Fingolimod-effect on brain atrophy and clinical/MRI correlations in three phase 3 studies – TRANSFORMS, FREEDOMS and FREEDOMS II

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- **G Francis** is an employee of Novartis Pharmaceuticals Corporation
Background

- Brain volume loss (a measure of brain atrophy) is used to assess neurodegeneration and provides a sensitive measure of neuroprotection in clinical trials.1
- In patients with MS, brain atrophy occurs at ~5–10 times the rate of that observed in healthy individuals (0.1–0.3% per year); it begins early in the disease and continues throughout the disease course.1–3
- Studies have shown that brain atrophy correlates significantly with physical disability and cognitive dysfunction in patients with MS.4–8
- Brain atrophy that occurs early in the disease course and during the first 2 years of a clinical trial is predictive of future disability; brain atrophy may be a stronger predictor of disability than lesion-load MRI measures.7,10

The effect of approved therapies on brain atrophy in patients with RRMS

- Approved therapies either had no significant effect on brain atrophy or the effect is delayed until the second year of therapy.\(^1\)\(^-\)\(^5\)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>0–1 year</th>
<th>1–2 years</th>
<th>0–2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN beta-1a IM</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>IFN beta-1a SC</td>
<td>–</td>
<td>–</td>
<td>X</td>
</tr>
<tr>
<td>IFN beta-1b</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>X</td>
<td>✓*</td>
<td>–</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>–</td>
<td>–</td>
<td>X</td>
</tr>
</tbody>
</table>

- Data not reported/available   X no significant effect  ✓ significant effect

Data reported are from placebo-controlled trials
* Significant effect at 9–18 months
IFN, interferon; IM, intramuscular; RRMS, relapsing–remitting multiple sclerosis; SC, subcutaneous
Fingolimod phase 3 study designs

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

**TRANSFORMS**
- N = 1280
- Oral fingolimod 1.25 mg once daily (n = 420)
- Oral fingolimod 0.5 mg once daily* (n = 429)
- IFN beta-1a 30 µg IM once weekly (n = 431)

**FREEDOMS**
- N = 1272
- Oral fingolimod 1.25 mg once daily (FREEDOMS n = 429, FREEDOMS II n = 370)
- Oral fingolimod 0.5 mg once daily* (FREEDOMS n = 425, FREEDOMS II n = 358)
- Placebo (FREEDOMS n = 418, FREEDOMS II n = 355)

**FREEDOMS II**
- N = 1083

*Approved dose. MRI scans at screening were performed within 30 days of randomization.

EDSS, Expanded Disability Status Scale; IFN, interferon; MRI, magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis.
SIENA: a fully automated method for identifying changes in brain volume over time

- Structural Image Evaluation, using Normalisation, of Atrophy (SIENA) was used to assess changes in brain volume in the phase 3 studies
  - It estimates the percentage brain volume change (PBVC) between two input images, taken of the same subject, at different points in time
  - Analysis programs strip the non-brain tissue from the two images, register each brain image (skulls are used to hold the scaling constant) and analyse the brain volume change between the two time points
Brain volume at baseline correlated with MS duration, disability and MRI lesion burden

<table>
<thead>
<tr>
<th>Normalized brain volume vs.</th>
<th>FREEDOMS N = 1272</th>
<th>FREEDOMS II N = 1083</th>
<th>TRANSFORMS N = 1280</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(-0.42^{***})</td>
<td>(-0.44^{***})</td>
<td>(-0.34^{***})</td>
</tr>
<tr>
<td>Duration of MS</td>
<td>(-0.38^{***})</td>
<td>(-0.35^{***})</td>
<td>(-0.28^{***})</td>
</tr>
<tr>
<td>EDSS</td>
<td>(-0.35^{***})</td>
<td>(-0.28^{***})</td>
<td>(-0.21^{***})</td>
</tr>
<tr>
<td>MSFC</td>
<td>(0.40^{***})</td>
<td>(0.34^{***})</td>
<td>(0.20^{***})</td>
</tr>
<tr>
<td>T2 lesion volume</td>
<td>(-0.44^{***})</td>
<td>(-0.37^{***})</td>
<td>(-0.35^{***})</td>
</tr>
</tbody>
</table>

\(^{*}P < 0.0001\) for all correlations
\(r = \) Pearson correlation co-efficient
EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite
Fingolimod significantly reduced brain volume loss over 1 year compared with IFN beta-1a IM

Fingolimod significantly reduced brain volume loss over 2 years compared with placebo
- These reductions were observed after 6 months (first post-baseline scan)

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**TRANSFORMS**

- **31% reduction**

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**FREEDOMS**

- **35% reduction**

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**FREEDOMS II**

- **33% Reduction**

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*0.5 mg vs. placebo

TRANSFORMS *** p < 0.001 versus IFN beta-1a. p value calculated using Wilcoxon rank sum test.

FREEDOMS/FREEDOMS II * p < 0.05; ** p < 0.01; *** p < 0.001 versus placebo. p values calculated using rank ANCOVA adjusted for treatment, region and baseline normalized brain volume. IFN, interferon; IM, intramuscular
Effect of presence or absence of Gd-enhancing lesions at baseline on PBVC treatment effect

- Data shown are for FREEDOMS
- Findings were comparable in FREEDOMS II (24 months) and TRANSFORMS (12 months)

PBVC, percentage brain volume change
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ versus placebo. $p$ values calculated using rank ANCOVA adjusted for treatment, region and baseline normalized brain volume.
On-study brain volume loss correlated with new T2 lesion formation and worsening of disability measures

<table>
<thead>
<tr>
<th>PBVC vs.</th>
<th>FREEDOMS N = 1272 (Baseline–month 24)</th>
<th>FREEDOMS II N = 1083 (Baseline–month 24)</th>
<th>TRANSFORMS N = 1280 (Baseline–month 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ T2 lesion volume</td>
<td>−0.17***</td>
<td>−0.10*</td>
<td>0.03</td>
</tr>
<tr>
<td>Δ T2 lesion number</td>
<td>−0.29***</td>
<td>−0.17***</td>
<td>−0.26***</td>
</tr>
<tr>
<td>Δ EDSS</td>
<td>−0.11***</td>
<td>−0.03</td>
<td>−0.03</td>
</tr>
<tr>
<td>Δ MSFC</td>
<td>0.13***</td>
<td>0.09*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

R = Pearson correlation co-efficient, *** p < 0.001, * p < 0.05
EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite
Conclusions

- Brain volume at baseline correlated best with indicators of MS disease severity (MS duration, EDSS, T2 lesion volume)

- Baseline T2 lesion volume and presence of Gd+ T1 lesions significantly predicted PBVC over the course of the clinical trials
  - Effect of number of Gd-lesions at baseline was apparent
  - Brain volume loss in placebo-treated patients with a low T2 lesion burden and no inflammation is still higher than that reported in healthy individuals
  - Brain volume loss in fingolimod-treated patients was reduced compared with controls, regardless of baseline factors

- Brain volume loss on-study correlated with new T2 lesion formation and increases in the level of disability (EDSS, MSFC)

- Fingolimod is the only approved MS treatment that provided a consistent and significant treatment effect on PBVC across all phase 3 studies, compared with placebo or interferon beta-1a IM
  - The treatment effect was evident as early as month 6 in both FREEDOMS studies*

*First scan post-baseline. EDSS, Expanded Disability Status Scale; IM, intramuscular; PBVC, percentage brain volume change