compared with placebo
  - There was no evidence of treatment effect heterogeneity[a] between trials



[a]Statistical heterogeneity test : *p* value 0.419; if non-significant the treatment effect reported in the pooled analysis applies to both studies.
Negative binomial regression of number of new or newly enlarged T2 lesions, with treatment as a factor and number of relapses in the past 2 years as a covariate. Adjusted by the time since last MRI scan, with ln(time) used as offset variable

Brain volume loss

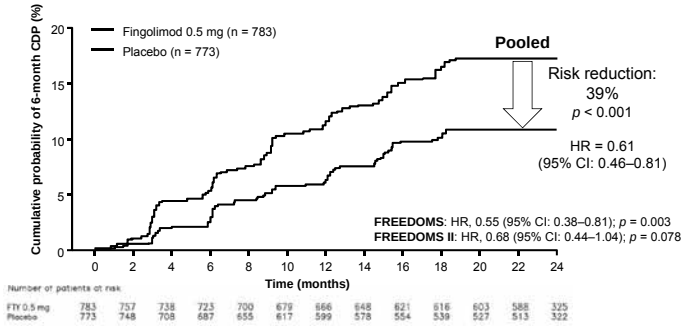
- Fingolimod 0.5 mg reduced brain volume loss by 33% compared with placebo
  - 0.71% per year versus 0.48% per year, respectively
  - There was no evidence of treatment effect heterogeneity[a] between trials



[a]Statistical heterogeneity test : *p* value 0.941; if non-significant the treatment effect reported in the pooled analysis applies to both studies.
ARBA data are LS means; values beneath bars are LS mean between-treatment differences (95% CIs)
ANCOVA model of ARBA with treatment as a factor and T2 lesion volume and Gd+ T1 lesion count at baseline as extra factors
ARBA, annualized rate of brain atrophy; BVL, brain volume loss; CI, confidence interval; GD+, gadolinium-enhancing; LS, least squares

6-month confirmed disability progression

- Fingolimod 0.5 mg was associated with a 39% reduction in the risk of 6–month CDP compared with placebo
  - There was no evidence of treatment effect heterogeneity[a] between trials



[a]Statistical heterogeneity test : *p* value 0.578; if non-significant the treatment effect reported in the pooled analysis applies to both studies.
Data are proportions of patients with CDP after 6 months of treatment in the pooled population
CDP, confirmed disability progression; CI, confidence interval; HR, hazard ratio

Summary and conclusions

- Fingolimod significantly reduced MS disease activity and worsening in patients with RRMS compared with placebo
  - 52% reduction of ARR ($p < 0.0001$)
  - 76% reduction of new or enlarging T2 lesions ($p < 0.0001$)
  - 33% reduction of brain volume loss ($p < 0.0001$)
  - 39% reduction of risk of disability progression ($p < 0.001$)
- For all four endpoints, the treatment effect was consistent across the FREEDOMS and FREEDOMS II trials

ARR, annualized relapse rate; RRMS, relapsing–remitting multiple sclerosis