Multiple Sclerosis: Too Crowded, or Still Room to Play?

Ginger S. Johnson, PhD
Vice President

David Lomb, PhD
Associate Consultant

Defined Health
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Multiple Sclerosis: Too Crowded, or Still Room to Play?

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
MS Has Been a Good Place to Be

- The worldwide market for multiple sclerosis (MS) disease modifying therapies is in excess of $11B.
- Considering the relatively small patient population (versus other neurodegenerative disease such as Parkinson’s disease and especially Alzheimer’s), this is pretty impressive.

2010 MS Market $11.1B WW

- Merck Serono 20%
- Bayer/Novartis 16%
- Biogen Idec/Elan 34%
- Teva/Sanofi 28%

* Gilenya is Novartis only
Five Blockbusters on the Market and One in the Making

• The MS market consists of injectables -- three β-interferons (Avonex, Betaseron/Extavia and Rebif), glatiramer acetate (Copaxone) – so-called ABCER therapy, and an alpha-4 integrin (Tysabri), and the first oral option, Gilenya (Fingolimod).

• All products are immunomodulatory addressing relapsing forms of the disease (~ 50% of the patient population).

<table>
<thead>
<tr>
<th>Approved Disease-Modifying MS Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td><strong>Active agent</strong></td>
</tr>
<tr>
<td><strong>Company Indication</strong></td>
</tr>
<tr>
<td><strong>Approved for:</strong></td>
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<tr>
<td>Reduction in exacerbations</td>
</tr>
<tr>
<td>Slowing of disability</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
</tr>
</tbody>
</table>

Source: Cowen and Company
Healthy Price Hikes Have Helped Boost Revenue in the US

- The MS market continues to grow at a significant pace, driven by aggressive US price hikes (but only mid-single-digit patient growth).

- All MS agents raised price as new agents set higher benchmarks.

- With the 2010 introduction of Novartis’ Gilenya just under $48,000 a year, the others are busy catching up.

- Gilenya established a new ceiling at $3,700 per month with all other brands increasing 25% between 1Q2010 and Jun 2011

- Tysabri the former price leader, had been averaging only 9% increases from 2006 through 2010, but has now played catch-up with a 27% increase

- Copaxone took the most aggressive price increases averaging 20% per annum since 2005

- There appears to be little contracting since the ASP is usually within 5% of the WAC for the corresponding sales period (4-6 months earlier)

*Compass Strategic Consulting; WAC: annual edition of Red Book; Rite Aid (Jun 20, 2011)*
While Pricing in the EU has Remained Fairly Constant

• MS agents rose significantly in price in the US between 2006 and 2011, while prices in the EU3 are usually below 2006 US levels.

Compass Strategic Consulting; WAC: annual edition of Red Book; Rite Aid (Jun 20, 2011); ZenRx.org
Skyrocketing MS Drug Prices Hit Patients Hard, Prompting Compliance Problems

When the first oral drug for multiple sclerosis, fingolimod (Gilenya), entered the market last fall, neurologists and patients alike experienced sticker shock: the medication was priced at a jaw-dropping $48,000 a year. …

And then the price hikes for other MS drugs followed. Teva’s glatiramer (Copaxone) now comes at a rack rate of over $42,000 per year — a jump of nearly 40 percent over prices at the beginning of 2010. Biogen has also raised prices further for both natalizumab (Tysabri) and interferon-beta-1a (Avonex).

Of course, virtually no patients are paying out of pocket the full listed price for these costly medications. “I have 1,400 MS patients and I don’t have a single patient paying full price. I can’t even conceive of someone with a salary high enough where that would be a consideration,” Dr. Fox said.

But the price increases are still driving more and more people with MS and their families into desperate situations. That’s because as the prices paid by third-party insurers have gone up, so too have patients‘ copays and other shared costs. “On a weekly basis, I’m dealing with patients who have what I would call a medication crisis,” Dr. Fox said. “Many of my patients have copays of between $300 and $800 a month. There aren’t too many families who can easily absorb that cost.”
The “Relapsing” Pie is Not Growing, So It’s All About Share

• Currently available disease modifying therapies address the relapsing forms of MS (about 50% of patients; ~200,000 in the US; ~400,000 in G7). The treatment rate is about 80% in the US and about 60% in Europe.

• Currently available therapies compete for a share of the “relapsing pie”, as well as attempt to drive “quitters” back into the treatment pool.

- Relapsing-remitting MS (RRMS): Recurring attacks, neurological dysfunction, periods of recovery and stability between episodes.

- About 50% of MS patients have a relapsing form of the disease.

- The majority of these patients will develop progressive disease over time (50% within 8-10 years; 90% in 25-30 years).
Current Players are Jockeying for Position in the Treatment Landscape for Relapsing MS

**Copaxone** is rapidly moving into place as the preferred first-line therapy

**Avonex** is establishing itself as the interferon beta of choice

**Rebif**, **Betaseron** and **Extavia** are running in the middle of the pack

**Tysabri** is cementing its position as the best last hope
It’s Not Easy to Get (or Stay) on Top

- Copaxone (Teva, glatiramir acetate) took over the #1 position in the MS market in 2008, supported by price increases but also backed by a better tolerability profile (no flu-like symptoms), superior head-to-head data (BEYOND and REGARD studies) and continued efforts by Teva to differentiate.

![Graph showing US Sales MS Disease Modifying Therapy (2005-2010)](attachment:graph.png)
Teva Continues to Increase the Gap

- Teva is conducting multiple post-marketing studies in efforts to differentiate Copaxone (EvaluatePharma lists ~40 Phase IV studies) and developing a new three-times weekly formulation (vs. current daily administration).

Teva Announces Presentation of New Data on Multiple Sclerosis Disease Treatments at 2011 American Academy of Neurology Annual Meeting

Preliminary analysis of the Cooptimize study, assessing disease course and quality of life outcomes of patients switching to Copaxone® (glatiramer acetate injection) from other approved injectable and infused disease modifying therapies for RRMS. Additional data from the QualiCop study demonstrating the effects of Copaxone® treatment on progression of disability, cognition and fatigue and the impact of these factors on compliance and adherence.

Data demonstrating remyelination, motor neuron preservation and a neuroprotective effect of COPAXONE® in experimental autoimmune encephalomyelitis (EAE).

Teva completes enrollment in Phase III multiple sclerosis evaluating glatiramer acetate three times weekly
At the Same Time, Teva is Making Moves to Reduce Reliance on Copaxone*

Teva Pharmaceutical Shares Tumble the Most in 11 Months

June 19, 2011 10:49 AM ET

Teva Pharmaceutical Industries Ltd. (TEVA) slid the most in 11 months after declining in the US in the last two trading days.

Teva retreated 4.8 percent, the most since July 2010, to 162.50 shekels at the 4:30 p.m. close in Tel Aviv. The company’s American depositary receipts finished at $47.49 in the US on June 17.

Teva, which agreed to buy Cephalon Inc. in May for $6.2 billion to insure future growth, sees 21 percent of its revenue coming from the multiple-sclerosis medicine Copaxone, which is facing increasing competition. Mylan Inc. said on June 17 that a US District Court had decided to go ahead with a trial regarding Copaxone, an announcement Alper said was bad news for Teva.

*Copaxone loses patent exclusivity in 2014. Momenta and Mylan have filed Paragraph IVs. The timing of generic entry is a subject of much debate as there appear to be significant legal and technical hurdles. In addition, to acquiring Cephalon, Teva has oral laquinimod in Phase III with hopes of converting the market from Copaxone.

Bloomberg
Avonex is the Interferon Beta of Choice

Biogen Idec is replacing the commercial team, increasing patient services and support, reinvigorating the brand, countering “more is better” (messaging for Rebif and Betaseron) and developing a long-acting pegylated version.

-- On January 7, 2010, Biogen Idec announced that Francesco Granata had been named Executive VP of Global Commercial Operations. In addition, Tony Kingsley was appointed Senior VP of US Commercial Operations, and Dr. Frederick Munschauer was named VP of US Medical Affairs.

-- On January 11, 2010, Biogen Idec announced that Baron Baptiste, bestselling author and founder of Baptiste Power Vinyasa Yoga, and Dr. Elliot Frohman, one of the world’s leading authorities on MS, had teamed up to develop My MS Yoga, a new program created especially for people with MS.

-- Q4:10 Biogen Idec expected to announce interim analysis of ADVANCE study which includes an MRI-based assessment of disease activity that should provide the first indication of PEG-Avonex’s activity as no Phase II studies were performed. Dosing in studies is once every 2-4 weeks.

SG Cowen Therapeutic Categories Outlook; 2010 Biogen Idec Industry Guidance Report

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MS Insight Briefing
More May Not Always Be Better, But These are Still Billion Dollar Drugs

- In 2002, **Rebif** was approved in the US, thus overturning Avonex’s orphan drug status, based on the head-to-head EVIDENCE trial.
- The EVIDENCE trial also went a long way to support higher, more frequent doses of interferon-beta as providing greater efficacy.
- Merck Serono hoped that the subsequent REGARD study comparing Rebif 44 mcg three times per week with Copaxone 20 mg daily would spur growth in Rebif sales. However, results showed relative equivalence for the two drugs and instead boosted confidence in Copaxone’s efficacy.
- Rebif’s prescription share in the US stands at ~20.0% flat year over year, but it is the market leader ex-US.

*SG Cowen Therapeutic Categories Outlook; Company reports*
More May Not Always Be Better, But These are Still Billion Dollar Drugs

• Like the Rebif EVIDENCE study, Betaseron’s INCOMIN trial results provide support that higher, more frequent doses of interferon-beta have better efficacy (studies showed superiority to Avonex).
• Like the REGARD study, the BEYOND study showed no difference in efficacy between Betaseron and Copaxone.
• Betaseron has a loyal following, but is associated with tolerability/side effect issues (injection site necrosis, depression).
• Betaseron’s ~15% prescription share in the US is in slow decline.
• Novartis introduced a second brand of interferon-beta 1b, Extavia, in 2008 to establish a footprint in the MS market prior to the launch of Gilenya.
Tysabri is Entrenched as Last-Line Option for RRMS, But Continues to Battle PML

- Tysabri, natalizumab (Biogen Idec/Elan), was relaunched with significant restrictions in 2006 after being pulled for concerns over association with potentially life-threatening PML (progressive multifocal leukoencephalopathy) and now holds a steady ~10% market share.

- Tysabri shows reduction in relapse rates twice that of ABCER options, but PML risk just over the 1 in 1,000 mark for patients on drug more than one year and double that (2 in 1,000) for patients treated over 2 years.

Source: Biogen Idec

**Time Dependency Of PML Risk (As of February 2011)**

*SG Cowen Therapeutic Categories Outlook; Company reports*
Risk Stratification Test Seeks to Identify Patients at Risk of PML

- Biogen Idec and Elan have created an ELISA-based diagnostic assay aimed at identifying the subset of patients who may not be infected with JC virus and therefore may not be at risk for developing PML.
- Biogen Idec’s 1,096 patient STRATIFY-1 trial indicates that 40-50% of untreated MS patients do not harbor antibodies to the JC virus.
- Early data suggest that such patients are not at risk of developing PML while on Tysabri.
- In December, Biogen Idec and Elan submitted information to the FDA and EMA on the association between JCV antibodies and PML. The hope is that data from STRATIFY-1 combined with historical correlations might allow Tysabri’s label to be updated, facilitating greater adoption of JCV testing.
- STRATIFY 2 will enroll up to 20K+ US patients on Tysabri with the goal of confirming an association between JCV antibodies and PML risk. Convincing data could support a label update and much earlier use of Tysabri.
Gilenya is the First Oral Treatment for MS and has Impressive Efficacy Data

- In Sept. 2011, the FDA approved the first oral treatment for MS, Gilenya (fingolimod, a sphingosine-1-phosphate receptor modulator), for “treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.” This includes all forms of relapsing MS, including treatment naïve patients. Gilenya was approved in Europe in March 2011 with a more restrictive label.
- Phase 3 studies showed reduction in relapse rates just below those of Tysabri (though not head-to-head and hard to make cross study comparisons).

### Comparison of Relapse Data For Gilenya and Tysabri

<table>
<thead>
<tr>
<th></th>
<th>FTY720 FREEDOMS</th>
<th>Tysabri Study 1801</th>
<th>Tysabri Study 1802</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTY720 0.5mg</td>
<td>Tysabri Placebo</td>
<td>Tysabri+Avonex</td>
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<tr>
<td></td>
<td>FTY720 1.25mg</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Annualized relapse rate, mean</td>
<td>0.18</td>
<td>0.25</td>
<td>0.78</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>54%</td>
<td>66%</td>
<td>54%</td>
</tr>
<tr>
<td>Source: Cowen and Company: Company data; Prescribing information</td>
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</table>

*SG Cowen Therapeutic Categories Outlook; JP Morgan Analyst Report for Active Biotech (May 2011)*
But There are Safety Concerns, So a Slow and Cautious Uptake

- Gilenya’s strong efficacy and convenient oral administration does come with some safety issues and a label warning of increased risk of bradycardia, infections, macular edema, and liver toxicity.
- In addition the label requires a 6 hour observation at first dose due to associated decreased heart rate, as well as testing of visual acuity.
- Physicians are waiting for a couple of years worth of data before they aggressively adopt this product.

SG Cowen Therapeutic Categories Outlook; JP Morgan Analyst Report for Active Biotech (May 2011)
Gilenya is Taking Tysabri Candidates; Expected To Challenge Higher Lines of Therapy in the Future

Gilenya is challenging Tysabri’s foothold on last place and slowing moving up the treatment algorithm.
The Late Stage Pipeline: All Want a Piece of a Very Big Pie

**Phase 3 Oral Therapies**
- BG-12
- Laquinimod
- Teriflunomide
- Cladribine

**Phase 3 Biologicals**
- Daclizumab
- Ocrelizumab
- Lemtrada
# How the Phase III Orals Stack Up So Far

<table>
<thead>
<tr>
<th>Compound (moa); Company</th>
<th>Route of Admin./ Dosing</th>
<th>% Reduction in Relapse Rate v. Placebo</th>
<th>% Reduction in EDSS* Time to Progression v. Placebo</th>
<th>Side Effects/Safety issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG-12 (dimethyl fumarate); Biogen Idec</td>
<td>Oral (BID or TID)</td>
<td>53% over 2 yrs.</td>
<td>38% over 2 yrs.</td>
<td>Flushing, GI pain, diarrhea</td>
</tr>
<tr>
<td>Laquinimod (immunomodulator); Teva/Active Biotech</td>
<td>Oral (QD)</td>
<td>23% over 2 yrs.</td>
<td>36% over 2 yrs.</td>
<td>Chest pain, arthralgia, viral infections, ALT elevations</td>
</tr>
<tr>
<td>Teriflunomide (pyrimidine synthesis inhib.); Sanofi</td>
<td>Oral (QD)</td>
<td>31% (7 and 14 mg) over 2 yrs.</td>
<td>24% over 2 y.r.s (7 mg); 30% over 2 yrs. (14 mg)</td>
<td>ALT elevations, nasopharyngitis, diarrhea, alopecia</td>
</tr>
<tr>
<td>Cladribine (purine analog); Merck Serono</td>
<td>4 5-day courses per year</td>
<td>54% over months 7-10; 42% over 18 months</td>
<td>30% (wk 96) 3/5 mg/kg; 26.7% 5.25 mg/kg</td>
<td>Infections (RTI, UTI), muscle weakness, opportunistic infection; cancer; MOA associated with lymphopenia</td>
</tr>
</tbody>
</table>

*Expanded Disability Status Scale
<table>
<thead>
<tr>
<th>Compound (moa); Company</th>
<th>Key Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG-12 (dimethyl fumarate); Biogen Idec</td>
<td>CONFIRM study results comparing to Copaxone expected late 2011; potential approval est. early 2013</td>
<td>Long history of safety data (marketed as Fumaderm in Germany for treatment of psoriasis for over a decade), troubling but transient side effects (GI upset and flushing; resolve over first couple months of treatment) and impressive efficacy data suggest BG-12 is a first-line contender; however, Fumaderm contraindicated for pregnancy and TID (vs. BID) dosing may be a problem. May also have neuroprotective properties.</td>
</tr>
<tr>
<td>Laquinimod (immunomodulator); Teva/Active Biotech</td>
<td>BRAVO head-to-head vs. Avonex due later in 2011</td>
<td>Moderate efficacy, but relatively clean safety profile (however, linomide which is the same class is known to be embryotoxic). If BRAVO trial shows at least equivalence to Avonex, Teva may have another winner. May also have neuroprotective properties. Potential adjunct to Copaxone, but price of combination therapy is likely an issue.</td>
</tr>
<tr>
<td>Teriflunomide (pyrimidine synthesis inhib.); Sanofi</td>
<td>TERACLES study (due 2014) investigating teriflunomide in combination with Betaseron</td>
<td>Moderate efficacy, hair loss and physician concerns over teratogenicity (compared to level associated with other MS agents) suggest teriflunomide will primarily take a share in the second-line position; however, compelling TERACLES data could position as a first-line contender. Combination therapy likely to be prohibitively expensive.</td>
</tr>
<tr>
<td>Cladribine (purine analog); Merck Serono</td>
<td>Regulatory opinions</td>
<td>Twice rejected by the EMEA; refuse-to-file by the FDA. Safety concerns a major issue.</td>
</tr>
</tbody>
</table>

Note: June 22, subsequent to this original briefing, Merck Serono announced that they will not seek approval for cladribine for MS.
BG-12 & Laquinimod Could Challenge First-Line Tx

Phase 3 Oral Therapies

- BG-12
- Laquinimod
- Teriflunomide
- Cladribine

Note: June 22, subsequent to this original briefing, Merck Serono announced that they will not seek approval for cladribine for MS.
# How the Phase III Biologicals Stack Up So Far

<table>
<thead>
<tr>
<th>Compound (moa); Company</th>
<th>Route of Admin./Dosing</th>
<th>% Reduction in Relapse Rate v. Placebo</th>
<th>% Reduction in EDSS Time to Progression v. Placebo</th>
<th>Side Effects/Safety issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclizumab (Zenepax, anti IL-2R mAb); Biogen Idec/Abbott</td>
<td>Subcu; monthly</td>
<td>72% + Avonex; 35% v. Avonex; monotherapy v. placebo not available</td>
<td>Unknown</td>
<td>Serious infections, UTI, cutaneous events</td>
</tr>
<tr>
<td>Ocrelizumab (anti-CD 20 mAb); Roche</td>
<td>IV infusion; every 6 months</td>
<td>57% week 24; 44% week 48*</td>
<td>21.6% at 96 wks.*</td>
<td>Infusion reactions, UTI, fever, chills, PML?</td>
</tr>
<tr>
<td>Lemtrada (Campath/alemtuzumab, anti-CD52 mAb); Sanofi/Genzyme</td>
<td>IV infusion; 5 days or 3 days per year</td>
<td>74% over 3 yrs.</td>
<td>Unknown</td>
<td>Immune thrombocytopenia purpura (ITP), infections (RTI), Graves disease</td>
</tr>
</tbody>
</table>

*Rituxan data

*JPMorgan Active Biotech Analyst Report; AAN 2011, Company Reports*
# How the Phase III Biologicals Stack Up So Far

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<tbody>
<tr>
<td>Daclizumab (anti IL-2R mAb); Biogen Idec/Abbott</td>
<td>Phase 2 SELECT reporting H2:11; Phase 3 DECIDE head-to-head vs. Avonex</td>
<td>Combination therapy not likely; waiting to see if monotherapy trial shows strong efficacy, but not suggested by earlier studies. Despite less frequent dosing, side effect profile and what may be modest efficacy will put this product at a disadvantage for a 2nd line option.</td>
</tr>
<tr>
<td>Ocrelizumab (anti-CD 20 mAb); Roche</td>
<td>Phase 3 OPERA I &amp; II head-to-head vs. Rebif</td>
<td>Discontinued for Lupus and RA due to serious infection risk including PML; MS patients may not be as susceptible? Efficacy and safety profile similar to Tysabri, but less frequent dosing. Limited uptake expected.</td>
</tr>
<tr>
<td>Lemtrada (Campath/alemtuzumab, anti-CD52 mAb); Sanofi/Genzyme</td>
<td>Phase 3 MS CARE I &amp; II head-to-head vs. Rebif reporting late 2011</td>
<td>Could have best effect on reduction of relapse of any therapy available or in the pipeline and very attractive dosing regimen, but significant safety issues. Likely to compete most directly with Tysabri for last-line therapy (potentially the 50% who are seropositive for JC virus antibodies).</td>
</tr>
</tbody>
</table>

*JPMorgan Active Biotech Analyst Report; AAN 2011, Company Reports*
Biogen Idec, Teva & Sanofi/Genzyme Look to be Major Contenders

Phase 3 Oral Therapies

- BG-12 (Biogen Idec)
- Laquinimod (Teva/Active Biotech)
- Teriflunomide
- Cladribine

Phase 3 Biologicals

- Daclizumab
- Ocrelizumab
- Lemtrada (Sanofi/Genzyme)
There is Still Room to Play

- Across the continuum of the disease, unmet need remains.
- While the treatment space for relapsing MS is crowded and noisy, several new players with disease modifying therapies are attempting to find a niche.
- Few good options exist for the debilitating non-core symptoms of the disease, and virtually no treatment options are available for progressive MS.

[Diagram showing Preferred 1st Line Therapy, Safer 2nd/3rd Line Options, and Effective Therapy for Progressive MS with clinical thresholds, brain volume, inflammation, axonal loss, frequent inflammation, demyelination, axonal transection, plasticity, and remyelination, continuing inflammation and persistent demyelination, infrequent inflammation, chronic axonal degeneration, and gliosis.]
Non-Core Symptoms of MS can be the Most Troubling Aspects of the Disease

- MS patients suffer from a plethora of comorbid symptoms that are considered by many patients to be even more disabling than symptoms directly related to nerve damage, particularly at the earlier stages of the disease.

- CNS-related symptoms such as fatigue, cognitive impairment, depression and unstable mood appear to be those causing the most day-to-day issues and with less than adequate treatment options.

http://www.news-medical.net/health/Multiple-Sclerosis-(MS).aspx
Two New Supportive MS Products Approved in 2010

- **Ampyra** (Acorda/Biogen Idec), an extended-release oral agent that blocks axonal potassium channels, was approved in Jan. 2010
  - Ampyra is indicated in the US to improve walking in patients with MS.
  - After an initial rejection early this year, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) recommended conditional marketing authorization of Ampyra (Fampyra in Europe) in May 2011.
  - Ampyra is priced at a WAC of nearly $13,000 a year and analysts predict $500-$600M in US sales by 2016. After an impressive launch, prescriptions appear to be slowing.

- **Nuedexta** (Avanir Pharmaceuticals) is approved for the treatment of pseudobulbar affect (PBA), although the label specifically includes studies that support use in amyotrophic lateral sclerosis (ALS) and MS, and states that Nuedexta has not been shown to be effective in other types of emotional lability that can occur with Alzheimer’s disease and other neuropsychiatric conditions. Analysts estimate peak WW sales of nearly $400 million.
  - Avanir recently addressed the slow script trends and managed expectations on its 2Q11 call, claiming the April shortfall has been due in part to the AAN meeting that drew a large fraction of neurologists and 10% of the Avanir sales forces to Hawaii from 4/8-4/16 and potentially impacted subsequent weeks due to physicians taking additional vacation time.
Virtually No Treatment Options are Available for Progressive MS

http://isites.harvard.edu/fs/docs/icb.topic637464.files/October22ndBIOSE108.pdf; DH analysis
Classification of MS Into Subtypes is Used Clinically to Guide Treatment and Predict Prognosis

- **Relapsing-remitting (RRMS):** Recurring attacks, neurological dysfunction, periods of recovery, and stability between episodes. ~80% of MS patients present with RRMS.

- **Secondary progressive (SPMS):** Slow neurological deterioration, typically with acute relapses in a patient who previously had relapsing-remitting disease.

- **Primary progressive (PPMS):** Gradual and nearly constant neurological degeneration from onset of symptoms affecting 10-15% of patients.

- **Progressive relapsing (PRMS):** Slow neurological deterioration from onset but with subsequent superimposed relapses. PRMS affects less than 5% of patients.

- A primary goal of therapy for RRMS is to prevent or delay progression to SPMS.
RRMS is Associated with More Inflammation, While PPMS/SPMS Involves More Neurodegeneration

- There is considerable evidence that the nature of MS changes at the point of transition to SPMS from a mainly inflammatory process to a neurodegenerative one, with a different type and pattern of inflammatory response.
- However, the relationship between inflammation, demyelination, and axonal and neuronal degeneration is complex, and the biological differences between MS subtypes are not absolutely clear.
- MRI abnormalities may be similar in RRMS, SPMS, and even PPMS (e.g. Gd-enhancing lesions and T2 abnormalities may be observed in all subtypes).
- Neurodegeneration begins early and may be evident even at the clinically isolated syndrome (CIS) stage.
Current Therapies Primarily Address the Inflammatory Component of MS

- Multiple treatments that reduce relapses, decrease MRI activity, and possibly slow progression of permanent neurological disability in patients with RRMS are now available.
  - Glatiramir acetate
  - IFNβs
  - Natalizumab
  - Fingolimod
- These drugs inhibit the formation of new inflammatory lesions, but they do not appear to stop tissue loss or promote remyelination or axonal repair.
At Some Point, MS Therapies Targeting Only Inflammation Stop Working

- Current anti-inflammatory/immunomodulatory treatments do little to prevent neurodegeneration and clinical disability in the progressive phase of MS.
- Only two drugs are FDA approved for the treatment of SPMS and no drugs are approved for PPMS.
  - Novantrone/mitoxantrone is approved for SPMS but its use is limited by the potential for cardiotoxicity.
  - Betaseron is approved for SPMS patients who are still having relapses.
- PPMS and SPMS are areas of high unmet need and untapped commercial potential, but the development risk associated with these forms of MS is extremely high, with a history of multiple compounds failing in late-stage clinical trials.
Clinical Trials of Immunomodulatory Agents in Progressive MS Have Been Disappointing So Far

<table>
<thead>
<tr>
<th>Agent</th>
<th>Subtype</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramir (PROMiSe)</td>
<td>PPMS</td>
<td>No difference in TCPD. Post hoc analysis suggests GA may have slowed progression in male patients who showed more rapid progression when untreated.</td>
</tr>
<tr>
<td>IFNβ-1a</td>
<td>PPMS</td>
<td>No effect on TCPD.</td>
</tr>
<tr>
<td>IFNβ-1a (SPECTRIMS)</td>
<td>SPMS</td>
<td>No difference in TCPD; slightly less deficit accumulation as measured by composite measure incorporating five separate clinical and MRI outcomes.</td>
</tr>
<tr>
<td>IFNβ-1b</td>
<td>PPMS</td>
<td>No effect on TCPD assessed with EDSS, but significant effect on MSFC score.</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>PPMS</td>
<td>No effect on time to sustained treatment failure using a composite measure consisting of EDSS score and nine-hole peg test.</td>
</tr>
<tr>
<td>Rituximab (OLYMPUS)</td>
<td>PPMS</td>
<td>No difference in TCPD; subgroup analysis showed that TCDP was delayed in young men and those with Gd-enhancing lesions.</td>
</tr>
<tr>
<td>Cladribine</td>
<td>PPMS/SPMS</td>
<td>No significant treatment effects in terms of changes in EDSS or SNRS.</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>SPMS</td>
<td>No effect on disease progression.</td>
</tr>
<tr>
<td>Dirucotide (MAESTRO-01)</td>
<td>SPMS</td>
<td>No effect on TCPD assessed with EDSS.</td>
</tr>
<tr>
<td>IVIG (ESIMS)</td>
<td>SPMS/PPMS</td>
<td>No effect of TCPD assessed with EDSS.</td>
</tr>
</tbody>
</table>
Mitoxantrone Slows Disease Progression in Patients with Active and Rapidly Progressive SPMS

• The safety and efficacy of NOVANTRONE in SPMS were assessed in two randomized, multicenter clinical studies.

• 188 patients were randomized to receive placebo, 5 mg/m² NOVANTRONE, or 12 mg/m² NOVANTRONE administered IV every 3 months for 2 years. High-dose methylprednisolone was administered to treat relapses.

• A multivariate analysis of five clinical variables (EDSS, Ambulation Index, number of relapses requiring treatment with steroids, months to first relapse needing treatment with steroids, and Standard Neurological Status) was used to determine efficacy.

• Mitoxantrone’s effectiveness appears to correlate with the number of relapses prior to treatment, indicating that inflammatory activity may determine treatment response.

<table>
<thead>
<tr>
<th>Table 1: Efficacy Results at Month 24: Study I</th>
<th>Treatment Groups</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end points</td>
<td>Placebo (N = 64)</td>
<td>NOVANTRONE (N = 64)</td>
</tr>
<tr>
<td>Primary multivariate analysis*</td>
<td>-</td>
<td>-12 mg/m²</td>
</tr>
<tr>
<td>Primary clinical variables analyzed:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS change** (mean)</td>
<td>0.23</td>
<td>-0.23</td>
</tr>
<tr>
<td>Ambulation Index change** (mean)</td>
<td>0.77</td>
<td>0.41</td>
</tr>
<tr>
<td>Mean number of relapses per patient requiring corticosteroid treatment (adjusted for disconitnuation)</td>
<td>1.20</td>
<td>0.73</td>
</tr>
<tr>
<td>Months to first relapse requiring corticosteroid treatment (median [1st quartile])</td>
<td>14.2 [6.7]</td>
<td>NR [6.9]</td>
</tr>
<tr>
<td>Standard Neurological Status change** (mean)</td>
<td>0.77</td>
<td>-0.38</td>
</tr>
<tr>
<td>MRI#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with new Gd-enhancing lesions</td>
<td>5/32 (16%)</td>
<td>4/37 (11%)</td>
</tr>
<tr>
<td>Change in number of T2-weighted lesions, mean (n)**</td>
<td>1.94 (32)</td>
<td>0.68 (24)</td>
</tr>
</tbody>
</table>

NR = not reached within 24 months; MRI = magnetic resonance imaging.
* Wilcoxon test.
** Month 24 value minus baseline.
† A subset of 110 patients was selected for MRI analysis.
MRI results were not available for all patients at all time points.
Axonal Degeneration is the Primary Cause of Irreversible Neurological Disability in MS

• **Primary neurodegeneration** – direct neurodegeneration resulting from primary neuronal and/or axonal mediated mechanisms of pathology.

• **Secondary neurodegeneration** – indirect neurodegeneration resulting from axonal and/or neuronal injury mediated by other pathological processes such as inflammation.

• The MS research community has not yet reached a consensus regarding the primary cause of neurodegeneration.

• Although immunomodulatory therapies may prevent neurodegeneration secondary to inflammation, available treatments are no longer effective when patients transition from RRMS to SPMS.

• Even if neurodegeneration is entirely secondary to inflammation, the immune system can only be suppressed to a certain limit before unacceptable side effects occur (i.e., Tysabri and PML).
Opportunities Beyond Inflammation: Remyelination and Neuroprotection

REMYELINATION

- Anti-LINGO-1 Antibodies
- IgM Number 22

NEUROPROTECTION

- **Na⁺ Channel Antagonists:** phenytoin, carbamazepine, lamotrigine
- **Glutamate Antagonists:** riluzole, NBQX
- **Miscellaneous Agents:** glatiramer, natalizumab, fingolimod, ibudilast, BG-12, laquinimod
Measuring the Effectiveness of Potentially Neuroprotective Treatments Requires New Methods

- Traditional imaging modalities (i.e. Gd-enhancing lesions) do not yield sufficient information regarding the structure of myelin and axons.
- Therefore, a combination of new MRI imaging modalities and biomarkers will be required to assess the neuroprotective properties of novel MS treatments.
- **Hypointense T1 weighted lesions (black holes)** – identifies areas of axonal loss.
- **Magnetization transfer imaging (MTI)** – measures structural integrity of myelin.
- **Diffusion tensor imaging (DTI)** – measures degree of diffusibility, an independent measure of structural integrity.
- **Magnetic resonance spectroscopy (MRS)** – measures the abundance of metabolites such as NAA, a marker of neuronal and axonal integrity.
- **Brain parenchymal fraction (BPF)** – measures the fraction of intracranial volume occupied by brain parenchyma, reflects the volume of intact brain.
- **CSF markers** – neurofilament light (NFL), myelin basic protein (MBP), glial fibrillar acidic protein (GFAP)

*Prog Neurobiol. 2011 Apr 16*
REMYELINATION
Myelin Increases the Speed at Which Action Potentials are Conducted and Helps to Conserve Energy

- Activation of voltage dependent Na$^+$ channels propagates the action potential along a neuronal axon.
- Voltage gated Na$^+$ channels are present only at nodes of Ranvier.
- Myelin is an electrically insulating material that forms a layer around axons called the myelin sheath.
- Myelin is produced by oligodendrocytes in the CNS and Schwann cells in the PNS.
- Action potentials “jump” from one node of Ranvier to the next.
Chronic Demyelination Contributes to Neurological Disability and Leads to Axonal Degeneration

• Consequences of demyelination:
  — Demyelination slows the conduction of action potentials and reduces structural integrity of axons.
  — Chronic demyelination leads to axonal transection which blocks the conduction of action potentials completely.
  — Demyelinated axons undergo transection and Wallerian degeneration in part due to the loss of myelin-derived trophic support.
Possible Strategies to Promote Remyelination or Prevent Demyelination

**Possible strategies to promote remyelination or prevent demyelination include:**

- Enhance the endogenous process of remyelination
- Prevent or limit damage to oligodendrocytes
- Transplant exogenous myelin forming cells (e.g. oligodendrocyte precursor cells, neural stem cells)
It May be Possible to Stimulate Endogenous Myelin Repair Mechanisms in Patients with MS

- In response to demyelination, oligodendrocyte precursor cells (OPCs) become activated and migrate to demyelinated axons where they proliferate and differentiate into oligodendrocytes with the *potential* to remyelinate damaged axons.
- Oligodendrocyte differentiation and axonal remyelination have been reported in MS and may even be extensive in a subset of patients.
- However, demyelination is irreversible in most cases of MS.
- MS lesions contain undifferentiated OPCs.
- The presence of undifferentiated OPCs in MS lesions suggests that inhibitory factors in the lesion environment prevent remyelination.

LINGO-1 is a Negative Regulator of Remyelination

- Loss of LINGO-1 function by Lingo1 gene knockout or by exposure to an anti-LINGO-1 antibody leads to functional recovery from EAE.
- This is reflected biologically through improved axonal integrity, as confirmed by magnetic resonance diffusion tensor imaging and by newly formed myelin sheaths, as determined by electron microscopy.

LINGO-1 is a Transmembrane Signal-Transducing Molecule Selectively Expressed on Oligodendrocytes and Neurons

**Biogen Idec Presentation**
BIIB 033 (Biogen Idec) – Anti-LINGO-1 Antibody

• BIIB 033 is an anti-LINGO-1 antibody which emerged from an antibody discovery collaboration between Biogen Idec and Dyax.

• Phase 1: A Randomized, Blinded, Placebo-Controlled, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of BIIB033 in Healthy Adult Volunteers (NCT01052506).
  — Healthy volunteers are receiving a single dose of placebo or BIIB 033 by IV infusion.
  — Primary endpoint is safety and tolerability as assessed by adverse event monitoring, laboratory investigations, and MRI.
  — Trial completion expected in June 2011.

• Phase 1: A Randomized, Blinded, Placebo-Controlled, Serial-Cohort, Multiple Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of BIIB033 in Subjects With MS (NCT01244139).
  — Two IV infusions of BIIB 033 administered two weeks apart in patients with MS.
  — This study aims to enroll 42 patients in the US and is expected to be completed by June 2012.
rHlgM22/Number 22 (Acorda) Promotes Myelin Repair in Several Animal Models of Demyelination

- rHlgM22/Number 22 is a recombinant human monoclonal IgM antibody which has been shown to promote myelin repair in three animal models of MS.
- rHlgM22/Number 22 was originally developed at the Mayo Clinic, but is now part of Acorda’s therapeutic antibody-based remyelination research program.
- Acorda and Mayo Clinic plan to file an IND to initiate clinical trials for the treatment of multiple sclerosis in the near future.

J Neurosci Res. 2007 Apr;85(5):967-76
NEUROPROTECTION: Na⁺ Channel Blockers
Demyelinated Axons Conduct Signals Poorly, are Prone to Injury, and Consume More Energy

- **Neurons compensate for the loss of myelin by increasing the number of Na\(^+\) channels in the axonal membrane.**
- Because of the extra Na\(^+\) channels, Na\(^+\)/K\(^+\) ATPase activity must increase to maintain the proper gradient of Na\(^+\) ions across the membrane.
- Eventually, the Na\(^+\)/K\(^+\) ATPase is unable to keep up and increased levels of cytosolic Na\(^+\) drive the Na\(^+\)/Ca\(^{2+}\) exchanger (NCX) in reverse.
Demyelinated Axons Conduct Signals Poorly and are Prone to Injury

• Under normal conditions, the NCX transports Ca\(^{2+}\) out of the cytoplasm.
• Therefore, driving the NCX in reverse results an increase in cytosolic Ca\(^{2+}\).
• Ca\(^{2+}\) overload activates Ca\(^{2+}\)-dependent enzymes that damage axons by fragmenting neurofilaments and depolymerizing microtubules.
• *Thus, decreasing Na\(^{+}\) current into axons with a Na\(^{+}\) channel blocker would be expected to protect axons from Ca\(^{2+}\)-dependent cell death.*
Phenytoin, a Na\textsuperscript{+} Channel Blocker, Protects Spinal Cord Axons in EAE Mice

- Clinical scores in phenytoin treated EAE mice at 28 days were significantly improved compared with untreated mice.
- Loss of dorsal corticospinal tract and dorsal column axons in EAE mice was significantly ameliorated by treatment with phenytoin (CST 63% vs 28%; dorsal 43% vs. 17%).
- Spinal cord compound action potentials (CAP) were significantly attenuated in untreated EAE, whereas spinal cords from phenytoin-treated EAE had robust CAPs, similar to those from phenytoin-treated control mice.
- **These results demonstrate that phenytoin has a protective effect in vivo on spinal cord axons, preventing their degeneration, maintaining their ability to conduct action potentials, and improving clinical status.**
- Similar results have been seen with flecainide and Lamotrigine in EAE rats.

*J Neurophysiol. 2003 Nov;90(5):3566-71*
Withdrawal of Phenytoin and Carbamazepine Causes Severe Exacerbations in EAE Mice

- Phenytoin was administered on day 10 after MOG injection and was withdrawn on day 28.
- Phenytoin withdrawal resulted in acute exacerbation and increased inflammatory infiltrate within the CNS.
- Death occurred in more than 50% of EAE mice following withdrawal of phenytoin.
- These adverse effects were not seen when phenytoin was given to healthy mice for a similar period and then abruptly withdrawn.
- In another study, exacerbation of EAE was seen after withdrawal of carbamazepine, although not as severe as with phenytoin.
- A clinical trial of phenytoin in PPMS patients was planned at Yale University but this trial was postponed as a precautionary measure following the release of these data.

*Ann Neurol* 62: 21–33
Lamotrigine Did Not Meet its Primary Endpoint in SPMS, but Did Reduce Rate of Decline of Timed Walk

• A Phase II, randomized, double-blind, placebo-controlled trial of lamotrigine in 120 SPMS patients:
  — Primary outcome was the effect of treatment on rate of change of cerebral volume after 24 months.
  — Lamotrigine had no significant influence on cerebral atrophy, but reduced the rate of decline of timed walk (secondary outcome).
  — 13% of the patients (11 Lamotrigine, 5 placebo) stopped treatment because of adverse effects, which were mainly deterioration of gait and ataxia.

• The jury is still out with respect to the safety and efficacy of Na+ channel blockers as neuroprotective agents in patients with MS.

NEUROPROTECTION: Glutamate Antagonists
Glutamate Causes Excitotoxic Cell Death, in Part by Opening Ca\(^{2+}\) Channels

- Glutamate homeostasis is delicately balanced in the brain, as this excitatory neurotransmitter can be toxic to both neurons and oligodendrocytes.
- Safe levels of glutamate are maintained through active reuptake by astrocytes via glutamate transporters.
- Activated microglia and macrophages secrete cytokines such as TNF\(\alpha\) which inhibit glutamate transporters thereby increasing the levels of glutamate.
- Activation of glutamate receptors (AMPA, kainate, NMDA) on neurons and oligodendrocytes causes neurotoxicity by promoting Ca\(^{2+}\) influx and activation of Ca\(^{2+}\)-dependent enzymes.
- **Maintenance of subtoxic extracellular glutamate levels or blockade of glutamate receptors may be a potential target for preventing or ameliorating neurodegeneration in MS.**
Glutamate Receptor Blockade with NBQX Attenuates EAE and Preserves Oligodendrocytes

- NBQX treated EAE mice had better clinical scores than untreated mice.
- The number of dorsal column oligodendrocytes was less in untreated EAE mice compared to NBQX treated EAE mice.
- NBQX reduced dephosphorylation of neurofilament H, an indicator of axonal damage (not shown).

Riluzole Showed a Limited Neuroprotective Effect in a Pilot Trial of 16 Patients with PPMS

- Riluzole inhibits release of glutamate from nerve terminals and modulates glutamate receptors (approved for ALS).
- Riluzole inhibits excitotoxic injury in several animal models of neurodegeneration.
- 16 patients with PPMS and EDSS scores from 3.0-7.5 were observed for 1 year without specific treatment and then treated for another year with riluzole.
- Primary outcome parameters were spinal cord atrophy and T1-hypointense brain lesions on MRI.
- Riluzole reduced the rate of cervical cord atrophy and the development of T1 hypointense lesions on MRI, but the rate of brain atrophy was only slightly decreased.
- This study had several limitations: unblinded treatment, small sample size, lack of a parallel control group.
- Memantine, an NMDA glutamate receptor antagonist, caused blurred vision, fatigue, severe headache, muscle weakness, and gait problems in a high proportion of treated subjects, but not controls, in a small randomized, placebo-controlled trial.

Table 1
Baseline data for spinal cord area, T1 and T2 lesion load and brain parenchymal fraction, and percentage change during follow-up

<table>
<thead>
<tr>
<th>MRI</th>
<th>Baseline</th>
<th>Delta year 1</th>
<th>Delta year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord area</td>
<td>66.7 (9.1)</td>
<td>−2.0%</td>
<td>−0.2%</td>
</tr>
<tr>
<td>T1 LL b</td>
<td>271 (0–7032)</td>
<td>+15%</td>
<td>+6.0%</td>
</tr>
<tr>
<td>T2 LLb</td>
<td>2160 (513–32892)</td>
<td>+7.0%</td>
<td>+10.0%</td>
</tr>
<tr>
<td>PF</td>
<td>0.82</td>
<td>−1.0%</td>
<td>−0.7%</td>
</tr>
</tbody>
</table>

a Mean, mm² (SD).
b Median, mm³ (range).

NEUROPROTECTION: Miscellaneous Agents
In a Phase 2 Trial, Ibudilast Reduced the Number of Black Holes and Preserved Brain Volume in RRMS Patients

- Ibudilast, a phosphodiesterase inhibitor, has *in vitro* neuroprotectant properties via modulating inflammatory mediators such as TNFα, leukotrienes, and nitric oxide.

- In a phase 2 trial, RRMS patients treated with ibudilast had fewer T1 black holes and less brain atrophy.

- In addition, post-hoc analysis suggested that inflammatory lesions were less likely to evolve into black holes in the ibudilast group than in the placebo group.

- Over 2 years, there were fewer patients with confirmed progression on the EDSS.

*Neurology. 2010 Mar 30;74(13):1033-40*
Glatiramer acetate (GA) is a disease-modifying therapy for RRMS with several putative mechanisms of action.

- GA promotes deviation of myelin specific Th1 to Th2 cells; this suppresses inflammation in response to myelin antigens.

- GA-reactive T cells elaborate neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin-4/5 (NT4/5).

GA has been shown to decrease the rate of axonal damage as measured by MRS determination of N-acetyl aspartate (NAA), a marker of neuroaxonal integrity.

GA also appears to reduce the probability of an inflammatory plaque evolving into a black hole.

*Neurology. 2001 Aug 28;57(4):731-3*
Natalizumab Reduces Axonal Damage in Patients with RRMS

- CSF samples from 92 patients with RRMS were collected prior to natalizumab treatment and after 6 or 12 months. Levels of neurofilament light (NFL) and glial fibrillary acidic protein (GFAP) were measured using ELISA.
- Natalizumab treatment led to a 3-fold reduction of NFL levels, but no differences in GFAP were detected.
- These data suggest that natalizumab treatment may reduce axonal injury in relapsing forms of MS.

Fingolimod May have Neuroprotective Properties in Additional to its Immunomodulatory Effects

- Fingolimod is thought to act by altering lymphocyte trafficking through the S1P receptor subtype S1P1.
- However, S1P receptors are also found in the neurons, astrocytes, and oligodendrocytes.
- In a recent study, conditional null mice lacking S1P1 in neurons or astrocytes were challenged by experimental autoimmune encephalomyelitis (EAE).
- **EAE was attenuated and fingolimod (FTY720) efficacy was lost in CNS mutants lacking S1P1 in astrocytes but not on neurons.**
- Reductions in EAE clinical scores were paralleled by reductions in demyelination, axonal loss, and astrogliosis.
- These data suggest that fingolimod may have nonimmunological CNS mechanisms and implicate S1P signaling within the CNS as targets for MS therapies.

*Proc Natl Acad Sci U S A. 2011 Jan 11;108(2):751-6*
Next Generation MS Therapies Will Likely Attempt to Position Themselves as Neuroprotective

- **BG12 (Biogen Idec)** – *in vitro* studies of oral dimethylfumarate indicate multiple potential MOAs for this compound:
  - BG-12 is able to switch the T-helper response from Th1 to Th2 phenotype.
  - BG-12 inhibits the accumulation of leukocytes at sites of inflammation.
  - BG-12 activates the Nrf2 pathway which may promote neuroprotection by reducing oxidative stress, protecting the BBB, and regulating maintenance of myelin.
  - BG-12 reduced the rate of disease progression by 38% in the phase 2 DEFINE trial.

- **Laquinimod (Teva)** – preclinical studies suggest laquinimod reduces demyelination and protects axons.
  - Laquinimod increased neurotrophins in serum of patients with RRMS.
  - Reduced inflammation, demyelination and axonal damage were observed in laquinimod treated EAE mice
  - In the phase 3 ALLEGRO trial, RRMS patients treated with laquinimod had a 36% reduction in risk of confirmed disability progression (EDSS) and a 33% reduction in progression of brain atrophy.
Neuroprotective Strategies May Be More Likely to Succeed in MS for a Number of Reasons

- MS is diagnosed early
- Patients with MS retain an innate ability to repair damage to myelin
- MS is relatively common for an orphan disease and large trials are feasible
- Potentially neuroprotective therapeutics can be “on-board” prior to relapse
- Imaging correlates of repair will soon be validated
### A Number of Agents in the Pipeline Report Effects on Remyelination

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Effect on Remyelination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>Novartis</td>
<td>M</td>
<td>S1PR modulator</td>
<td>Enhanced post-insult remyelination in EAE mice</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Biogen/Elan</td>
<td>M</td>
<td>α4 integrin</td>
<td>Promoted regeneration and stabilization of myelin sheath damage in a case-control trial</td>
</tr>
<tr>
<td>Olesoxamine</td>
<td>Trophos</td>
<td>PC</td>
<td>Cholesterol-oxime</td>
<td>Promoted oligodendrocyte maturation and myelination in several models of MS</td>
</tr>
<tr>
<td>Thymosin β-4</td>
<td>RegeneRX</td>
<td>PC</td>
<td>Peptide hormone</td>
<td>Promoted remyelination in rat model of stroke</td>
</tr>
<tr>
<td>GGF2</td>
<td>Acorda</td>
<td>PC</td>
<td>Neuregulin GF</td>
<td>Stimulated remyelination in animal models of MS</td>
</tr>
<tr>
<td>GRNOPC 1</td>
<td>Geron</td>
<td>PC</td>
<td>Stem cell therapy</td>
<td>Produces remyelination and functional recovery in animal models of spinal cord injury</td>
</tr>
<tr>
<td>COG-112</td>
<td>Cognosci</td>
<td>PC</td>
<td>ApoE mimetic peptide</td>
<td>Demonstrated remyelination-promoting effects in <em>in vitro</em> and <em>in vivo</em> preclinical models of MS</td>
</tr>
<tr>
<td>Pxt 00002</td>
<td>Pharnext</td>
<td>PC</td>
<td>Undisclosed</td>
<td>Protected against demyelination and promoted remyelination in an <em>in vitro</em> model</td>
</tr>
<tr>
<td>VX 15</td>
<td>Vaccinex</td>
<td>PC</td>
<td>Anti-Sem4D</td>
<td>May promote remyelination</td>
</tr>
<tr>
<td>AFC 5128</td>
<td>Affectis</td>
<td>PC</td>
<td>P2X7 antagonist</td>
<td>Reduces demyelination in EAE mice</td>
</tr>
<tr>
<td>Remyelination Ab program</td>
<td>Acorda Mayo Clinic</td>
<td>PC</td>
<td>IgM antibodies</td>
<td>Promotes remyelination in a mouse model of chronic progressive MS</td>
</tr>
</tbody>
</table>
## Potentially Neuroprotective Agents in the Pipeline for MS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perampanel</td>
<td>Eisai</td>
<td>P2 (EU)</td>
<td>AMPA receptor antagonist</td>
</tr>
<tr>
<td>Idebenone</td>
<td>Santhera/NINDS</td>
<td>P1/2</td>
<td>Antioxidant, mitochondrial membrane transport protein</td>
</tr>
<tr>
<td>Olesoxime</td>
<td>Trophos</td>
<td>PC</td>
<td>Cholesterol-oxime, apoptosis inhibitor, GABA A receptor modulators, MPTP modulator</td>
</tr>
<tr>
<td>RPI 78M</td>
<td>ReceptoPharm</td>
<td>P1</td>
<td>Protein; nicotinic receptor antagonist</td>
</tr>
<tr>
<td>Cenplacel-L</td>
<td>Celgene</td>
<td>P1/2</td>
<td>Stem cell therapy</td>
</tr>
<tr>
<td>UC-MSCT</td>
<td>Beike Biotechnology</td>
<td>P2</td>
<td>Stem cell therapy; umbilical cord mesenchymal stem cells</td>
</tr>
<tr>
<td>GSK 1223249</td>
<td>GSK</td>
<td>P1</td>
<td>Anti-Nogo-A Ab; Nogo-A is a neurite outgrowth inhibitor</td>
</tr>
<tr>
<td>V 85546</td>
<td>Vernalis</td>
<td>P1 (UK)</td>
<td>Matrix metalloproteinase 12 inhibitor</td>
</tr>
<tr>
<td>NTx 488</td>
<td>Stem Cell Therapeutics</td>
<td>PC</td>
<td>Prolactin plus erythropoietin; increase progenitor cells that mature into neurons and promotes remyelination</td>
</tr>
<tr>
<td>ApoE mimetic</td>
<td>Cognosci</td>
<td>PC</td>
<td>Apolipoprotein E agonist</td>
</tr>
<tr>
<td>RP: Stem cell therapy</td>
<td>Cryo-Cell International</td>
<td>PC</td>
<td>Stem cell therapy</td>
</tr>
<tr>
<td>RP: Stem cell therapy</td>
<td>Cell Cure Neurosciences</td>
<td>PC</td>
<td>Neural progenitor cells derived from human embryonic stem cells</td>
</tr>
<tr>
<td>SB 618</td>
<td>SanBio</td>
<td>PC</td>
<td>Stem cell therapy</td>
</tr>
</tbody>
</table>
...More on Select Neuroregenerative/Neuroprotective Agents

**Anti-SEMA4D Monoclonal Antibody: VX15 (Vaccinex, Inc.)**

A

**EAE scores in SJL EAE Model**

- A graph showing EAE scores in SJL EAE Model.
- SJL female mice were immunized with PLP\textsubscript{139-151} in CFA. Weekly antibody treatment at 600 µg/dose started on day 7.

B

**Average EAE Score**

- A graph showing the average EAE score.
- SJL donor mice were immunized with PLP\textsubscript{139-151}/CFA emulsion on Day 0. Ten days later, CD4\textsuperscript{+} T cells were isolated and re-stimulated in vitro for 10 days. Two million T cells were transferred into each naïve recipient SJL mouse. Starting on the day of transfer, animals were treated weekly with 600 µg/dose of antibody.

C

**Myelination Index**

- A graph showing myelination index.
- Brain slices were harvested from mouse pups and cultured in vitro. After 10 days the slices were demyelinated with lysolecithin, and then treated with recombinant SEMA4D or recombinant SEMA4D + MAb VX15 for 15 days before determining the extent of remyelination.

Semaphorin 4D (SEMA4D/CD100) is expressed at varying levels on most lymphocytes.

SEMA4D signaling through its receptor Plexin B1 (PLXNB1) has been shown to induce growth cone collapse of neurons, inhibit differentiation of oligodendrocyte precursor cells, and induce apoptosis of oligodendrocytes.

SEMA4D has also been shown to play an important role in the induction of B cell and T cell responses and in the activation of microglia.

The human VX15 antibody and its parent murine antibody neutralize the activity of rodent and human SEMA4D.

Treatment with anti-SEMA4D MAb attenuates the severity of EAE in the SJL active immunization (A) and adoptive transfer (B) EAE models, and treatment with SEMA4D inhibits remyelination in vitro (C).

Based on these observations, the neutralization of SEMA4D by VX15 monoclonal antibody could reduce the severity of demyelinating diseases through the dual mechanisms of both reducing inflammation and providing neuroprotection.

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MS Insight Briefing
...More on Select Neuroregenerative/Neuroprotective Agents

AFC-5128 (Affectis Pharmaceuticals AG)

- Brain penetrant P2X7 antagonist
- Targets activated microglia, astrocytes and oligodendrocytes
- P2X7 inhibition shown to reduce inflammation, prevent demyelination and restore normal axon conduction velocity
- Compelling preclinical data in EAE and neuropathic pain animal models
- IND filing planned 2012
rHlgM22 (Acorda Therapeutics)

- Human IgM antibodies identified by Moses Rodriguez at Mayo Clinic
- Protect oligodendrocytes and promote remyelination
- Compelling preclinical data in 3 animal models, effects include:
  - Protection of oligodendrocytes
  - Promotion of remyelination
  - Functional benefit
- Lead Selected – rHlgM22
- Exclusive worldwide license from Mayo Clinic
Histopathological Analysis: COG133 prevented spinal cord demyelination in MOG-induced EAE mice. The animals were sacrificed 30 days after MOG immunization and the whole spinal cord was dissected out and 5-m thick sections were made from cervical segments of COG133-treated animals (B) and Normal Saline treated ones (A). These sections were stained with Luxol fast blue (for myelin, stained in blue) and then counterstained with eosin (showing peripheral infiltrates, in purple).

• Small synthetic peptides of 10 to 17 amino acids that are based on the multifunctional apoE protein, and have potent in vitro and in vivo anti-inflammatory activity.
• Directly protect nerve cells by blocking activity of endogenous neurotoxins released by injured brain cells.
• Neuro-reparative activity where the compounds promote repair of damaged nerve cells to restore normal function.

Cultured primary cerebellar granular cells obtained from day 8 post-natal rat pups were pre-treated with buffer or COG133 (2.5 M) for one hour before exposure to 100 M NMDA. Cell viability was determined with an MTT assay at 24 hr. Bars represent the mean S.D. of 6 replicates of 6 and COG133 p < 0.05 compared to cells treated with NMDA.
Key Takeaways

The MS market (focused on relapsing disease) has enjoyed great success, but it is getting tougher to play.

New market entrants will compete for a piece of a very big pie.

Payers are taking notice of the high price tags, more heavily managing the category and pushing some of the cost burden down to the patients. Combination therapies are likely to be prohibitively expensive, even with the potential introduction of biosimilars.

Treatment of comorbid symptoms, particularly those CNS-related, remains an unmet need; but for many of these conditions, it is tough to compete with what is usually a generic standard of care (e.g., antidepressant). Supportive neurology may find a place in life cycle management.

Treatment for progressive MS is the greatest unmet need. Strategies aimed at stimulating remyelination of demyelinated axons (i.e. anti-LINGO-1) offer the most promise in the near term. Although Biogen Idec has a head start on the LINGO-1 approach; additional targets in this pathway may soon be discovered providing novel opportunities for intervention.
Key Takeaways

Similar to other neurodegenerative diseases (e.g., Alzheimer’s, Parkinson’s), clinical proof of concept for neuroprotective/neuroregenerative approaches requires long, expensive studies to show slowed progression of disease. In addition, there are fundamental uncertainties in trial design – such as, stage of patients to include in studies (earliest phase, progressive?) and the value of traditional endpoints (MRI lesions, EDSS score progression).

Advancement of more appropriate biomarkers and the identification of similar, but more “clinically friendly” disease states may help companies establish relevance as a neuroprotective/neurodegenerative treatment for MS at an early point in development.

For example: Transverse Myelitis (TM), a “one-time” disease that affects only the spinal cord and is similar to MS in terms of underlying mechanism. TM may be a unique model system to study novel neuroprotective and neurorestorative therapies. All injury and subsequent disability in TM can be attributed to one lesion in the spinal cord and outcomes can be more readily and rapidly measured. This approach is being investigated by the Johns Hopkins Project Restore (REcover, STOp and REgenerate).
Defined Health's Therapeutic Insight will be a featured track at these 2011 and 2012 EBD conferences: