Emerging MS Therapies

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Director, OSU MS Center
The Ohio State University
What Is MS?

Autoimmunity = Friendly Fire
Changing therapy options

IFNβ-1b SC (Betaseron®)
IFNβ-1a IM (Avonex®)
glatiramer acetate (Copaxone®)
mitoxantrone (Novantrone®)
IFNβ-1a (Rebif®)
natalizumab (Tysabri®)
IFNβ-1b (Extavia®)
Fingolimod (Gilenya®)
Alemtuzumab (Campath®)
Fumarate (BG-12)
Laquinimod
Teriflunomide


Approved therapies

Approval date

Phase III completed

Interferon Beta

- Proposed MOA: Tightens up the blood brain barrier
Glatiramer Acetate

Pro-inflammatory “let’s go get into a fight tonight!”

Anti-inflammatory “let’s just order a pizza and watch Oprah re-runs”
Emerging MS Therapies

Monoclonal Antibodies
- Natalizumab (update)
- Alemtuzumab
- Rituximab
- Ocrelizumab
- Ufatumumab
- Daclizumab

Oral Medications
- Fingolimod
- Teriflunomide
- Laquinimod
- BG12
**Nata / li / zu / mab**

- **Li** – immune target
- **Zu** – humanized
- **Mab** – monoclonal antibody

- Humanized monoclonal antibody against $\alpha_4\beta_1$ integrin
- Proposed MOA: Inhibits binding of lymphocytes and monocytes to their endothelial receptor, vascular-cell adhesion molecule 1 (VCAM-1)
- Rationale in MS: Reduction of leukocyte extravasation into CNS
Natalizumab - Mechanism of Action
AFFIRM: Placebo-Controlled Trial of Natalizumab in RRMS\(^1\)

**SecondaryEndpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Net Reduction (vs Placebo)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean new or enlarging T2 lesions</td>
<td>-83%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Mean new GdE lesions</td>
<td>-92%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Risk of sustained disability progression</td>
<td>-42%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- Common adverse effects include hypersensitivity reactions, mild headache, fatigue, peripheral edema, infections\(^2\)

ARR: annualized relapse rate; GdE: gadolinium-enhancing.

Trends Across Clinical Trials: ARR

ARR = annualized relapse rate.
New Concept: Freedom From Disease Activity

- Freedom from clinical activity
  - No relapses
  - No progression of disability (sustained for 12 weeks)

- Freedom from MRI activity
  - No Gd+ lesions at years 1 and 2
  - No new or enlarging T2 lesions over 2 years

- Freedom from disease activity

Patients with no disease activity

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>NTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of relapses</td>
<td>71%</td>
<td>43%</td>
</tr>
<tr>
<td>Percentage</td>
<td>71%</td>
<td>43%</td>
</tr>
<tr>
<td>n</td>
<td>304</td>
<td>600</td>
</tr>
</tbody>
</table>

Free of relapses

71% NTZ
43% Placebo

Free of clinical disease activity

64% NTZ
39% Placebo

Free of sustained disability progression

84% NTZ
72% Placebo

Free of disease activity

37% NTZ
7% Placebo

Free of Gd+ lesions

95% NTZ
57% Placebo

Free of MRI disease activity

58% NTZ
14% Placebo

Free of new or enlarging T2 lesions

58% NTZ
15% Placebo


*Defined as no radiological or clinical activity.
New Concept: Sustained Improvement in Physical Disability

Defined as EDSS 1 point decrease sustained for 12 weeks.

Adjusted Hazard Ratio = 1.69 (95% CI: 1.16, 2.45)  
\( P = .006 \)

Natalizumab Significantly Increases the Cumulative Probability of Sustained Improvement in Physical Disability (post hoc analysis of AFFIRM)  
F. Munschauer, et. al. Poster #P474 Presented at the World Congress in Treatment and Research in Multiple Sclerosis September 17-20, 2008

Number of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>NTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>203</td>
<td>417</td>
</tr>
<tr>
<td>12</td>
<td>186</td>
<td>362</td>
</tr>
<tr>
<td>24</td>
<td>166</td>
<td>317</td>
</tr>
<tr>
<td>36</td>
<td>156</td>
<td>297</td>
</tr>
<tr>
<td>48</td>
<td>145</td>
<td>279</td>
</tr>
</tbody>
</table>

aDefined as EDSS 1 point decrease sustained for 12 weeks.  
Data on file, Biogen Idec.
PML Risk Stratification in MS Patients Based on the 3 Known Risk factors


**Table:**

<table>
<thead>
<tr>
<th>Nataлизумаб Exposure</th>
<th>Anti-JCV Antibody Negative</th>
<th>Anti-JCV Antibody Positive with No Prior Immunosuppressant Use</th>
<th>Anti-JCV Antibody Positive with Prior Immunosuppressant Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 Years</td>
<td>≤0.11/1000 (95% CI: 0–0.59)</td>
<td>0.35/1000 (95% CI: 0.19–0.60)</td>
<td>1.2/1000 (95% CI: 0.58–2.2)</td>
</tr>
<tr>
<td>&gt;2 Years</td>
<td></td>
<td>2.8/1000 (95% CI: 2.0–3.8)</td>
<td>8.1/1000 (95% CI: 5.4–11.6)</td>
</tr>
</tbody>
</table>

*Estimate based on all anti-JCV antibody negative patients receiving at least 1 dose of natalizumab and 1 hypothetical PML case that was anti-JCV antibody negative at the time of PML diagnosis.

PML incidence in anti-JCV antibody positive patients was calculated on the basis of the following assumptions: 55% of natalizumab-treated MS patients were anti-JCV antibody positive, the proportion of natalizumab-treated patients with prior IS use was 20% based on TYGRIS data, and 100% of confirmed cases of PML were anti-JCV antibody positive prior to the onset and diagnosis of PML.
Alemtuzumab - Mechanism of Action
Trends Across Clinical Trials: ARR

ARR—2 Years

Glatiramer acetate
IFNb1a sq
Natalizumab
Rituximab
Fingolimod
Teriflunimide
Alemtuzumab

ARR=annualized relapse rate.
CAMMS223 Study Design

- Phase 2, randomized, open label, comparator-controlled, rater-blinded trial
- 334 treatment-naïve patients with early, active relapsing-remitting MS (RRMS)
- Primary endpoints: Relapse rate; time to sustained accumulation of disability (SAD) by EDSS

Note: All treatment arms received 1g methylprednisolone QDx3 at months 0, 12, and 24.
CAMS223: Proportion of Patients Free From Disease Activity at 5 Years

- 65% of alemtuzumab patients were free of CDA vs 27% of SC IFNβ-1a patients
- 69% reduction in the 5-year relative risk in alemtuzumab-treated patients (p < 0.0001)

SAD = Sustained accumulation of disability (6 months); CDA = Clinical disease activity (relapse or disability progression)

## CAMS223: Adverse Events

<table>
<thead>
<tr>
<th>Selected AEs, n (%)</th>
<th>IFN β-1a</th>
<th>Alemtuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism (ie, Graves disease)</td>
<td>1 (0.9)</td>
<td>32 (14.8)</td>
</tr>
<tr>
<td>Hypothyroidism (ie, Hashimoto's disease)</td>
<td>1 (0.9)</td>
<td>15 (6.9)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1 (0.9)</td>
<td>9 (4.2)</td>
</tr>
<tr>
<td>ITP</td>
<td>1 (0.9)</td>
<td>6 (2.8)</td>
</tr>
</tbody>
</table>
# Alemtuzumab
## Phase III Press Release

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARES I</td>
<td>(1) ALEM (2 annual cycles)</td>
<td><strong>Primary Endpoint:</strong> ALEM resulted in 55% ARR reduction compared to IFN arm  ( P &lt; .0001 )</td>
</tr>
<tr>
<td>RRMS</td>
<td>(2) IFNb-1a sq TIW</td>
<td><strong>Secondary Endpoint:</strong> Sustained disability progression seen in 8% ALEM patients vs. 11% IFNb1a patients (Hazard Ratio=0.70, ( p=0.22 )).</td>
</tr>
</tbody>
</table>

PRESS RELEASE 7/2011: “Sanofi Reports Positive Top-Line Results from First Phase 3 Study of Alemtuzumab (Lemtrada™ (*)) in Multiple Sclerosis”
Rituximab - Mechanism of Action
Trends Across Clinical Trials: ARR

ARR—2 Years

- Glatiramer acetate
- IFNb1a sq
- Natalizumab
- Rituximab
- Fingolimod
- Alemtuzumab
- Teriflunimide

ARR=annualized relapse rate.
Ocrelizumab Phase II Study: Annualized Relapse Rate (ARR)

220 RRMS randomized to 1:1:1:1 OCR at 600mg : OCR at 2000mg : PCBO : IFNb1a IM q wk open label

SAEs and serious infections similar in all groups

More infusion reactions in treatment arms

One Death in high dose arm

Systemic inflammatory syndrome and DIC

ARR relative reduction at week 24 for ocrelizumab vs placebo
600 mg: 80%, \( P = 0.0005 \)
2000 mg: 73%, \( P = 0.0014 \)

Ofatumumab
(Fully humanized anti-CD20 monoclonal antibody)
24-week, placebo-controlled, double-blind, phase II clinical trial

- 26 patients randomized 2:1 to 3 doses of OFAT vs. PCBO
- Primary end point: Decreased gad vs placebo
- Only high dose lowered ARR more than placebo
- Well tolerated

<table>
<thead>
<tr>
<th>Mean cumulative # new Gd lesions on monthly MRI from wk 8-24</th>
<th>Combined OFAT arms</th>
<th>PCBO</th>
<th>Relative reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.04 (SD 0.2)</td>
<td>9.69 (SD 24.86)</td>
<td>99.8%</td>
</tr>
</tbody>
</table>

Sorensen, ECTRIMS 2010, Platform 136
Daclizumab

- A humanized monoclonal antibody directed at IL-2 receptor alpha chain, aka CD25
  - Expressed on activated T cells, B cells, NK cells, monocytes and eosinophils

- Originally developed to block the proliferation of virally transformed T-cells in adult T-cell leukemia (ATL) induced by HTLV-1

- Currently approved for the treatment of renal transplant rejection

- Promising effects in the treatment of noninfectious uveitis

Daclizumab

Phase 2 study in active relapsing MS patients receiving IFN β

- At 24 weeks, addition of daclizumab at 1 (Q4W) or 2 mg/kg (Q2W) to IFN β:
  - ↓ new/enlarged GdE lesions in high-dose group vs IFN β alone; \( P = .004 \)
  - ↓ new/enlarged T2 lesions in high-dose daclizumab groups vs IFN β alone; \( P = .007 \)

- Presence of IFN β neutralizing antibodies in daclizumab groups not associated with increase in new/enlarged lesions

Adverse Events

- Rash
  - Most are benign and easily treated
  - Significant inflammatory dermatitis can occur

- Lymphadenopathy with evidence of EBV infection required temporary cessation of treatment in one patient

- Post-infusion febrile reactions of short duration have also occurred

- Minor GI disturbances following infusions have been noted


### Emerging Monoclonal Antibodies

#### MOA

<table>
<thead>
<tr>
<th>Antibody</th>
<th>MOA</th>
<th>Dosing</th>
<th>Pivotal Phase III Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td>Inhibits leukocyte egress from vascular compartment</td>
<td>q 4 wk</td>
<td>AFFIRM SENTINEL</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Depletes T &amp; B cells</td>
<td>q year</td>
<td>CARES I/II</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Depletes B cells</td>
<td>q 6 mo</td>
<td>OLYMPUS</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Inhibits T lymphocyte activation / expansion</td>
<td>SC q mo</td>
<td></td>
</tr>
</tbody>
</table>
Emerging MS Therapies

Monoclonal Antibodies
- Natalizumab (update)
- Alemtuzumab
- Rituximab
- Ocrelizumab
- Ufatumumab
- Daclizumab

Oral Medications
- Fingolimod
- Teriflunomide
- Laquinimod
- BG12
Fingolimod - Mechanism of Action
Trends Across Clinical Trials: ARR

ARR = annualized relapse rate.

ARR—2 Years

Glatiramer acetate
IFNb1a sq
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Johnson 1995
Jacobs 1996
IFNb-1b study group, 1993
PRISMS 1998
Kappos TRANSFORM 2006
Polman 2006
REGARD 2007
BEYOND 2007
BECOME 2007
CAMMS223 2008 3 years
HERMES FORTE 2008 48 weeks
TEMSO 2010 1 year
CLARITY 2010 2 year

0.59
0.67
0.84
0.87
0.16
0.23
0.29
0.30
0.34
0.35
0.32
0.28
0.10
0.36
0.37
0.33
0.30
0.14
### Fingolimod: The First Orally Administered DMT for Patients With MS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **TRANSFORMS**¹ | (1) Fingolimod 0.5 mg  
(2) Fingolimod 1.25 mg  
(3) IFN β-1a 30 µg | **Outcome**                      |
| N = 1,292; RRMS  
Aged 18-55 years  
EDSS 0-5  
12-mo study |                                                                 | **Fingolimod** | 0.5 mg | 1.25 mg | **ARR** | −52% (P < .001) | −38% (P < .001) |
|            |                                                                 | **Active T2** | -35% (P = .004) | -42% (P < .001) |
|            |                                                                 | **GdE lesions** | -55% (P < .001) | -73% (P < .001) |
|            |                                                                 | **CDPD** | -25% (P, NS) | -15% (P, NS) |
| **FREEDOMS**² | (1) Fingolimod 0.5 mg  
(2) Fingolimod 1.25 mg  
(3) Placebo | **Outcome**                      |
| N = 1,272; RRMS  
Aged 18-55 years  
EDSS 0-5  
24-mo study |                                                                 | **Fingolimod** | 0.5 mg | 1.25 mg | **ARR** | −54% (P < .001) | −60% (P < .001) |
|            |                                                                 | **Enlarging T2** | -74% (P < .001) | -74% (P < .001) |
|            |                                                                 | **GdE lesions** | -82% (P < .001) | -82% (P < .001) |
|            |                                                                 | **CPDPa** | -26% (P < .03) | -31% (P < .01) |

*a Confirmed at 3 mo.

CDPD: cumulative probability of disability progression.
Effect of Fingolimod on MSFC-Defined Disability Progression in Phase III

Statistically significant vs control for both fingolimod doses in both trials

IFN = Interferon; MSFC = Multiple Sclerosis Functional Composite
## Key Safety Outcomes

### FREEDOMS:

<table>
<thead>
<tr>
<th>Event*</th>
<th>Placebo (n = 418)</th>
<th>Oral fingolimod 0.5 mg (n = 425)</th>
<th>Oral fingolimod 1.25 mg (n = 429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal laboratory liver function tests</td>
<td>21 (5.0)</td>
<td>67 (15.8)</td>
<td>80 (18.6)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (3.6)</td>
<td>34 (8.0)</td>
<td>39 (9.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (0.2)</td>
<td>12 (2.8)</td>
<td>27 (6.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2 (0.5)</td>
<td>15 (3.5)</td>
<td>23 (5.4)</td>
</tr>
<tr>
<td>Bradycardia or bradyarrhythmia</td>
<td>3 (0.7)</td>
<td>9 (2.1)</td>
<td>14 (3.3)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (0.7)</td>
<td>4 (0.9)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>3 (0.7)</td>
<td>2 (0.5)</td>
<td>6 (1.4)</td>
</tr>
<tr>
<td>Macular edema</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (1.6)</td>
</tr>
</tbody>
</table>

*Occurred ≥ 2-fold higher in either fingolimod dose group compared to placebo


### TRANSFORMS:

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>IFNβ-1a 30 µg IM once weekly (n = 431)</th>
<th>Oral fingolimod 0.5 mg/day (n = 429)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like illness</td>
<td>159 (36.9)</td>
<td>15 (3.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>77 (17.9)</td>
<td>18 (4.2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>44 (10.2)</td>
<td>14 (3.3)</td>
</tr>
<tr>
<td>Hepatic ALT elevation</td>
<td>8 (1.9)</td>
<td>28 (6.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (0.5)</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0.0)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes viral infections</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECTRIMS 2010 Update: 1<sup>st</sup>-Dose effect of FTY: pooled safety data

<table>
<thead>
<tr>
<th>Pooled safety data from TRANSFORMS and FREEDOMS</th>
<th>FTY 0.5mg (n=854)</th>
<th>PCBO (n=418)</th>
<th>IFN (n=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HR decrease (bpm @ 4-5hr)</td>
<td>-8</td>
<td>No change</td>
<td>+8.3</td>
</tr>
<tr>
<td>% pts HR &lt;50 bpm</td>
<td>6.1</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>% pts 1&lt;sup&gt;st&lt;/sup&gt; degree heart block</td>
<td>4.7</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>% pts 2&lt;sup&gt;nd&lt;/sup&gt; degree heart block (2:1 / Mobitz I)</td>
<td>0 / 0.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Symptomatic Bradycardia</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transient decr. BP (mmHg)</td>
<td>-3.5</td>
<td>-1.8</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

DiMarco, ECTRIMS 2010, Poster 830

ECTRIMS 2010 UPDATE: Lymphocytes & FTY720: temporal pattern & relationship with infections

- Rapid drop after initiation and approaches steady state in 4 weeks
- Mean lymphocyte counts returned to normal range by 45 days
- 3-mo post cessation lymphocyte counts are:
  - 86% of baseline in treated arm
  - 93% baseline in PCBO arm

Francis, ECTRIMS 2010, Poster 442

<table>
<thead>
<tr>
<th>Mean Lymphocyte count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Month 1 0.5mg dose</td>
</tr>
</tbody>
</table>
Fingolimod FDA approved 9/2010

- Before starting:
  - Labs: VZV, CBC, LFTs
  - Testing: EKG, PFTs
  - Examinations: dermatologic and ophthalmologic
  - Exclude certain patients

- Time of First Dose:
  - Observe patient for 1st 6 hours (prepare to treat bradyarrythmias)

- Every 3-6 months:
  - Follow LFTs
  - Repeat dermatologic and ophthalmologic examinations
Teriflunomide - Mechanism of Action
Trends Across Clinical Trials: ARR

ARR—2 Years

0.00 0.20 0.40 0.60 0.80 1.00

ARR=annualized relapse rate.

Glatiramer acetate
IFNb1a sq
Natalizumab
Rituximab
Fingolimod
Teriflunimide
Alemtuzumab
IFNB1b

GA
IFNβ-1b
IFNB1a IM
IFNB1b
IFNB1a sq
natalizumab
Glatiramer acetate
IFNB1a sq
Natalizumab
Rituximab
Fingolimod
Teriflunimide
Alemtuzumab
IFNB1b

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Jacobs 1996
IFNβ-1b study group, 1993
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 REGARD 2007
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BECOME 2007
Vesalius 2008 3 years
HERMES FORTE 2008 48 weeks
TEMSO 2010 1 year
CLARITY 2010 2 year

0.59 0.67 0.84 0.87 0.16 0.23 0.29 0.30 0.34 0.35 0.32 0.28 0.10 0.36 0.37 0.33 0.30 0.14
### Study

#### TEMSO

- **N = 1,088**
- **RRMS**

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Teriflunomide 7 mg</td>
<td>Relative ARR reduction vs PBO</td>
</tr>
<tr>
<td>(2) Teriflunomide 14 mg</td>
<td>- 7 mg = 31.2%; <em>P</em> &lt; .01</td>
</tr>
<tr>
<td>(3) Placebo</td>
<td>- 14 mg = 31.5%; <em>P</em> &lt; .01</td>
</tr>
<tr>
<td></td>
<td>- 30% reduction in confirmed disability progression</td>
</tr>
<tr>
<td></td>
<td>- Significant reductions in MRI activity noted with 14-mg teriflunomide dose</td>
</tr>
</tbody>
</table>

#### Adverse events

- No between group difference in serious opportunistic infections or liver enzyme elevations >3X ULN

---

### Adjusted annualized relapse rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relapse Rate</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 363)</td>
<td>0.370</td>
<td>0.0005</td>
</tr>
<tr>
<td>7 mg (n = 365)</td>
<td>0.369</td>
<td>0.0005</td>
</tr>
<tr>
<td>14 mg (n = 358)</td>
<td>0.370</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

### Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>7 mg</th>
<th>14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>363</td>
<td>336</td>
<td>306</td>
</tr>
<tr>
<td>7 mg teriflu</td>
<td>365</td>
<td>343</td>
<td>309</td>
</tr>
<tr>
<td>14 mg teriflu</td>
<td>358</td>
<td>329</td>
<td>302</td>
</tr>
</tbody>
</table>

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O'Connor P et al. 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS2010). Abstract 79.
Laquinimod - Mechanism of Action
# Laquinimod

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
<th>Adverse events, n (laquinimod vs PBO)</th>
</tr>
</thead>
</table>
| **ALLEGRO**<sup>1</sup> | (1) Laquinimod 0.6 mg  
(2) Placebo | **Laquinimod vs PBO**  
- 23% reduction in ARR; \( P = .0024 \)  
- 36% reduction in sustained disability progression; \( P = .0122 \)  
- 33% reduction in brain atrophy; \( P < .0001 \)  
- Significant reductions in MRI activity noted |  
- Pericarditis: 1 in PBO arm  
- Appendicitis: 5 vs 1  
- Herpes virus: 17 vs 20  
- Thrombosis or embolism: 3 vs 2  
- Neoplasms: 8 vs 6 |
| **BRAVO**<sup>2</sup> | (1) Laquinimod 0.6 mg  
(2) Placebo  
(3) IFN beta-1a IM q wk | **Laquinimod vs PBO**  
- Unadjusted ARR reduction NS, \( p = .075 \)  
- **Adjusted for differences in baseline MRI characteristics:**  
  - ARR reduction 21.3%, \( p = .026 \)  
  - Risk of disability progression 33.5%, \( p = .044 \)  
  - Reduction brain volume loss 27.5%, \( p < .0001 \) | |

2. TEVA Neuroscience Press Release August 1<sup>st</sup>, 2011
BG12 - Mechanism of Action
BG12 (Dimethyl Fumarate):

- A second-generation fumaric acid ester
- Based on Fumaderm® (a psoriasis product marketed in Germany)
  - Formulation for better gastrointestinal tolerability
  - Multiple daily doses (BID or TID)

- Fumaderm causes lymphocytopenia and decreases Th1 cytokines in psoriasis
  - Other mechanistic properties may include upregulation of Th2 cytokines and decreased expression of adhesion molecules

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| DEFINE² | (1) BG-12 240 mg BD (2) BG-12 240 mg TID (3) Placebo | % pts relapsed at 2 y lower in BG-12 arms vs PBO; $P < .0001$  
Significant reductions in MRI activity noted in favor of BG-12  
Significant reductions in disability progression in favor of BG-12 | Adverse event incidence similar between all three treatment groups |

# Emerging MS Therapies: Oral Medications

<table>
<thead>
<tr>
<th>MOA</th>
<th>Dosing</th>
<th>Pivotal Phase III Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>Sequesters lymphocytes in periphery</td>
<td>QD</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Inhibits lymphocyte proliferation</td>
<td>QD</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>Shift from Th1 to Th2/Th3</td>
<td>QD</td>
</tr>
<tr>
<td>BG12</td>
<td>Anti-inflammatory &amp; neuroprotective properties</td>
<td>BID/TID</td>
</tr>
<tr>
<td>Fampridine</td>
<td>Restore conduction in focally demyelinated neurons</td>
<td>BID</td>
</tr>
</tbody>
</table>
Changing therapy options

5-19

Approved therapies

Phases III completed

1. IFNβ-1b SC (Betaseron®)
2. IFNβ-1a IM (Avonex®)
3. gatiramer acetate (Copaxone®)
4. mitoxantrone (Novantrone®)
5. IFNβ-1a (Rebif®)
6. natalizumab (Tysabri®)
7. IFNβ-1b (Extavia®)
8. Fingolimod (Gilenya®)
9. Alemtuzumab (Campath®)
10. Fuamarate (BG-12)
11. Laquinimod
12. Teriflunomide

Approval date
