Trends-in-Medicine

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by Lynne Peterson

SUMMARY

European neurologists viewed Biogen Idec's decision to put itself up for sale as a sign that the company's pipeline is not as robust as claimed. ♦ European use of Tysabri has just really gotten going, so the outlook is for use there to double over the next year, from ~7% of RRMS patients on therapy to about 16%, with a peak of about 25% market share by 2010. ♦ The monoclonal antibody neurologists are most excited about is Genzyme/Bayer Schering Pharma's Campath (alemtuzumab), which they expect to use ahead of Tysabri. Doctors predicted that enrollment in the Phase III alemtuzumab trials will go quickly. ♦ There wasn't the same enthusiasm for Biogen Idec's Rituxan, and a new case of PML in a Waldenstrom's disease patient on Rituxan increases the likelihood it will require a PML risk management program like Tysabri. ♦ Preliminary results of the Phase II CHOICE trial showed Biogen Idec/PDL BioPharma's daclizumab to be effective at both doses tested, with serious infections the serious adverse event to watch. ♦ Merck Serono's cladribine is the lead oral agent, but neurologists are more excited about Novartis's fingolimod (FTY-720) because it has more data, and the efficacy data look very good. The question with fingolimod is safety. ♦ With the results of the REGARD trial showing no difference between Rebif and Copaxone in a head-to-head comparison, neurologists predicted that Copaxone market share would increase, mostly at the expense of Rebif but probably affecting all interferon-βs.

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In the past year and a half there have been two big acquisitions affecting the MS drug companies. Merck KgA bought Serono, and Bayer merged with Schering AG to form Bayer Schering Pharma AG (but in the U.S. it is called Bayer HealthCare, with no mention of Schering). Bayer sources said there has been a lot of turnover as a result, with many of the Schering sales reps leaving. Merck sources said most of their Serono people stayed. However, integration appears to be going well at both companies. A Merck official said, "Integration has been a challenge for sure. I think we are focused very much on being the best pharma, not the biggest…We've done quite a nice job of integration." A Bayer source said, "Things appear to be settling down, and we have some great new people."

During ECTRIMS, neurologists learned that another of the MS drug companies may be changing. At the meeting Biogen Idec officials were emphasizing the robustness of the company's pipeline, which Dr. Alfred Sandrock, senior vice president of neurology research and development, called "the most extensive in the industry." However, later the same day, the company announced that it was considering putting itself up for sale.

Neurologists said they interpreted that as, "This is the peak, it's all downhill from here" for Biogen Idec. They described the timing as "odd," saying it sent a clear message that the competitiveness of the future Biogen Idec products is questionable.

Physician Reaction to Biogen Idec Pipeline

Drug	Status	Physician comments
BG-12	Phase III	TID dosing problematic
Rituxan	Phase II	May need RiskMap for PML
Daclizumab	Phase II	No comments
CDP-3234	Phase II	Lack of awareness
Anti-LINGO-1	Preclinical discovery	Lack of awareness

Yet, there definitely is an unmet need for new drugs in MS. It has been estimated that 62%-75% of patients on immunomodulators relapse within two years, and 20%-27% worsen on EDSS by ≥1 point within two years. Furthermore, adherence to therapy is generally poor, with 14%-20% of patients discontinuing therapy annually. Dr. Sandrock estimated that 100,000 patients worldwide have attempted therapy but quit.

The biology of MS suggests it may not be just one disease, Dr. Sandrock pointed out. He said there are two stages: Typically patients start with relapsing-remitting MS (RRMS), which is highly inflammatory, and then they progress to secondary progressive MS (SPMS) over 10-15 years, where the inflammation seems to die

Key Drugs to Treat MS: Approved (*in blue*) and Under Investigation (*in red*)

Company	Immunomodulators	Monoclonal antibodies	Oral agents	Others
Merck Serono	Rebif and **Rebif New Formulation**	**Atacicept *with ZymoGenetics***	**Cladribine**	---
Bayer Schering	Betaseron/Betaferon	**Campath (alemtuzumab) *with Genzyme***	---	---
Novartis	**NVF-233 (bioequivalent to Betaseron)**	---	**Fingolimod (FTY-720)**	---
Biogen Idec	Avonex	1. Tysabri (natalizumab), *with Elan* **2. Daclizumab (*with PDL BioPharma*)** **3. Rituxan (rituximab)** **4. Anti-LINGO-1**	**1. BG-12 (fumaric acid)** **2. CDP-3234 (*with UCB Pharma*)** **3. Simvastatin**	---
Sanofi-Aventis	Copaxone (*with Teva*)	---	**Teriflunomide**	---
Teva	Copaxone (*with Sanofi-Aventis*)	---	**Laquinimod, *with Active Biotech***	---
Other	---	---	---	**Wyeth's temsirolimus, an mTOR inhibitor**

down and neurodegeneration takes over as the driver of disability. Interferons, which can delay disease progression in RRMS, don't appear to work well in the degenerative stage.

There may even be four different types of lesions in RRMS and four types of RRMS:

1. T cells + macrophages.
2. Type 1 + Ab and complement deposition.
3. Distal oligodendrogliopathy.
4. Oligodendrocyte apoptosis.

In SPMS, there may also be two different types of SPMS. Dr. Sandrock said 52% of patients have one type of ectopic germ centers, and 48% don't have ectopic germ centers. He said, "We would like to understand more about what is the right drug for the particular patient…If we can distinguish four lesion types on biopsy, is there a way to do that less invasively – with serum markers or imaging – and tailor therapy that way? When we see types of MS that might indicate drug A or B is better, that is where we are heading as a company."

European access to and use of MS drugs is considerably lower than in the U.S. On average only 28% of European MS patients (30% in Sweden, 12% in the U.K.) have access to Biogen Idec's Avonex, Bayer Schering Pharma's Betaseron/Betaferon, Merck Serono's Rebif, or Teva Pharmaceuticals' Copaxone. The European MS Platform (EMSP), an umbrella organization of 32 national European MS societies, representing more than a half million MS patients, is working to change that. EMSP has been advocating a European Code of Good Practice.

THERAPEUTIC ORAL AGENTS

Everyone would like an oral therapy for MS, Dr. Peter Rieckmann, a neurologist from the University of British Columbia in Canada, admitted, but he warned that an oral therapy won't solve all the problems. Non-compliance is still likely to be an issue. The average rate of non-compliance across all other diseases is 43%, he pointed out. Another expert said, "All the oral therapies in late stage development are very reasonable first-line treatments. Their efficacy seems relatively similar on MRI lesions, reducing new lesions 45%-60%. Clearly, they don't have the same effect as Tysabri; none will be as effective as Tysabri, but their safety profiles look good."

Prof. Ludwig Kappos of Switzerland said therapeutic oral agents are expected to improve compliance, offer the same or higher efficacy, have a more specific mode of action, and be easier to give in combination therapy. **There has been a suggestion in cell line and animal studies that some oral agents may promote repair or regeneration**, but there is not even Phase I data to prove that yet.

Will it take much to convert the market to orals? Anthony Coombs, vice president of marketing/neurology for Merck Serono (called EMD Serono in the U.S.), said, "There are a lot of patients who are tired of injections…Some patients won't

Oral Agents With Positive Phase II Results

Company	Drug	Dosing	Rating *	Data
Biogen Idec	BG-12	TID	+	Met the primary endpoint
Merck Serono	Cladribine	QD for 2-4 weeks annually	(+)	Some reservations or doubts about the available data
Novartis	Fingolimod	QD	++	Met the clinical endpoint as well as the primary endpoint
Sanofi-Aventis	Teriflunomide	QD	+	Met the primary endpoint
Teva/ Active Biotech	Laquinimod	QD	(+)	Some reservations or doubts about the available data
Wyeth	Temsirolimus (CCI-779)	N/A	(+)	Some reservations or doubts about the available data

*** Source: Dr. Kappos' lecture**

even look at an injection (7%-8%)…And there are a lot of people, particularly younger people who are diagnosed with MS, and it hangs over them like a life sentence, and the thought of a life sentence, of injecting every day or three times a week or weekly…I think is quite a frightening thought for the patients I've talked to…To them, to say we have the option of an oral treatment, especially intermittent oral therapy, is a very good option…I imagine that oral therapies will be used as first-line options – that is where they are being trialed – and there is a very high chance of that for new patients or for patients who dropped off therapy and want to come back to an oral…As more drugs become available, we will see more combinations, different sequencing, different therapeutic combinations…with patients not doing well on interferon-beta adding on to those...and there will be some switches as well…But I think it will take some time before patients switch who are doing well on interferons."

BIOGEN IDEC:

1. BG-00012 (BG-12), a second generation fumaric acid

There were no new data at ECTRIMS on BG-12, which is approved in Germany for the treatment of psoriasis. In MS it may have both anti-inflammatory and neuroprotective effects. A Biogen Idec official said an enteric coating was added which improved GI tolerance.

A Phase II study of three doses (120 mg QD, 120 mg TID, 240 mg TID) met the primary endpoint at the highest dose, with a 69% reduction in Gd+ lesions, a 48% reduction in new/enlarging T2 lesions, and a 53% reduction in new T1 lesions. Infections were infrequent and no different from placebo.

Two Phase III trials – DEFINE and CONFIRM – began enrolling patients earlier this year. Both are two-year, international, multicenter, randomized, placebo-controlled trials with a total of >2,000 RRMS patients, looking at two doses of BG-12 compared to both placebo and Copaxone.

BG-12 Phase III Trials

Measurement	DEFINE	CONFIRM
Arms	BG-12 240 mg TID BG-12 240 mg BID Placebo	BG-12 240 mg TID BG-12 240 mg BID Placebo Copaxone 20 mg QD
Blinding	Double-blind	Rater-blinded for all groups and double-blind only for BG-12 and placebo
Number of patients	1,000 in 26 countries	1,200 in 23 countries
Open-label rescue option	Yes	Yes
MRI scans	500 patients	450 patients
Primary endpoint	Proportion of patient relapses at 2 years	Rate of clinical relapse at 2 years

2. CDP-3234, a small molecule with the same target as Tysabri – alpha-4-integrin

There were no new data at ECTRIMS on CDP-3234. It is being developed in partnership with UCB Pharma, which initiated a Phase II trial in RRMS in 2Q07. Three Phase I trials were completed in 75 healthy volunteers, which found preliminary safety and tolerability up to 1000 mg BID when given for seven consecutive days. Dr. Sandrock said, "Continued blockage of peripheral leukocytes can be maintained with twice-a-day dosing. The short half-life increases the potential for initial indications. When you stop it, it clears quickly (out of a patient's system)."

3. Simvastatin

An investigator-led pilot trial was conducted in the Nordic countries, sponsored by Biogen Idec. It tested 80 mg/day and found a 44% reduction in Gd+ lesions and a 41% reduction in volume of Gd+ lesions. Now, the SIMCOMBIN trial is underway. This is a multicenter, randomized, 12-month, double-blind, placebo-controlled, parallel group study of simvastatin as add-on therapy to Avonex. As of October 1, 2007, 180 patients had been enrolled, with 124 of these randomized. The last patient is expected to be enrolled in November 2008, with the end of the study November 2009.

Safety is a concern because a double-blind trial of Pfizer's Lipitor (atorvastatin) at 40 mg or 80 mg added to interferon-beta-1a therapy in 24 patients found new and enhancing MRI lesions in 9 statin patients but only 1 placebo patient. Therefore, an interim safety analysis of the SIMCOMBIN trial was done on 61 randomized patients. More than 90-day follow-up was available on 22 patients in one still-blinded arm and 25 in the other still-blinded arm. As of May 2007, the annualized relapse rate was 0.37 for all patients, and in October 2007, it was 0.31, with no statistically significant difference between the treatment groups. A speaker concluded, "There was no support of a weakened interferon-beta effect in either treatment group in the SIMCOMBIN study…By MRI, there was no difference in Gd+ lesions between the two arms, new T2 lesions showed no difference between the treatment groups ($p=0.76$), and by real-time PCR, all patients showed a full response in mRNA, MxA, and TRAIL, indicating that IFN-β bioactivity was preserved…the DSMB (data safety monitoring board) concluded that it sees no safety concern regarding the continuation of the trial."

MERCK SERONO'S cladribine, a purine analog

Cladribine is approved in many countries to treat hairy cell leukemia and chronic lymphocytic leukemia (CLL). The key potential advantage of this drug is the need for only intermittent therapy – just a few days once a year. It causes preferential and long lasting reduction of lymphocytes in the periphery and in the central nervous system (CNS).

In the SCRIPPS-C trial in RRMS, it led to a 51% reduction in relapse rates from Months 7-18 and a 2% reduction in relapses from Months 1-18. Dr. Thomas Leist of Thomas Jefferson University in Philadelphia said, "This was the first indication of a clinical benefit in the outcomes we are interested in besides imaging."

Two key trials are ongoing, but the company intends to submit cladribine to the FDA based on only one Phase III trial. Merck Serono's Coombs said, "We talked to the FDA and the EMEA (European Medicines Agency), and there is one Phase III study. There is very strong supportive evidence from three Phase II studies with the IV formulation. Those Phase II studies were done in different patient populations (one RRMS and two mixed)…All three studies (~150 patients total) looked at different dose levels, so it is unfair to say there was no dose finding study."

The ongoing trials include:

- **CLARITY.** Recruitment is finished for this 2-year, prospective, global, randomized, double-blind, 3-arm Phase III trial in 1,322 RRMS patients, and the study is likely to finish in 2009. There is no planned interim analysis, but the FDA granted it fast track status, which generally means a six-month approval process. The trial is comparing two different doses of cladribine (0.7 mg/kg and 1.4 mg/kg) vs. placebo. The primary efficacy endpoint is the release rate at Week 96. Coombs said, "Every time the DSMB met, the drug came through quite nicely…The safety profile from the trial is looking quite good…And there is more than 15 years of experience in oncology… We know very well what the safety profile is, and that breadth of knowledge with FTY-720 is not quite there yet."
- **ONWARD.** This is a Phase IIb safety and efficacy trial in the U.S. and Spain, looking at cladribine as add-on therapy to Rebif New Formulation in patients with breakthrough disease. Dr. Leist explained the rationale for the add-on approach, "MS is a multifactorial disease. The addition of an agent that controls T-cell populations may give synergistic benefits to interferon." ONWARD is a 2-year, randomized, double-blind, placebo-controlled, 3-arm, multicenter trial in 260 patients. The primary safety endpoints include Grade 3/4 toxicity on selected hematologic and liver function parameters and on drug-related and opportunistic infections; the primary efficacy endpoint is the mean change in new T1 Gd+ lesions per patient per scan from baseline to 96 weeks.

Dr. Leist said thought is also being given to studying cladribine's effect on regulatory T-cell populations that may have different sensitivity to it to "better understand the overall regulatory cascade in patients."

Asked why there appears to be more excitement about FTY-720 than cladribine, Coombs said, "There is more published about FTY-720, and so there is more noise. It is hard to make noise without publications, but the awareness is pretty even." Dr. Mark Freedman of the University of Ottawa, Canada, called cladribine "truly a promising compound."

A combined analysis of five MS trials totaling 78 patients getting cladribine subcutaneous or intravenously was presented at ECTRIMS. The researchers reported that:

- Repeated periods of cladribine therapy were generally well tolerated.
- Dosing 10-20 days per year appear supported.
- Injection site reactions were common (26% with first round of therapy and 40% with the second round).

Pooled Safety Analysis of Cladribine

Adverse event	Treatment period 1	Treatment period 2
Neurologic and neurologic-related	74%	45%
Infection-related	69%	45%
Application site	54%	46%
Peripheral nervous system	24%	17%
Neoplasia	8%	5%
Hepatobiliary system	5%	4%

Another pooled safety analysis, this time of four randomized, double-blind trials totaling 268 patients, was reported at ECTRIMS, and that study also found cladribine was generally well tolerated. Only 2% of cladribine patients discontinued therapy because of adverse events vs. none on placebo. The study found:

- Serious adverse events occurred more frequently in patients getting 2.8 mg/kg cladribine than with lower doses (0.7-2.1 mg/kg) or placebo.
- The most common treatment-emergent adverse events with cladribine *and* with placebo were upper respiratory tract infections, headache, and injection-site reactions.
- Hypertonia, purpura, muscle weakness, and upper respiratory tract infections were more common in cladribine-treated patients.
- A dose-related increase in infections was observed with cladribine, but most infections were mild or moderate and resolved with appropriate therapy.
- Administration of cladribine was associated with a pronounced and sustained dose-dependent reduction in mean lymphocyte count, which remained suppressed at the end of the double-blind treatment phase.
- Mean hemoglobin, neutrophil, and platelet counts declined dose-dependently with cladribine, but counts generally recovered by Month 12.

NOVARTIS'S fingolimod (FTY-720), a sphingosine 1-phosphate (S1P) receptor modulator

Last year, Novartis speakers were encouraging the use of the generic name of this drug. This year, without explanation, everyone was calling it FTY-720 again, though fingolimod was usually at least mentioned or listed on a slide.

The new data at ECTRIMS on FTY-720 came from some posters on preclinical experiments outlining the direct CNS effects of the drug – suggesting a direct beneficial effect on the brain, reducing neurodegeneration and enhancing repair of the CNS. This mechanism of action may be in addition to the established anti-inflammatory role of FTY-720 that is mediated by the reduction of lymphocytes. Dr. Chris Polman of the Netherlands said, "If this turns out to be clinically relevant, it could mean that FTY-720 has a direct impact on the CNS and could have an impact on slowing progression."

In an EAE (experimental autoimmune encephalomyelitis) rat model, the administration of FTY-720 directly into the CNS results in a statistically significant reduction in disease severity, and this was seen in the absence of a reduction of lymphocytes in the blood stream, which researchers said suggested that there is a direct and favorable effect in the CNS independent of the effects on peripheral lymphocytes.

Dr. Polman said there are now three possible mechanisms of action of FTY-720:

1. Reduced CNS inflammation.
2. Protection of neuronal function. FTY-720 might have a direct effect on oligodendrocytes (promoting survival) and on neuronal cells.
3. Reduced demyelination.

In addition, two posters were presented on the validation of patient-reported outcome tools that Novartis is using in the FTY-720 Phase III trial, one a measure of fatigue and the other the PRIMUS scale on overall health.

FTY-720 is currently being investigated in Phase III trials encompassing >3,800 patients, and the company plans to file it with regulators in 2H09. Ongoing or planned trials include:

- **FREEDOMS**, a 24-month, randomized, double-blind, placebo-controlled trial of >2,000 RRMS patients in Europe, Canada, Israel, Russia, and South Africa of 0.5 mg and 1.25 mg FTY-720. The primary endpoint is reduction in annualized relapse rate. Enrollment is complete.
- **TRANSFORMS**, an international 12-month, randomized, double-dummy trial of fingolimod (0.5 mg and 1.25 mg) vs. Avonex. Enrollment is complete. The primary endpoint is a reduction in relapse rates at 12 months.
- **FREEDOMS-II.** This U.S.-only trial is still ongoing, with enrollment described as "on-track." It is a 24-month, randomized, double-blind, placebo-controlled trial of >2,000 RRMS patients, testing 0.5 mg and 1.25 mg fingolimod. The primary endpoint is reduction in annualized relapse rate. There are more frequent assessments in certain subgroups to characterize the effects of fingolimod on the CV system, lungs, and eyes. Enrollment is expected to be completed in mid-July 2008.
- **Study 12091 in Japan.** This is an MRI study in RRMS patients of FTY-720 vs. placebo.
- **A primary progressive MS (PPMS) study** is expected to start in 2008. This is supposed to include several hundred patients and run at least 3 years. The protocol was still under discussion. A speaker said, "PPMS has no treatment, and every attempt to demonstrate a positive effect is welcome…But FTY-720 is very lipophilic and accumulates in the brain, so it could have some effect in the microglia which seem to have some role in PPMS." Another speaker said, "I think there is a strong biological rationale for how FTY-720 might work centrally, but we will only really know after it is given to patients. Some of the animal data is compelling, but the first direct test will be the PPMS trial. If FTY-720 works very well in that trial, that will help answer the question. Otherwise, we will have to do special imaging later on."

While FTY-720 has shown very good efficacy in Phase II, several safety issues have come up, and the FDA has mandated extensive patient testing, including Holter monitoring on at least 300 patients, echocardiography in 150 patients, blood pressure measurements at all visits, spirometry and diffusion capacity testing in all patients, and high resolution CT scans of the chest to confirm a lack of structural changes, etc. Investigators and company officials insist that none is serious enough to derail FTY-720, but all bear watching, and one speaker pointed out that there have been "very few" dropouts in the Phase II trials. The new information that came out at ECTRIMS was about blood pressure, bradycardia, and macular edema.

- **Bradycardia.** At ECTRIMS last year, this was described as only an initial, transient decrease in heart rate. Now, it is being called bradycardia. A speaker said this decreased heart rate occurs with the first dose, and he called it a reason to monitor patients carefully, but he said it "didn't result in real issues in Phase II." Within four hours of treatment, heart rate is reduced by a mean of 13.8 bpm with 1.25 mg and reduced by a mean of 16.6 bpm at 5.0 mg, but with continued treatment the heart rate returns to normal within a few days. An investigator said, "There is an immediate decrease in heart rate of up to 20 bpm that recovers in a week. It also happens with the second dose." A Novartis official said, "There may be issues with some individuals, but generally we have not seen anything that causes alarm."
- **Macular edema.** This was noticed in transplant patients, but at ECTRIMS last year, officials and investigators insisted there haven't been any confirmed cases in MS patients. However, **the news at this year's meeting was that macular edema has been reported in the ongoing**

Phase III trials. Because those trials are still blinded, it is not known whether the macular edema occurred in a drug arm or in the placebo patients.

- **Blood pressure.** Last year, this was referred to as an initial increase in blood pressure, with no further elevation of blood pressure with continued treatment beyond the effect seen at six months. However, it is now clear that the blood pressure elevation occurs quickly and remains elevated; it is not transient. Dr. Kappos said the increase is in the 3-5 mmHg range. Reportedly, <5% of FTY-720 patients in Phase II had a blood pressure increase vs. 1% of placebo patients.
- **FEV_1.** There is an initial dose-dependent decrease in expiratory air flow. A Novartis official said, "My expectation is that this is not that big a deal." Dr. Kappos said, "There is a potential effect on lung function, but you don't see it going up over time, but is it potentially reversible?...There was a slight increase in resistance and smooth muscle cells in the respiratory system. This effect was very minor and did not increase over time, especially in Phase II where we followed them >2 years…If the patient didn't have any additional factors, like asthma, they didn't have an impact on well-being or function. It has no impact on longer-term treatment, according to the evidence we now have available."
- **Liver enzymes.** Clinically asymptomatic increases in liver enzymes (ALT) have been reported.
- **Headache.** This was described as "not too worrisome to patients."
- **Infections.** There have been two reported serious infections – one case of facial herpes zoster at the 5.0 mg dose and one enterocolitis at the 1.25 mg dose. A speaker said that the reason the infection rate has not been problematic with FTY-720 may be due to its preservation of memory effector T cells.
- **Upper respiratory tract infections** (mainly nasopharyngitis). A Novartis official said, "There is the equivalent of a runny nose or the feeling of a slight scratchy throat, but not the flu-like symptoms of the interferons."
- **Dyspnea.**
- **Diarrhea.**
- **Nausea.**
- **Teratogenicity.**

Although FTY-720 is a little behind Merck Serono's cladribine in development, FTY-720 is the oral drug about which European neurologists are most optimistic. A Canadian doctor said, "FTY-720 is the most promising. It has more Phase II studies, and it seems more effective than the others. I'd be surprised if cladribine is effective." A German doctor said, "There are some signs of serious side effects, but it seems to be one of the most interesting oral agents because the annualized relapse rate in the proof-of-concept trial was terrifically done and seems stronger than the others. The cladribine data are too early."

Novartis has other S1P modulators under investigation, according to Dr. Shreeram Aradhye, Novartis's senior global medical director for clinical development and medical affairs - neuroscience. But he said these are "all truly still on the bench."

Will Novartis test FTY-720 in other diseases? Dr. Aradhye said, "We have thought about it…Indeed, it is possible FTY-720 might hold promise in other disorders, but our current focus is in successfully executing FTY-720 in MS...but we have not ruled out that, as time goes on, we will look at other areas."

Asked how FTY-720 might be used in combination with other therapies when it is approved, Dr. Fred Lublin of Mt. Sinai School of Medicine in New York said, "We think combination therapy is an attractive strategy, but it is a little bit complicated…and there are also potential toxicities…If this gets through Phase III, it will be as a single agent."

Asked how FTY-720 compares to other therapies in terms of efficacy, a speaker said, "the first impression is that it certainly is not worse than existing drugs…It has a different impact on the immune system, and maybe some direct CNS effects…So, qualitatively, this compound is more different from than similar to other agents."

Will patients experience rebound if FTY-720 is stopped? Dr. Kappos said, "Up to now, we have not seen that. There is no rebound effect after stopping. We have seen resumption of activity but not rebound."

SANOFI-AVENTIS teriflunomide

There was no news on this, the active metabolite of Sanofi-Aventis's Arava (leflunomide) which is used to treat rheumatoid arthritis (RA). Last year, a Phase II trial in both RRMS and SPMS patients with relapses, evaluating two doses (7 mg and 14 mg) vs. placebo, found teriflunomide nearly immediately suppressed significant inflammatory activity. After six weeks, patients had a statistically significant reduction in Gd+ lesions and T2 lesions, and that effect was sustained for more than 6 months. However, clinical outcomes were not as positive. At the higher dose, there was a reduction in EDSS progression, but this was not a pre-specified endpoint. Serious adverse events included pleural involvement, vasculitis, hepatotoxicity (also a problem with Arava), and possibly pancreatitis. It also is contraindicated in women of child-bearing potential and men who wish to father a child.

A two-year, randomized, double-blind, Phase III trial is underway testing both the 7 mg and 14 mg doses vs. placebo in 1,080 RRMS patients. It is expected to be completed in late 2009 or early 2010. In a talk on late-stage development of

oral therapies, Dr. Patrick Vermersch of France said enrollment has been a little slow and is not yet complete.

A Phase III trial is also planned in combination with Copaxone.

TEVA/ACTIVE BIOTECH'S laquinimod

There was no news at ECTRIMS about laquinimod, a derivate of linimone (which was developed as an anti-angiogenic agent for oncologic use but was associated with cardiotoxicity). A speaker said, "It is not clear how it acts. There is a lack of immunosuppression. Most probably there is a synergistic effect with interferon-beta. A study presented at the American Academy of Neurology (2007) showed a 40% reduction in Gd+ lesions in the last trimester of the study and a reduction in relapses that did not reach statistical significance. Only the 0.6 mg dose was effective; the 0.3 mg dose did not differ from placebo." A Phase II trial is now underway.

WYETH'S temsirolimus, an mTOR inhibitor

A Phase II trial compared three doses of temsirolimus (2 mg, 4 mg, and 8 mg) to placebo. The two lowest doses proved worse than placebo, but the high dose showed a statistically significant 48% reduction in new Gd+ lesions. At the high dose, there was also an effect on the number of relapses per patient, and atrophy reportedly did not seem to progress.

Other agents under investigation

➢ **Fluoxetine, an SSRI.** This was shown to reduce inflammatory activity in EAE, an animal model of MS, and psychiatrists have offered anecdotal reports of reduced MS activity in patients taking fluoxetine for depression. Dutch investigators decided to test it in a randomized, double-blind, placebo-controlled study in 40 RRMS/SPMS patients. The study found a 64% reduction in the primary endpoint of the cumulative number of new Gd+ lesions, but this was not statistically significant (p=0.15). The principal investigator, Dr. J. P. Mostert of the Netherlands, said further studies seem justified, but doctors in the audience were dubious about the outlook for this agent.

➢ **Cannabis extracts.** There have been conflicting results over the years, but mainly there was a trend to efficacy in pain and also perhaps in spasticity.

➢ **Memantine.** A 52-week, multicenter, placebo-controlled, double-blind trial of 20 mg/day was conducted in France. A speaker said it is "a good candidate to improve cognitive functions, and it may be a neuroprotective."

MONOCLONAL ANTIBODIES (Mabs)

The issue with monoclonal antibodies does not appear to be efficacy; it is safety. The three cases of progressive multifocal leukoencephalopathy (PML) with Biogen Idec/Elan's Tysabri (natalizumab) and the six cases of idiopathic thrombocytopenic purpura (ITP) – including one death – with Genzyme/Bayer Schering Pharma's Campath (alemtuzumab) have sensitized neurologists to safety concerns, and all of the new monoclonal antibodies in development are likely to require some form of risk management program. However, doctors are excited about them, and they are likely to find significant use. Dr. Robert Fox of the Cleveland Clinic said, "Safety will drive the choice. The efficacy is all in the same ballpark."

Monoclonal Antibodies in Late State Development to Treat MS

Company	Drug	Infusions per year
Biogen Idec/Elan	Tysabri (natalizumab)	4 times
Biogen Idec	Rituxan (rituximab)	13 times
Genzyme/Bayer Schering Pharma	Campath (alemtuzumab)	once

If Tysabri, Campath, Rituxan, and daclizumab were all approved today, doctors said they most likely would use Campath first. Tysabri has the advantage of being the agent with the most data and "the devil we know," but doctors were very impressed with the efficacy of Campath, and preliminarily the safety issues appear more manageable than Tysabri. Campath is the monoclonal antibody they believe has the most promise and the one they are most excited about. But there are numerous questions that still need to be answered about all monoclonal antibodies – and which the pivotal studies for these agents will not clarify – such as:

- If a patient fails on one, can you give another? For example, can you give Tysabri after Campath and vice versa? If so, in what order should they be given and how long do you have to wait between them?
- How long can you safely give any of the monoclonal antibodies?
- Can monoclonal antibodies be given before, after, or in combination with immunomodulators?
- How does efficacy compare among the monoclonal antibodies? While there definitely won't be any head-to-head comparisons before approval, can head-to-head studies even be done after at least two are on the market?

BIOGEN IDEC/ELAN:

1. Tysabri (natalizumab)

Use of Tysabri is expected to continue to ramp up steadily as doctors get more comfortable with the safety and with the risk management plan – and as European reimbursement improves, provided there are no new cases of PML. Neurologists from 14 European countries were asked about the outlook for

Tysabri, and, on average, they said they are currently using it for 7% of their MS patients, but they expect that to more than double to an average of 16% of patients over the next year. They also predicted that use would peak at about 25% market share in three or four years because new oral agents and new monoclonal antibodies are expected to be approved by then. Comments included:

- *Italy:* "I just put my first patient on Tysabri. I'm still very concerned about safety, but my use will go up."
- *Canada #1:* "I don't have any patients on Tysabri yet, but most of us (in my group) are thinking of starting it…If Tysabri proves safe, use of most other drugs will go down."
- *Belgium:* "Tysabri is approved in Belgium, but it is not yet reimbursed, so it is not used yet – but it should be reimbursed soon, and then I'll use it."
- *U.K.:* "I have two patients on Tysabri."
- *Canada #2:* "The biggest decision for us is to do the first Tysabri patient. Once that happens, use will increase significantly."
- *Germany:* "Tysabri use is steadily increasing even though our institution has added additional criteria (e.g., EDSS progression) that have to be met. Now, I prefer Tysabri where in the past I might have used Novantrone (EMD Serono, mitoxantrone)."
- *Austria:* "We have strict criteria for use of Tysabri, and we have to prove the patients qualify. The authorities even look into our medical charts…The biggest challenge to the monoclonal antibodies are the oral drugs. FTY-720 looks very promising."
- *Czech Republic:* "Tysabri is used only in studies because there isn't full reimbursement yet. Reimbursement will come through or we'll ask patients to be active. But when an oral agent is available, it will stop the growth of Tysabri."

Just before ECTRIMS, Biogen Idec announced that as of September 2007, ~17,000 patients were taking Tysabri, and no new ***confirmed*** cases of PML have been seen. Dr. Sandrock would not say whether any unconfirmed cases are being investigated.

- ~10,500 patients are on Tysabri in the U.S., and >2,100 doctors have prescribed it.
- ~5,500 patients are on Tysabri in Europe.
- Another ~1,000 patients are in global clinical trials of Tysabri.

The emphasis at ECTRIMS was on the quality of life impact of Tysabri. Dr. Sandrock said, "This is the first disease modifying therapy to actually show an impact on quality of life – on SF-36 PCS and MCS (the physical and mental components) over two years…Placebo patients worsened on both measures, and Tysabri patients improved. Patients will tell you they actually feel better on this drug…and we were able to measure this."

PML. Monitoring MS patients for JC virus (JCV) in their serum has so far proven neither predictive nor diagnostic. Dr. Eugene Major of the National Institutes of Health (NIH), a PML expert, made several points:

- "There is a point I want to make very clearly: We have never found JCV in CSF (cerebrospinal fluid) of non-PML patients. Reports in the literature indicating JCV present commonly or in a low percentage of individuals without PML – we have not seen this. The presence of JCV in a person with clinical signs of PML and neurological evidence of demyelination caused by this virus is a laboratory-confirmatory diagnosis."
- "There is no presence of JCV DNA in the plasma of non-PML patients…Antibodies to JCV are neither diagnostic nor prognostic."
- "Antibody titers do not correlate with disease or disease progression and are not a measurement of exposure/ongoing infection."
- "JCV DNA in the CSF is both diagnostic and prognostic."
- "About 2% of the population is viremic, and some individuals are persistently viremic. This is a new observation for us. That is, over many weeks, months, or even longer, some individuals will shed JCV into plasma."
- "JCV reactivation/viremia is a side effect with immunomodulatory therapies for autoimmune diseases – MS, Crohn's disease, rheumatoid arthritis, lupus."
- "The incidence of PML 'appears' to be increasing."
- "If 70% of the population is exposed to the JC virus, some will develop sites of latency – in the kidney or lymphoid tissues. There may be a subset of patients where a functional latency develops in lymphoid tissue. It could be at this site that immunomodulatory drugs are active and mobilize latent cells."
- "It isn't known whether all forms of the JCV are likely to produce PML…There isn't a unique neurotrophic strain of this disease. JCV is neurotrophic. No one has really identified a neurotrophic type of this virus."
- "It is my opinion that this virus gets from the blood to the brain. Being in blood is not a good thing. On the other hand, JCV, probably along with other ubiquitously spread human viruses, is in the human peripheral circulation at any time…I think we need to evaluate more patients and samples."

Dr. Dusan Stefoski of Rush University in Chicago said his MS center has ~3,000 patients, and 250 of these are now on Tysabri, and the 2,000th infusion has been given. Asked where he uses Tysabri in his practice, he said, "I use it quite a bit, and the numbers are going up. I'm less and less tolerant of

any disease progression, even if it is relatively trivial. My take is: No CNS inflammation is good for MS patients. And what looks good to me numerically and statistically is Tysabri." A researcher from the University of Pennsylvania said, "I don't doubt over time we will shift (to early treatment). If the safety profile is as good as it looks at the present time, I would."

Getting Tysabri out of the bloodstream. Dr. Fox said data are emerging that suggest that plasmapheresis can be used to accelerate the washout of Tysabri from a patient's blood-stream, "So, I'm more comfortable that PML may be a treatable complication." The PLEX study, of which Dr. Fox was an investigator, was presented at ECTRIMS, and it found that plasma exchange effectively accelerated the normal decline of serum Tysabri concentration over time in all patients. Two schedules were tested, and the most effective schedule was Monday-Thursday-Monday exchanges. On this schedule, two weeks after the third plasma exchange the Tysabri concentration was reduced by 97%. The Monday-Wednesday-Friday schedule also was effective, just not as effective as the Monday-Thursday-Monday schedule.

PLEX was a small (12-patient), open-label, single-arm, 2-center, pilot study in RRMS. Adverse events (most commonly hypotension) were generally mild or moderate and did not affect participation in the study. One serious adverse event required hospitalization for observation, but the patient recovered with hydration and continued in the study without further events. All patients re-started Tysabri after plasma exchange without complications.

Rebound. Yet, some questions remain beside PML. A study by Dutch researchers, published in September 2007 in ***Neurology***, the medical journal of the American Academy of Neurology, found that MS patients who stop taking Tysabri may experience a rebound (an increase in disease activity more than baseline). The study involved 21 MS patients who had MRI scans of their brains taken before starting Tysabri and again an average of 15 months after receiving the last infusion of the drug. The patients were divided into two groups: (1) those who took Tysabri for an average of three years and (2) those who took it for an average of two months. Patients developed more than three times as many brain lesions in the 15-month period after discontinuing Tysabri than they had developed before they started taking it. The results were most pronounced for those who took Tysabri for only a short time – a five-fold increase in brain lesions after stopping Tysabri than before they started it.

Dr. Machteld Vellinga of VU University Medical Center in the Netherlands, the study author, said it is not clear why discontinuing Tysabri would lead to increased disease activity, but an earlier animal study showed a similar result when rats with an animal model of multiple sclerosis were given a drug that suppresses the immune system. He explained, "All of our patients had an MRI shortly after the drug was suspended (in 2005), and our neuroradiologist noticed that in some patients a considerable number of new lesions developed on their MRIs in the following year. We decided to do a formal analysis to see if this was actually the case."

Another expert said the rebound is entirely driven by a subset of patients who got a median of two Tysabri infusions (range 1-8). Thus, the study might suggest that if a patient is going to take Tysabri, the patient should commit to more than eight infusions. However, he pointed out that other studies have not confirmed this finding. A study published recently found a return of disease activity but not overshoot in Tysabri patients (on the drug >6 months) who become antibody positive, which is a functional way of stopping Tysabri.

Biogen Idec's Dr. Sandrock dismissed the idea of any rebound (disease return greater than baseline) after discontinuation of Tysabri and criticized the Dutch study as too small: "We studied rebound. Every single patient in our trials was abruptly stopped because we had to withdraw it…We did scans and followed those patients, and we saw no evidence – we saw no overshoot – beyond patients on placebo…Our data are in thousands of patients, and it is pretty clear that we don't have rebound…We are puzzled by this recent paper. They suggested short-term treatment may cause rebound, but we looked at that and don't see it…You have to be careful looking at small patient samples."

Other Tysabri data:

- **Infusion reactions.** German researchers presented a 40-patient study which found that 10% of their Tysabri patients had significant and delayed infusion reactions, clinically resembling a serum sickness (Type III) reaction characterized by symptoms such as fever, headaches, arthalgia, edema, and lymphadenopathia, progressive over several days, which had not previously been described with Tysabri-treated patients. The symptoms in Nab+ and Nab− patients were clinically indistinguishable.

- **Safety.** Updated data from the TOUCH and TYGRIS trials were presented at ECTRIMS. Researchers reported that as of August 23, 2007:
  - TOUCH, the mandatory risk management program, included 319 patients who had received Tysabri for >12 months. Patients received a median of 6 infusions. Serious hypersensitivity reactions were 0.64%, with the majority occurring at the second infusion. Serious cases of herpes infections have been reported at an expected level.
  - In TYGRIS, a voluntary global observational study, 654 patients have been enrolled (and 572 infused): 414 from Germany, 137 U.S., 36 Austria, 40 the Netherlands, 23 Denmark, 2 Canada, and 2 Ireland. Six patients have discontinued treatment but remain in the study, and 10 patients withdrew from the study.
  - 24 pregnancies have been reported in the U.S. and Austria, and 21 of these are still ongoing. Of the other three, one was a live birth, one a spontaneous abortion, and one an elective termination.

- In a study of patients and subgroups from the AFFIRM trial using the MSSS (MS Severity Scale), researchers reported that Tysabri effectively reduced disease severity using this scale, regardless of baseline disease activity. Tysabri had a significant treatment effect in both the highly active and non-highly active subgroups. This is the first reported use of the MSSS to demonstrate therapeutic efficacy in RRMS patients.

➢ **Re-dosing.** Preliminary results from the STRATA study indicated that the risk of hypersensitivity reactions and immunogenicity with re-dosing of Tysabri is low and consistent with that seen in the Phase III trials. However, the impact of dose interruption on hypersensitivity in Nab+ patients remains unknown because these patients were excluded from STRATA. STRATA also found higher rates of injection site reactions and hypersensitivity reactions, and antibody formation was more common in patients with only 1 or 2 prior Tysabri infusions and was not observed in patients with longer courses of therapy prior to the dose interruption or those with brief treatment gaps. Researchers speculated that 1 or 2 doses are associated with eliciting a strong immune response to Tysabri while ≥3 doses result in some degree of immunogenic tolerance to Tysabri.

2. Rituxan (rituximab), a humanized anti-CD20

Case reports have hinted about the efficacy of IV Rituxan in MS, and some neurologists are already using it off-label in very select cases. In a Phase II trial presented at the American Academy of Neurology meeting earlier this year, Gd+ lesions were reduced 91% at 12 weeks. A Phase II/III study in PPMS is ongoing, with enrollment completed and data expected in 1H08. Biogen's Dr. Sandrock said additional RRMS trials are planned to start in 2008.

French researchers reported on what they said was the first case of PML with Rituxan in a 70-year-old woman treated for Waldenstrom's disease. This makes a fourth case of PML with Rituxan (previously 2 cases in SLE and 1 in vasculitis have been reported). The researcher concluded: MS patients on Rituxan should be monitored just like Tysabri patients for the risk of PML.

3. Anti-LINGO-1

This IV infusion is still in preclinical development, but the company plans to file an IND in 2H08 or early 2009. Dr. Sandrock said, "We think the MS lesion fails to re-myelinate not because of the absence of precursor cells but because they fail to differentiate. LINGO promotes OPC differentiation *in vitro* – and quickly. This is a very rapidly acting antibody… Anti-LINGO may allow for precursor cells naturally in the brain to complete their job and re-myelinate nerve fibers."

GENZYME/BAYER SCHERING PHARMA'S alemtuzumab, an anti-CD52

Neurologists are excited about alemtuzumab. They said the efficacy looks very good, perhaps better than Tysabri. Safety remains a concern, but several doctors pointed out that ITP is manageable, and PML is not. Comments included:

- *Canada:* "Very preliminary results say Campath is even more effective (than Tysabri), so I would choose that."
- *U.S.:* "Campath would be used before Tysabri. Campath failures should go in a trial (of another investigational agent)."
- *Czech Republic:* "For patients not doing well on Avonex, Betaseron, Rebif, or Copaxone, maybe Campath will be the drug of choice, but we don't know if we can give Tysabri before or after Campath, or whether Campath can be combined with an interferon."

Most neurologists know this drug by its oncology brand name, Campath, but there was a concerted – though spottily successful – effort at ECTRIMS to get speakers and other doctors to use the generic name, perhaps because a new name will be introduced for the MS market. Indeed, the pricing strategy remains challenging since the dose used in MS is one-tenth the oncology dose, though in MS a risk management plan will almost certainly be mandated by the FDA, which possibly would justify a higher cost if that plan were bundled with the drug or offered as a "free" service with the MS-branded drug.

Campath is approved to treat fludarabine-resistant chronic lymphocytic leukemia (CLL). In early data in MS, intermittent therapy with alemtuzumab reduced the relapse rate 97% in SPMS but no impact on disability progression. It also reduced relapses by 94% in RRMS.

New data presented at ECTRIMS indicated that the beneficial effect of alemtuzumab persists even two years after treatment is stopped. The 3-year, randomized, open-label, rater-blinded, Phase II CAMMS223 study, which began in 2002, was put on hold for almost two years after a patient died from immune ITP and five other patients developed ITP but recovered upon discontinuation of alemtuzumab.

CAMMS223 was allowed to restart in 2006 and finished in September 2007. It compared two doses of alemtuzumab (12 mg and 24 mg) pulsed annually to Rebif 44 µg TIW in treatment-naïve RRMS patients with early active disease, and all three arms were well-matched. Patients had to have onset of disease within the previous three years and a starting EDSS score ≤3.0 and ≥2 relapses in the last year. Patients will continue to be followed for another two years.

Prof. Alastair Compston of the University of Cambridge in the U.K. concluded, "Sustained treatment effect allows annual treatment cycles or even longer intervals. One can treat patients occasionally. Based on the early, open-label experience, treatment may be particularly effective early in the

disease course, and later it may not be possible to pick up the pieces and rebuild the nervous system."

Other findings alemtuzumab patients included:

- No opportunistic infections were observed in the trial, which an investigator called surprising. In the entire 870-patient year experience with alemtuzumab in MS, a "surprising small" number of serious infections (10-15) were reported.
- The serious adverse events of concern are:
  - **ITP.** However, no additional cases of ITP occurred in CAMMS223 after the trial was re-started in 2006. How were the ITP patients treated? Two with Rituxan, 2 with steroids, 1 required no therapy, and one died. No ITP patients have required a splenectomy. There is no predictive factor for ITP, but serial platelet monitoring of white blood cells can be useful by identifying platelet drops early, but an expert said frequent platelet monitoring is not the entire answer because platelet count falls can be abrupt and defy monthly platelet testing.
  - **Thyroid disorders,** such as Graves disease. Dr. Alasdair Coles of Cambridge, U.K., said four years of treatment with alemtuzumab is associated with a 20% risk of thyroid disease, "The presence of anti-thyroid peroxidase antibodies before treatment doubles the risk of developing thyroid disease, but there is still a 15% risk in negative cases." Dr. Hans-Peter Hartung of Germany said, "There is a higher incidence of hyperthyroidism with alemtuzumab, but it is treatable …It has to be factored into risk:benefit, but given the apparently high efficacy, this (agent) is worth considering." Testing TSH every three months identifies patients about six months before they develop symptoms, experts explained.
- 80% of the patients in the trial had only one course of alemtuzumab, so most of the patients had no therapy for nearly two years. The 3-year results in the trial reflect the impact of the drug two years after it was discontinued.
- Alemtuzumab does not limit the accumulation of disability in patients who have entered the SP phase but appears to affect the natural history of the disease if used early and before the onset of fixed disabilities.
- Of the 47 CAMMS223 "look-alike" patients treated from 1999-2005, none has yet acquired disability from relapses or entered the progression phase of MS. Conversely, five patients with a baseline EDSS ≥6 who were treated with alemtuzumab have all since progressed.

Critics of the alemtuzumab efficacy results argued that:

- The definition of disability used. A one point change in EDSS "doesn't mean anything," some experts claimed, explaining that EDSS scores can fluctuate that much from time to time in RRMS patients.
- The effects of prolonged immune suppression are unknown.

The alemtuzumab Phase III trials have begun, including:

- **CARE-MS-I.** This is a randomized, open-label, rater-blinded, global, multicenter trial of ~525 treatment-naïve RRMS patients. It will test 2 annual cycles of low dose alemtuzumab (12 mg x 5 to start, then 12 mg x 3 a year later) vs. Rebif 44 µg TIW for a minimum of two years. The primary endpoints are: (1) SAD at 6 months, using EDSS progression and (2) annualized relapse rate. Enrollment has already begun in the U.S. and the U.K. and is expected to start soon in the rest of Europe, Australia, and South America.
- **CARE-MS-II.** This is a randomized, rater-blinded, dose-blinded, multicenter trial in ~1,200 "treatment-experienced" MS patients (240 with Rebif 44 µg TIW, 480 with alemtuzumab 12 mg annually, and 480 with alemtuzumab 24 mg annually). Enrollment is about to begin

Alemtuzumab Results in CAMMS223 Trial

Measurement	Rebif n=111	Alemtuzumab 12 mg n=112	Alemtuzumab 24 mg n=110
Reduction in annual relapse rate			
At 1 year	---	78% vs. Rebif (p<.001)	Down significantly
At 2 years	---	72% vs. Rebif (p<.001)	87% (p<.0001)
Number needed to treat (NNT) at 2 years to prevent a relapse	---	4.1	3.3
At 3 years	~ 3.25	~ 1.0	~ 1.6
		73% vs. Rebif (p<.001)	
Other findings			
Grade 3 infections	48 infections	1 infection	
T2 lesion load at 2 years	Down 11	Down 22 (p<.05 vs. Rebif)	Down 20 (p<.05 vs. Rebif)
MSFC Z-score	Up ~ 3.5	Up ~ 4.5 (p<.0001 vs. Rebif)	Up ~ 6.0 (p<.0001 vs. Rebif)
Time to sustained accumulation of disability (SAD failure rate)			
At 1 year	---	Down 83%	
At 2 years	~ 20%	~ 4% Down 66%	~ 8% Down 88%
At 3 years	---	Down 71%	
Mean EDSS score			
Disability over time	Worsens	Stable or improved	
Delay in confirmed disability progression	N/A	Down 88% (p<.0008)	Down 66% (p<.0098)
EDSS change at 2 years	Up 0.22	Down 0.35	Down 0.51 (p<.0005)
EDSS change at 3 years	Up 0.39	Down 0.39	(p<.05)

in Australia and Europe, and U.S. sites are screening patients now. Another difference from CARE-MS-I is that patients in this trial must have had ≥6 months of continuous treatment with Rebif or Copaxone and at least one relapse on therapy to enter the trial. The two primary endpoints are SAD and relapse rate. Patients will be carefully monitored for autoimmune diseases, particularly thyroid disorders and ITP. Only 20% of patients will be in the control arm, which an investigator said would provide more safety information.

The Phase III trials cannot be double-blind because there is a characteristic but transient rash which patients get from alemtuzumab. This rash is mediated in part but not completely by co-administration of methylprednisolone.

In both Phase III trials, doctors will be educated to recognize – and patients will be carefully monitored for – thyroid disorders and ITP. There will be monthly platelet monitoring, and a CBC abnormality may trigger increased frequency of monitoring (to weekly). There will also be a monthly monitoring survey – with a reminder and inquiries about signs/symptoms of ITP. Dr. Hartung said, "One might consider that important defensive actions are interfered with or regulatory functions may be disturbed, but I can't tell now, but no danger signals emanated from the (CAMMS223) trial in terms of opportunistic infections, but one will have to carefully monitor it and set up a good pharmacovigilance program. Based on what is known today, this kind of impact on T cells or B cells is not attended by an overwhelming danger signal."

A Genzyme official said the company is seeking to amend the CAMMS223 extension trial protocol to have two arms: (1) re-treatment on a maintenance schedule and (2) re-treatment on progression.

Neurologists predicted that enrollment in these trials will go quickly since there is a lot of excitement and optimism about this agent. In fact, one doctor asked about alemtuzumab said he had no plans to participate in these trials, but after listening to an alemtuzumab symposium, he said he will now try to get in a trial because he was impressed with the Phase II data. A Canadian doctor said, "Enrollment will be easy. A colleague of mine already has 405 patients waiting to enroll."

New data. Researchers from Texas and Michigan also reported at ECTRIMS on the two-year MSFC (MS Functional Composite) Scale results in 45 refractory RRMS patients from an investigator-initiated study. The efficacy results were reported earlier this year, showing a 94% reduction in the relapse rate (p<.0001) with two annual cycles of alemtuzumab.

In addition, 44% of patients had stable EDSS at Year 2, and 42% were stable on EDSS (p<.0001). This translates to patients who had progressed on an interferon being 6.2 times more likely to improve or remain stable than to decline with alemtuzumab treatment.

MSFC at Year 2 with Alemtuzumab

Measurement at Year 2	Improved	Stable	Declined
MSFC scale	36.0%	34.0%	30.0%
25-foot walk	10.0%	62.5%	27.5%
9-hole peg test (9 HPT)	10.0%	75.0%	15.0%
PASAT	30.0%	57.5%	12.5%
Adverse events	**Grade 1**	**Grade 2**	**Grade 3-4**
ITP	0	0	0
Thyroid disorders	22%	6.7%	0
Thrombocytopenia	1 patient not requiring treatment		
DVT	0	0	1 Grade 4
Pulmonary embolism	0	0	1 Grade 3 1 Grade 4 in same patient

MERCK SERONO/ZYMOGENETICS' atacicept (TACI-Ig)

Phase II trials in optic neuritis and RRMS are about to begin. Dr. Hartung said, "I am quite confident that this promises to be an interesting approach."

A Merck Serono official said the company is looking into multiple indications for this antibody, including oncology and MS. Asked how this antibody might be different from other MS antibodies, he said, "Probably the safety profile will be much milder than Campath or Tysabri…There seems to be a growing belief that B cells at least in Type 2 MS are likely to be a good target."

BIOGEN IDEC/PDL BIOPHARMA'S daclizumab, a humanized anti-CD25

Daclizumab, which is sold by Roche as Zenapax for renal transplant, is in Phase II development in MS. Previously, an NIH Phase I/II pilot study looked at daclizumab in patients not responding to interferon-β therapy. That trial showed a 78% reduction in relapses and a reduction in new contrast-enhancing lesions (CELs) on MRI after 7 months of therapy, an improvement in EDSS that became statistically significant over time, and a significant improvement in timed ambulation, but patients began to relapse as soon as therapy was stopped.

Currently, daclizumab is in the Phase II CHOICE trial, as an add-on to Rebif in 230 RRMS patients at 51 sites in North America and Europe. (**NOTE:** That means most sites will have very few patients.) The primary endpoint of this randomized, multicenter, placebo-controlled, double-blind study is the number of new Gd+ lesions by MRI. In preliminary results presented at ECTRIMS, Dr. Xavier Montalban of Spain reported that the trial demonstrated proof-of-concept, with a positive effect evident by Week 4 of therapy, "Daclizumab substantially reduced the number of new or enlarged Gd+ lesions in patients who were not responders to interferon-beta. Safety supports moving forward into the next clinical studies. A larger study is planned to determine clinical efficacy and to more clearly define the safety risk, particularly infections and cutaneous events. An additional analysis of the (CHOICE)

data at Week 44 and Week 72 will assess longer-term safety and efficacy."

After adjusting for baseline differences, Dr. Montalban said there did not appear to be any difference in the two daclizumab doses tested.

The Phase II SELECT monotherapy trial vs. placebo is expected to start by the end of 2007. Dr. Montalban speculated that a placebo-controlled Phase III trial would be possible – in Europe – but difficult to do for two or three years without very clear inclusion criteria and escape rules.

Preliminary 24-Week Results of CHOICE Trial

Measurement	Placebo n=77	Daclizumab 1 mg/kg Q4W + interferon-beta * n=78	Daclizumab 2 mg/kg Q2W + interferon-beta * n=75
Completers	74 patients	70 patients	70 patients
Primary endpoint: New or enlarged Gd+ T1 lesions from Weeks 8-24	6.9	4.7 (25% reduction from baseline, Nss, p=0.501)	2.1 (72% reduction from baseline, p=0.004)
Secondary endpoint: Relapse rate from Weeks 8-24	70%	45% (Nss)	37% (Nss)
Infections	52%	51%	47%
Cutaneous events	27%	37%	31%
Serious infections	1.3%	4.6%	
Urinary tract infections	13%	N/A	17%
Drug-related serious adverse events	2.6%	6.4%	6.7%
Injection site reactions	24.7%	16.7%	18.7%
Deaths or opportunistic infections	0	0	0

*** About one-third were on low dose interferon-β and two-thirds on high dose interferon-β.**

SYMPTOMATIC THERAPIES FOR MS

Erythropoiesis stimulating agents (ESAs)

EPO, a hematopoietic growth factor involved in brain development, is not being investigated as a therapy for MS but as a potential neuroprotective. Several studies in EAE (animal model of MS) have shown it to be both neuroprotective and neuroregenerative. German researchers reported at ECTRIMS on a small, open label, pilot trial of EPO in chronic progressive MS (CPMS) which found that high dose EPO but not low dose given IV weekly for 24 weeks lead to motor and cognitive improvement even long after the drug is stopped. Dr. Hannelore Ehrenreich of Göttingen, Germany, said, "The effects on the nervous system are independent of its hematopoietic action, and the functional iron deficiency caused by EPO may be an additional benefit in MS." She also noted that EPO is well tolerated and safe in CPMS patients.

The trial compared three patients on low dose (8,000 IU weekly) to five patients on high dose (48,000 IU weekly). The control was two EPO-naïve Parkinson's disease patients. Dr. Ehrenreich said, "There was no effect with low dose EPO, but high dose EPO was statistically significantly better than baseline after approximately 12 weeks. Then, it plateaus for some time and does not revert to baseline even six months after EPO is stopped. EDSS is a very crude measure, but we see improvement in the high dose that lasts at least 12 weeks… So, there is a persistent effect…The same holds for motor conduction time." There was also a statistically significant improvement in memory tests with high dose (but not low dose) EPO.

Asked if non-erythropoietic analogs might be even better for chronic use in MS, Dr. Ehrenreich said, "I think the non-erythropoietic analogs are very interesting classes for diseases like schizophrenia and stroke, but for MS it may be we even have profit out of exploiting the hematopoietic effect of EPO. I think the iron deficiency we are causing is not real, but the shift of iron stores may be beneficial…but that is my hypothesis that needs to be further explored."

Safety was described as good, with no adverse events, no blood pressure changes and "blood letting" at <5% of visits. Dr. Ehrenreich said, "We do have to carefully monitor these patients, and, if necessary, do blood letting…Also, what is important is never to substitute iron in these patients or you will induce inflammation and stimulate erythropoiesis."

Asked if patients who developed antibodies would also develop pure red blood cell aplasia (PRCA), a potentially fatal adverse reaction, Dr. Ehrenreich said no antibody formation was seen in the trial patients, but the incidence in other diseases treated with EPO is very low, and all but 1 recovered.

IMMUNOMODULATORS

If any of the immunomodulator companies got a boost from ECTRIMS, it was Teva. European neurologists said they currently are using almost equal amounts of each of these drugs, and at the beginning of the ECTRIMS meeting, doctors were predicting that this market share balance would remain constant over the next 6-12 months. However, after hearing the efficacy results of the head-to-head REGARD trial comparing Rebif 44 µg TIW to Copaxone 20 mg QD, their prediction changed. Most sources said they now expect Copaxone use to pick up a little, mostly at the expense of Rebif, but other interferons could be affected somewhat. A German doctor said, "My impression in the past was that Copaxone was less immune modulatory, but the opposite was shown, so the trial will strengthen Copaxone use." A Canadian doctor said, "REGARD will have no impact on us, but it will give strength to the use of Copaxone in patients who do not necessarily have early or mild disease."

The QUASIMS study by European researchers found all the approved IFN-β therapies – Rebif, Betaseron, and Avonex – to be similar over two years in RRMS. Even in patients with higher baseline annualized relapse rates or EDSS scores, there was no clear benefit of one IFN over another. QUASIMS was a retrospective, multinational, comparative, observational study of 7,542 patients in 13 countries.

QUASIMS: 2-Year Comparison of Interferons

Drug	EDSS mean change from baseline	Progression-free patients	Year 2 anualized relapse rate	Therapy changes *
Avonex	0.9	84.7%	0.47	17%
Betaseron	0.25	76.8%	0.50	21%
Rebif 22 µg	0.16	81.5%	0.50	22%
Rebif 44 µg	0.24	75.8%	0.58	11%
p-value	<.0001 for all groups	Nss between groups	Rebif 44 µg <.05 vs. all other therapies	---

* Most often due to perceived lack of efficacy

BAYER SCHERING'S Betaseron/Betaferon

Interim 2-year (1,746-patient) and 4-year (298-patient) data from the 5-year, prospective, observational, international BEST trial in early RRMS found:

- The proportion of progression-free patients was lower at 4 years than at 2 years but still fairly high.
- Dropout rates were higher than previously seen in randomized controlled trials – 17.4% at 2 years and 34.8% at 4 years – but the dropouts generally were ***not*** due to adverse reactions or lack of efficacy but to pregnancy, moving, lost to follow-up, withdrawal of consent, etc.
- The proportion of responders was constant from 2 to 4 years, which researchers said indicated long-term stability and a good level of disease control.
- Mean annual relapse rates were reduced and similar at both time periods.

2-Year and 4-Year Interim Results of BEST Trial

Measurement	Betaseron at 2 years	Betaseron at 4 years
Improvement in EDSS from baseline in completers	17.4%	13.2%
Progression-free ***and*** relapse-free vs. pre-study period in completers	83.9%	73.6%
Mean annual relapse rate	0.42 (Down 56.7%)	0.41 (Down 57.3%)
Quality of life improved (FAMS-TS)	16.5%	10.9%
Quality of life stable (FAMS-TS)	67.7%	62.9%

MERCK SERONO'S Rebif New Formulation (RNF)

This was approved in Europe in August and Canada more recently, but the company only started selling it about three weeks before ECTRIMS. In the U.S., discussions are still ongoing with the FDA. A Merck Serono official said the company has been "answering questions and interacting" with the FDA and is hoping for approval "next year some time." He said the program for Rebif New Formulation focuses on improved tolerability and lower immunogenicity, "That whole area (immunogenicity) is controversial…But certainly some doctors in some countries say it is better to have lower neutralizing antibodies." Pricing of Rebif New Formulation is the same as standard Rebif, and it comes in the same 22 µg and 44 µg doses and titration packs.

In a preclinical mouse study, RNF was less immunogenic than either Avonex or Rebif (when administered by the same route and with the same frequency), and in a Phase I study in humans, tolerability was better than Rebif.

Efficacy and safety data from a 96-week, multicenter, single-arm, open-label Phase IIIb study of RNF in RRMS was reported at ECTRIMS. They compared 260 RNF-treated patients from Europe and North America to historical data from the EVIDENCE trial of Rebif. Of the RNF patients reporting flu-like symptoms, 49.6% characterized them as mild, 24.6% as moderate, and 2.7% as severe. Likewise, headache and injection site reactions were mostly mild.

Comparison of Immunomodulators

Company	Brand name	Generic name	Dosing	Dosage	Type of MS treated
Bayer Schering Pharma (Bayer HealthCare in the U.S.)	Betaseron/Betaferon	rhu interferon beta-1b	SC	250 µg EOD	RRMS (In Europe: also SPMS)
Biogen Idec	Avonex	rhu interferon beta-1a	IM	30 µg QW	RRMS
Merck Serono	Rebif	rhu interferon beta-1a	SC	44 µg TIW	RRMS
Merck Serono	Rebif New Formulation	rhu interferon beta-1a	SC	44 µg TIW	RRMS (when approved)
Teva Pharmaceuticals	Copaxone	Copolymer-1, glatiramer acetate	SC	20 mg QD	RRMS

96-Week Results with Rebif New Formulation

Measurement	Rebif new formulation n=260	Rebif in EVIDENCE trial n=339
Baseline		
Mean age	34.0 years	39.0 years
Number of relapses	1	2
Key safety results		
Injection site reactions	30.8%	85.8%
Nab+	13.9%	24.4%
Persistent Nabs	2.5%	14.3%
Flu-like symptoms	71.5%	49.0%
Hypersensitivity reactions	5.8%	5.6%
Other safety results		
Any adverse event	86.9%	95.3%
Serious adverse events	5.8%	8.6%
Cytopenia	13.5%	13.0%
Depression and suicidal ideation	6.5%	22.7%
Hepatic events	14.2%	18.6%
Patients with persistent Nabs (Nab+ at the last 2 consecutive 6-month visits)	17.0%	16.3%
Patients spontaneously seroreverting to Nab negative status (*ITT analysis*)	1.5%	6.0%
Nab+ patients with titers <200 NU/mL	29%	28%
Nab titers >1000 NU/mL	8.1%	9.8%
Efficacy results		
Relapse free and EDSS score stable throughout the study	53.3%	34.8%

Another Phase III trial is underway to see if RNF can be dosed less frequently than Rebif – QW vs. TIW in patients with a first clinical event at high risk of converting to MS. REFLEX is a 480-patient, Phase III, randomized, double-blind, placebo-controlled, two-year, multicenter trial with three arms: RNF 44 µg QW, RNF 44 µg TIW, and placebo.

NOVARTIS'S NVF-233

When Novartis bought Chiron, which manufactured Betaseron for Bayer Schering, it got the right to make and sell its own bioequivalent interferon-beta-1b. There isn't a pathway for getting FDA approval of biosimilar biologics, but this is not biosimilar; it is identical, so Novartis is optimistic that it will not have to do a clinical trial to get approval. A Novartis official said the company plans to introduce it in 2009, "It is essentially the exact same molecule as Betaseron…We will now have the ability to market the exact molecule under a Novartis brand name."

TEVA'S Copaxone (glatiramer acetate, copolymer-1)

At a Teva-sponsored satellite symposium, a speaker emphasized:

- Copaxone's unique mechanism of action modulates peripheral immune responses as well as inducing changes in the CNS.
- Imaging studies demonstrate the effect of Copaxone on both visible and invisible pathology of the disease, suggesting an effect on maintaining axonal metabolic function and ***possibly*** promoting a reparative environment independent of the blood brain barrier.
- Copaxone represents a reasonable first-line treatment, with the only prospective long-term clinical data supporting both efficacy and safety over a decade of continuous use.
- Non-conventional MRI techniques should be incorporated into exploratory and definitive clinical trials to assess the therapeutic effects, independent of the blood brain barrier.

Copaxone vs. Rebif. REGARD, an open-label, randomized, multicenter trial of 764 RRMS patients sponsored by Merck Serono, failed to show any statistically significant difference between Rebif and Copaxone on the primary endpoint of time to first relapse. There were some interesting findings in REGARD on other endpoints, but no real conclusions could be drawn about these because the trial missed its primary endpoint. For instance, patients did significantly better on Rebif than Copaxone if:

- EDSS baseline score was ≤2.
- They came from the U.S. rather than Russia.
- Their baseline T2 lesion count was below the median (≤2.0).

Dr. Daniel Mikol, director of the University of Michigan's MS Center, offered several explanations for the trial's failure:

1. **Power.** The trial was 80% powered to show a 30% difference in the two agents, based on 460 events occurring over 96 weeks, but far fewer events occurred, giving the trial just 56% power to show a difference. There were ~45 fewer relapses than expected. Asked for his personal opinion of the results, Dr. Mikol said, "Even with sufficient power (more events), there was still a chance we wouldn't have seen a difference, but it would have been desirable to have had more events to approach that question…Had this study been carried out longer, I doubt there would be a difference, but with a different patient population, it might be a different story…I think one conclusion is there is no difference in the efficacy of the agents on the primary endpoint, but I don't know if we can say that…The other conclusion is that the study is not well enough powered. That is my take-home message."
2. **Baseline differences.** The two patient populations were well matched except that there were more patients in the Rebif arm with >1 relapse in the 24 months prior, a lower baseline EDSS score, and a lower baseline number of T2 lesion volume.
3. **Russian patients.** The results could have been confounded by the inclusion of so many (256) patients from Russia.

4. **Changing patient population.** There seems to be a declining annual relapse rate in both Rebif and Copaxone trials over time, which may have contributed to the lack of any significant difference in the trial – and which may have implications for other ongoing and planned trials, including the trials of oral agents and monoclonal antibodies. Dr. Mikol said, "This suggests there is a change in the population being recruited into current MS trials…This is a less active population which has implications for this and perhaps other ongoing and future studies."

Copaxone vs. Betaseron

Final data from the BECOME trial, which was a head-to-head comparison of Copaxone and Betaseron, sponsored by Bayer Schering, also may give some strength – or at least confidence – to Copaxone use. The MRI data in that trial at both 12 and 24 months showed no statistically significant difference between the two drugs on the primary endpoint (median per patient combined active lesions per scan) or on most secondary endpoints, thus indicating that there is no validity to the claim that Copaxone is less potent than interferon-betas. BECOME was a randomized trial of 75 patients, mostly with RRMS, monitored by MRI as well as other methods.

Neutralizing antibodies (Nabs)

One of the issues with all the immunomodulators is antibody formation and the effect of that on the efficacy of the immunomodulator. Researchers from Canada and Wisconsin presented a poster which looked at 1,447 MS patients (560 of whom had Nab testing) and found that Nabs in Betaseron- and Rebif-treated patients decreased the efficacy of the treatment (when evaluated on relapse rates).

- In Rebif patients, the neutralizing antibodies tended to disappear less rapidly than in Betaseron-treated patients.
- Nab+ patients had more relapses than Nab– patients in Years 3 and 4.
- The number of relapse-free patients was higher in Nab– patients in Years 3 and 4.
- The clinical effect of Nabs peaked in Year 3 for Betaseron and in Year 4 for Rebif.

Another study – a retrospective analysis of 327 patients sponsored by Teva – by U.K. researchers found that at 24 months, neutralizing antibodies occurred in 8% of Avonex patients, 27% of Rebif patients, and 33% of Betaseron patients. They also reported that the risk of relapse is greatest in patients with the highest Nab titers.

96-Week REGARD Trial Results

Measurement	Rebif	Copaxone	p-value
Baseline differences			
Time since first relapse	5.36 months	7.31 months	<.05
T2 lesion volume	5,508.2	10,478.36	<.05
Time to first relapse			
Primary endpoint: Overall	432 days HR=0.943	492 days	Nss, 0.643
In patients with baseline EDSS ≤2	Significantly better HR=0.648	---	0.022
In patients with baseline EDSS >2	---	Nss better HR=1.25	Nss, 0.19
Other results			
Secondary endpoint #1: Mean number of T2 lesions (new or enlarging per patient per scan)	~ 6.7	~ 8.2	Nss
Secondary endpoint #2: Mean number of T1 Gd+ lesions per patient per scan	Significantly better	---	<.05
Mean number of combined T1 and T2 lesions	Significantly better	---	0.010
Proportion of scans per patient with CUA lesions	Significantly better	---	0.009
Annualized relapse rate	0.30	0.29	Nss, 0.828

24-Month BECOME Trial Results

Measurement	Betaseron n=36	Copaxone n=39	p-value
Results at 12 months			
Median per patient combined active lesion (CAL) counts per scan	0.63	0.67	Nss, 0.62
Post-treatment patient CAL averaged per month by treatment	0.63	0.67	Nss, 0.54
Post-treatment patient new enhancing lesion counts averaged per scan	0.41	0.25	Nss, 0.40
Difference of pre-drug CAL vs. on-drug CAL	p=0.0035	p=0.12, Nss	---
Difference of pre-drug CAL vs. on-drug CAL in patients with >0 CAL at baseline	p=0.002	p=0.056, Nss	---
Results at 24 months			
Primary endpoint: Median per patient CAL counts per scan	0.78	0.62	Nss, 0.45
Secondary endpoint #1: Post-treatment patient CAL averaged per month by treatment	0.60	0.38	Nss, 0.24
Secondary endpoint #2: Post-treatment patient new enhancing lesion counts averaged per scan	0.39	0.27	Nss, 0.20

Other data on disease modifying therapies (DMTs)

➢ **Brain atrophy.** A 5-year imaging study of the effect of DMTs on brain atrophy in 300 RRMS patients found that:

- All DMTs are effective in reducing the rate of brain atrophy vs. no treatment.
- Copaxone had the best effect on brain atrophy and was significantly better than Betaseron or Rebif.

- Low dose Avonex had a lower rate of brain atrophy than high dose Betaseron or Rebif over a long-term period, which may not be evident over a shorter period of observation.
- Long-term brain atrophy studies – not just 1-2 years – should be considered.

➢ **Switching strategies.** A study by researchers at the University of California, San Francisco (UCSF), found that when an RRMS patient fails a first DMT, changing to another immunomodulator can be a successful strategy. They also concluded that switching may be a reasonable consideration in poor responders before initiating a second-line treatment such as Tysabri or chemotherapy.

SPASTICITY

ACORDA THERAPEUTICS'S fampridine slow-release (SR)

Dr. Patrick Vermersch of France called this a "very interesting" compound to improve muscle weakness and spasticity in MS patients. He said a Phase II trial of 120 patients, which was completed in 2Q04, showed significant improvement in mobility and muscle strength. Another trial of 301 patients, completed 3Q06, showed improved walking speed during 14 weeks of treatment. A Phase III trial is planned.

Dr. Vermersch said the concern is safety, "Some cases of epileptic seizure have been associated with it, but we think the new slow-release formulation will decrease the peak concentration of the drug, and that peak has been related to epileptic seizure." Another expert said, "The main issue is occasional seizures, which is especially an issue if the patient is driving…Any use of fampridine will be nice because it meets an unmet need. It is a symptomatic treatment for a condition for which there is no treatment now. But we need to see what type of patients it helps."

If extended release baclofen (a common drug used to treat spasticity) were available and if doctors wanted to use it, they said they would be inclined to prescribe Acorda's agent rather than asking a compounding pharmacy to prepare a generic preparation. A Canadian doctor said, "There is a need (for fampridine SR), but it will be on a case-by-case evaluation. In some cases the drug will help…Baclofen is not very active. Only rarely can you use >60-80 mg. Usually you give a 10 mg or 20 mg pill, and the duration is not long, so the patient takes it four times a day. When spasticity is worse at the end of the day, patients can use it on a PRN (as needed) basis, so I'm not sure if I would use an extended release form because that may put the patient on the maximum dose – and some patients respond to Botox (Allergan, botulinum toxin A)."

XENOPORT'S XP-986

Xenoport is working on an extended release version of baclofen for spasticity associated with MS or Parkinson's disease that will be QD or BID and possibly have better efficacy. A German doctor said, "I went away from baclofen in the past year because of sedation and fatigue. I prefer gabapentin because it is less sedating, and most patients with spasticity prefer gabapentin. Baclofen was helpful three or four years ago, but times have changed." Another German doctor said, "Extended release baclofen would be useful, but I'll still need immediate release baclofen to start patients. The extended release formulation would have to have fewer side effects to be useful."

MISCELLANEOUS

BAYER SCHERING PHARMA AG

In addition to alemtuzumab, Bayer Schering has a microglia drug about to start Phase I development. A CCR-1 was in development but was found not to be effective and dropped.

MEDICINOVA'S MN-166

MN-166 is used clinically in Japan, originally for asthma and subsequently for post-stroke recovery, but it failed to show a neuroprotective benefit in MS at one year in the MN-166-CL-001 trial. This was a randomized trial in 297 RRMS and/or SPMS patients with continued relapses and an EDSS ≤5.5. Patients (>90% RRMS) were excluded who had taken cladribine in the past or who had taken an interferon-beta within 45 days of the baseline MRI scan. Before the trial started, placebo patients were pre-randomized to get either high or low dose MN-166 in the second year of the trial. The drug was well tolerated with no adverse lab or ECG findings. Side effects were described as mild and self-limiting, mostly GI. Researchers concluded that higher doses should be tested.

1-Year Results of MN-166-CL-001 Trial

Measurement	Placebo n=100	MN-166 30 mg/day n=94	MN-166 60 mg/day n=98	p-value
Discontinuations	6 patients	13 patients	14 patients	---
Primary endpoint: Cumulative active lesions by MRI	---	---	~ 18% reduction vs. placebo (Nss)	Nss difference among treatments
% brain volume reduction	---	---	~ 38% reduction vs. placebo	<.05 of high dose vs. placebo
Time to first relapse	244 days	255 days	>365 days	0.04 for high dose vs. placebo
% of patients relapse-free in Year 1	41%	41.5%	56%	0.03 for high dose vs. placebo
GI adverse events	7.8%	14.7%	22.2%	---
Serious adverse events	4% *	2% *	6% *	---
Deaths	0	0	0	---

*** All considered not or unlikely to be attributable to treatment.**

MS Trial Design Issues

Combination agents

The FDA requires that a combination trial have three arms – Drug A+B, Drug A, and Drug B – and the combination arm has to beat both the other arms, showing at least an equivalent if not superior benefit. Thus, combination trials require larger sample sizes and/or longer follow-up. Dr. Gary Cutter of the University of Alabama at Birmingham suggested three other potential designs, but he said these are not accepted yet by the FDA:

- Start with Drug A and then add Drug B.
- Compare early vs. late treatment.
- Randomized withdrawal of Drug A after giving the combination of Drugs A and B. He said this is "enticing but confounds the time course of the disease with unknown safety issues."

He noted that using an EDSS measurement is particularly problematic in combination trials, "We assume a common event rate across the whole trial, but the probability of a 1-point increase in EDSS varies by where you are on the scale …The idea of having different mixes of patients in different groups may give rise to very different progression rates in the different treatment arms. It is even more likely to occur when you have three arms…And the mix of EDSS patients matters. With three groups there is more chance of a slight imbalance (in baseline EDSS)…For example, in a study powered to detect a 50% reduction of progression over two years with combination therapy, the power was reduced from 80% to 70% due to the probability of progression by EDSS…and I don't think this has been taken into account."

Neuroprotection studies

No surrogate measure of neuroprotection (including brain atrophy) has yet been confirmed as a consistent predictor of clinical outcome and therapeutic response in MS, but biomarkers are needed for MS neuroprotection studies. Dr. Omar Khan director of the MS clinic at Wayne State University in Detroit, MI, said neuroprotection has been "somewhat slowed down, not hindered, somewhat by fascination with Gd enhancement as a marker in trials…It (Gd+) does allow a lot of statistical data…and it has helped us in screening out certain therapies…but at the same time, you are seeing such robust effects on Gd+ – with Tysabri as high as 92% – and the next generation of therapy (monoclonal antibodies) might come across with similar or even better Gd enhancement. At the same time, good analyses looking at the predictive value of Gd enhancement showed it was more or less none or very modest…The bottom line is we desperately need better outcomes (markers) that include tissue damage in a more global manner."

Dr. David Miller of the U.K. said potential biomarkers for neuroprotection are emerging, including:

- **T1 hypointense lesions.**
- **Diffusion tractography.**
- **Anti-myelin antibodies.** One study found a positive predictive value with CIS, but another study found a negative prediction of MS.
- **CSF neuroaxonal biomarkers.** Optical coherence tomography (OCT) may have a role here, particularly in optic neuritis where there is ~20% loss of the retinal nerve fiber layer (RNFL) after a single episode. New-generation OCT and scanning laser polarimetry (GDx) may be particularly useful here.
- **N-acetyl aspartate.** Dr. Miller said, "These are very interesting, but there is accumulating evidence they may be more specific for myelin. They may be good for monitoring proof-of-concept studies in neuroprotection."
- **CNS atrophy.** Dr. Miller said the degree of CNS atrophy correlates quite strongly with RNFL as measured by OCT. The limitation of spinal cord atrophy include: sensitivity over time, small changes in a small structure, inconsistent findings, and little published data from clinical trials. He suggested this may be more useful in PPMS.
- **Brain atrophy.** Dr. Miller described this as a "sensitive and plausible primary outcome measure." Dr. Khan said, "You do, unfortunately see a high loss of brain tissue in MS – 4 to 5 times healthy controls, and this can become a useful marker in so-called neuroprotection strategies… But in one study the median annualized rate of brain atrophy was ~15% that was not explained by the reduction in edema or T2 lesion volume."

One of the agents under investigation as a neuroprotectant is GlaxoSmithKline's Lamictal (lamotrigine), a sodium channel blocker. A 2-year, double-blind, placebo-controlled study sponsored by the U.K. MS Society started in January 2006. A speaker suggested there may be results in another year.

Novartis also suggested its oral fingolimod (FTY-720) may be neuroprotective and/or neuroregenerative.

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