MRI in Multiple Sclerosis

Features of Cerebral Atrophy with special focus on Multiple Sclerosis

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CNS effects of fingolimod in MS: potential for ‘neuroprotection’

- Potential preclinical effects of fingolimod may explain observed brain volume change in clinical trials

Preclinical evidence
- Reduction in inflammatory infiltrates and CNS inflammation
- Preserved BBB integrity
- Enhances remyelination and protects against demyelination, axonal loss, and dendritic loss
- Enhances survival of neurons and increases BDNF levels
- Reduces inflammatory infiltrates and CNS inflammation
- Preserves BBB integrity
- Potential preclinical effects of fingolimod may explain observed brain volume change in clinical trials

Image courtesy of Professor Barkhof, VU University Medical Center, Amsterdam.

References:
MRI measures of MS pathology
Acute combined activity

Gd-enhancing T1 lesions

New/enlarging T2 lesions

Relapse Rate
MRI outcome measures

**Inflammatory activity:**
- Number of new/enlarged T2 lesions,
- Number of Gd-enhancing T1 lesions
- Proportions of patients free from new/enlarged T2 lesions or Gd-enhancing lesions and relapses

**Burden of disease:**
- Absolute and per cent change from baseline in total T2 lesion volume

**Tissue loss or destruction:**
- Absolute and per cent change from baseline in total T1 hypointense lesion volume.
- Per cent change in brain volume from baseline
Sustained reductions in ARR with fingolimod were observed across long-term studies

Fingolimod Phase II and III studies

*<p<0.001 vs respective control; †patients may have received placebo for 6 months in the core study before switching to fingolimod 1.25 mg or 5.0 mg. Patients on fingolimod 5.0 mg were switched to open-label fingolimod 1.25 mg in Months 15-24. All patients transitioned to fingolimod 0.5 mg after 5 years until study end; ‡Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS.


*#p<0.001 vs respective control; †patients may have received placebo for 6 months in the core study before switching to fingolimod 1.25 mg or 5.0 mg. Patients on fingolimod 5.0 mg were switched to open-label fingolimod 1.25 mg in Months 15-24. All patients transitioned to fingolimod 0.5 mg after 5 years until study end; ‡Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS.


ARR

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Fingolimod 0.5 mg</th>
<th>Fingolimod 1.25, 5.0 mg</th>
<th>IFNβ-1a IM</th>
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<tbody>
<tr>
<td>TRANSFORMS 1 year¹</td>
<td>0.33</td>
<td>0.40</td>
<td>0.40</td>
<td>0.16</td>
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<tr>
<td>FREEDOMS 2 years²</td>
<td>0.18*</td>
<td>0.40</td>
<td>0.40</td>
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<td>FREEDOMS II 2 years³</td>
<td>0.21*</td>
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<td>FREEDOMS extension &gt;4 years⁴</td>
<td>0.19</td>
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<tr>
<td>TRANSFORMS extension ~4.5 years⁵,⁶</td>
<td>0.17</td>
<td>0.40</td>
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<tr>
<td>Phase II ≥7 years⁷,⁸</td>
<td>0.16</td>
<td>0.40</td>
<td>0.40</td>
<td>0.16</td>
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</tbody>
</table>

n = 431 429 418 425 355 358 425 429 281
TRANSFORMS extension study: inflammatory disease activity (Gd⁺ T₁ lesions)

Mean number of Gd⁺ T₁ lesions

<table>
<thead>
<tr>
<th></th>
<th>Core BL</th>
<th>Month 12</th>
<th>Month 24</th>
<th>Month 48</th>
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<tbody>
<tr>
<td>n = 425</td>
<td>n = 354</td>
<td>n = 285</td>
<td>n = 35</td>
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IFNβ-1a IM / fingolimod

<table>
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<tr>
<th></th>
<th>Core BL</th>
<th>Month 12</th>
<th>Month 24</th>
<th>Month 48</th>
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</thead>
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<tr>
<td>n = 427</td>
<td>n = 374</td>
<td>n = 307</td>
<td>n = 34</td>
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</table>

Continuous fingolimod 0.5 mg

Core ITT population. Gilenya™ 0.5 mg / day is the only dose approved for the treatment of MS. Sub analyses for which no formal statistical analysis was performed.

*Patients switched to fingolimod at Month 12; includes patients who received both fingolimod 0.5 mg and 1.25 mg. Khatri B et al. Oral 218 presented at ENS 2012
Patients free from MRI lesion activity up to 4 years

**FREEDOMS extension: 4-year results**

**Patients free from new or newly enlarged T_2 lesions**

- Placebo (Month 0–24) switched to fingolimod 0.5 mg (Month 24–48) (n = 69)
  - Month 0–24: 23.2%
  - Month 24–48: 55.1%
- Continuous fingolimod 0.5 mg (n = 163)
  - Month 0–24: 50.3%
  - Month 24–48: 69.3%

**Patients free from Gd{T1 lesions**

- Placebo (Month 0–24) switched to fingolimod 0.5 mg (Month 24–48) (n = 75)
  - Month 0–24: 32.0%
  - Month 24–48: 80.0%
- Continuous fingolimod 0.5 mg (n = 171)
  - Month 0–24: 74.9%
  - Month 24–48: 79.5%

Within group comparison – extension ITT population
Rate of brain volume loss lower for fingolimod vs placebo and IFNβ-1a IM

FREEDOMS, 2 years

-38% vs placebo p<0.001

-40% vs IFNβ-1a IM p<0.001

TRANSFORMS, 1 year

*p<0.05, **p<0.01, ***p<0.001 vs comparator; p values are for comparisons over months 0-6, Months 0-12, Months 0-24
Barkhof et al. ECTRIMS 2011; poster P907; Radue E et al. AAN 2011; poster P05.064; Gilenya™ (fingolimod) Summary of Product Characteristics, 4 April 2011
Phase III brain volume data: FREEDOMS overall and divided by Gd-activity at baseline

- Fingolimod 0.5 mg
- Placebo

**Rate of BV loss lower for fingolimod vs placebo at all time points for all groups independent of inflammation status**

**p<0.05, **p<0.01, ***p<0.001 vs placebo; †p=0.061 vs placebo; BV, brain volume; Gd, gadolinium, IFN, interferon

1. Radue E et al. AAN 2011, Poster P05.064
FREEDOMS extension study: fingolimod treatment resulted in a sustained reduction in brain volume loss over 4 years

Core ITT population. *Reduction in brain volume was calculated using SIENA. At baseline, a single-time-point SIENA method, SIENAX, was used to estimate the normalised brain volume. SIENAX uses brain extraction and tissue-type segmentation to calculate brain volume, followed by normalisation (for head size) to standard space; †In the extension, these patients were initially re-randomised to fingolimod 0.5 or 1.25 mg, and then all transitioned to open-label fingolimod 0.5 mg. Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS. No statistical analysis was performed n, number of patients with non-missing values. Radue EW et al. Oral O219 presented at ENS 2012
Meta-analysis of RCTs in RRMS: brain atrophy and T2 lesions as predictors of disability

- Analysis of published RCTs in RRMS, lasting ≥2 years
- If number of T2 lesions and atrophy are used in combination they predict the treatment effect on disability more strongly

R^2 = 0.7, p<0.001

RR, relative reduction
Sormani MP et al. Poster P07.096 presented at AAN 2013
Semiautomatic segmentation of the cerebellum in MS patients using ECCET
Semiautomatic segmentation of the cerebellum in MS patients using ECCET
Spinal atrophy

Mean Cross-sectional Area (CSA)

Cross-sectional area [mm²] vs. Distance along the spinal cord centerline [mm]

- Controls (green line)
- Patients (red line)

3T MPRAGE scans
1 mm³ resolution
11 MS patients
12 healthy controls
Reconstruction length: 50 mm

Mean CSA diff.: 6.94±1.29 mm²

Pezold, Amann et al.
Spinal cord volume and disease characteristics

Volume vs Disease Duration

Volume vs Brain T2 Lesion Volume

Volume vs EDSS

Model 3: R^2 = 0.398

<table>
<thead>
<tr>
<th>p-value</th>
<th>Age</th>
<th>Gender</th>
<th>Disease Duration</th>
<th>Cervical Cord Volume</th>
<th>T2 Brain Lesion Volume</th>
<th>GM Volume</th>
<th>WM Volume</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.135</td>
<td>&lt; 0.001</td>
<td>0.004</td>
<td>0.726</td>
<td>0.146</td>
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<tr>
<td>beta</td>
<td>0.305</td>
<td>0.253</td>
<td>0.100</td>
<td>-0.359</td>
<td>0.159</td>
<td>0.026</td>
<td>0.089</td>
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</table>
Relation between EDSS and thalamic volume

Magon et al., in revision
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