Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Patients are already demanding to know when oral MS therapies will be available. But the side effects of most are not insignificant, so neurologists do not yet know how they will use them. ♦ **Merck Serono's cladribine** could be the first oral agent, and efficacy seems durable, but toxicity means it will need careful risk minimization. The low dose appears to be equally as efficacious as the high dose. ♦ **Novartis's fingolimod** has very good efficacy, with the low dose both more effective and safer than the high dose. Neurologists are nervous about the side effects, particularly bradycardia, infections, and skin cancer. Novartis has moved a follow-on – BAF-312 – into Phase II testing. ♦ **Biogen's BG-12** is a relatively safe oral agent, but it isn't perceived as having particularly strong efficacy, and TID dosing is a drawback. ♦ **Teva's oral laquinimod** may be the dark horse. Efficacy is comparable to an interferon (IFN), it can be combined with IFN, and it is safe. ♦ **Genzyme/Bayer's alemtuzumab** has remarkable efficacy, which holds out to 4 years. Toxicity is serious but *may* be manageable. ♦ There are now 13 PML cases with **Biogen Idec/Elan's Tysabri**, and neurologists are not happy the companies are no longer providing updates on new cases. However, not all the PML patients are dying, and both alemtuzumab and cladribine have seen PML in oncology patients. ♦ Symptomatic therapy is getting more attention, most neurologists expect to use **Acorda Therapeutics' fampridine** for ~25% of their progressive MS patients, perhaps for fatigue and/or cognition as well as walking.

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EUROPEAN CONGRESS ON TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS)

Düsseldorf, Germany
September 9-12, 2009

Despite the economic downturn, attendance at ECTRIMS this year was comparable to two years ago, with more than 5,000 attendees. Last year was a joint North American/European meeting, so that comparison would be unfair.

There was a big emphasis at the meeting this year on:

- **Depression and cognitive dysfunction in multiple sclerosis (MS) patients.** Speakers said neurologists have to be more alert to these conditions in MS patients – recognizing them sooner and treating them. For depression, SSRIs often work. For cognitive impairment, which reportedly affects more than half of MS patients, Pfizer's Aricept (donepezil) appears to be effective. There is some debate about the usefulness of Forest Lab's Namenda (memantine), and there were hints that Acorda Therapeutics' fampridine may prove to be useful, though additional data will be needed.
- **Symptom management.** Fampridine and GW Pharmaceuticals' Sativex (an oral cannabinoid-based spray) both appear to work in about half of MS patients, but the response in responders appears good – fampridine on walking ability and Sativex on spasticity.
- **Patient discontinuations.** The interferons – Biogen Idec's Avonex (interferon-β1a), Bayer Schering Pharma's Betaseron/Betaferon (interferon-β1b), Novartis's Extavia (interferon-β1b – Betaseron), and Merck Serono's Rebif and Rebif New Formulation (interferon-β1a) – as well as Teva Pharmaceuticals' Copaxone (glatiramer acetate) have high dropout rates that continue over time, and there was considerable discussion about how to reduce this.
- **Increased interest in finding biomarkers and better use of imaging.** A biostatistician from Italy argued that MRI markers can be useful endpoints during early disease in clinical practice, when the treatment effect on clinical outcomes is difficult to assess. She said a large meta-analysis of all randomized clinical trials in RRMS (relapsing-remitting multiple sclerosis) demonstrated a strong trial-level correlation between efficacy on MRI and on relapses. Optical coherence tomography (OCT) was also getting a lot of attention at ECTRIMS. Retinal nerve fiber layer (RNFL) is decreased over time in MS patients, and it is very strongly correlated with degree of brain atrophy. Proof-of-concept studies are needed, but doctors were looking at OCT machines on the exhibit floor and having their own RNFL mapped.
- **Increased use of disease-free measures** rather than simply annualized relapse rate (ARR) or Gd+ lesion counts.

- **Educating neurologists on the science behind the various options closest to market** – particularly oral agents. In fact, sometimes it got a little repetitive since there was not much really new news at the meeting, mostly just incremental new information. There was much less discussion of anti-CD-20 agents and monoclonal antibodies.

The real elephant at ECTRIMS was the question of how to use the new agents when they are approved – how to choose among them, when or how to use each, which patients should get which agent. Speakers were ***not*** providing doctors with any real guidance on this; they were generally just noting that the new agents will give doctors the opportunity to personalize therapy, to tailor therapy for individual patient needs.

Balancing the safety and efficacy of the new therapies (the risk:benefit ratio) is a major concern, and neurologists really do not have a good handle on this yet. There were very little new data at the meeting that will help doctors make these decisions. Talk after talk described each agent and the data on it, sometimes in boring detail, but much of it was repetitive. There were many unanswered questions, mostly about safety but also about usage and even efficacy. However, the company-sponsored sessions on new therapeutics were generally packed as neurologists sought to learn more about these agents.

A U.S. neurologist, Dr. Barry Arnason from the University of Chicago, made some rather controversial comments, showing that there remain many things in MS on which even the experts still do not agree:

- Perhaps a successful Epstein-Barr virus (EBV) vaccine could eradicate MS.
- There could be a link between MS relapses and the anti-biotic ciprofloxacin, which is often used to treat bladder infections. Another speaker challenged, "I've never heard that before. You have no proof."
- Contrary to common thinking, antibodies in MS may be *good*.

European regulators appear to be turning up scrutiny of at least some MS drugs. An ECTRIMS official said one of the priorities for the EMEA (European Medicines Agency) in 2010 is the long-term adverse events of immunomodulators, which is expected to include some if not all of the oral agents.

ECTRIMS 2009 Recap

On the last day of ECTRIMS, experts provided a review of the highlights of the meeting, with comments on currently approved drugs, drugs in development, and basic science.

Currently approved drugs

Dr. Jerry Wolinsky of the University of Texas Health Science Center at Houston offered his view of the highlights from the clinical trials presented at ECTRIMS.

- **Biogen Idec's Avonex.** The MECOMBIN study did not show a benefit on brain volume preservation or function preservation with monthly cycles of methylprednisilone in combination with Avonex in early RRMS, though relapse reduction and safety were successful.
- **Biogen Idec's Tysabri (natalizumab).** There were a lot of clinical papers, but one that caught his eye was a study on what happens when the drug is discontinued – maybe some rebound. Researchers suggested that not only does disease activity return, but "perhaps that return was a little faster, more accelerated, or more damaging to tissue than what would have been anticipated."
- **Merck Serono/OSI Pharmaceuticals' Novantrone (mitoxantrone).** Dr. Wolinsky stressed the importance of setting up either registries or careful follow-up of selected patients to understand the long-term safety of using this MS drug in larger patient populations.
- **Teva's Copaxone (glatiramer acetate).** He pointed to attempts (not yet successful) to define responders and non-responders and investigator-driven attempts to see if less frequent administration can give similar outcomes to standard therapy (again, not yet successful).

ECTRIMS Presentations on Currently Approved Drugs

Drug	Total presentations	Clinical presentations	Combination therapy attempts	Follow-on biologics	Notes
Interferon-beta (Avonex, Rebif, Betaseron, Extavia)	133	58	6	5	Field is mature. No benefit to combining Avonex and methylprednisilone cycles. Regulatory path for follow-on biologics is still unclear. Increased focus on biomarkers
Copaxone (glatiramer acetate)	47	21	1	2	No success yet with identifying responders or finding less frequent dosing schedule
Novantrone (mitoxantrone)	19	10	1	0	Dose limit, possible leukemia. Registries important
Tysabri (natalizumab)	65	43	0	0	13 cases of PML. Efficacy >2 years unknown. Possible melanoma and CNS lymphoma. **Possible rebound when discontinued**

- **Biomarker studies.** "Moving into the age of personalized medicine is, for some of us, a high priority for the field now." He pointed to data on IFN-stimulated genes as a biomarker for clinical response and a possible algorithm for defining response to interferon.
- **Follow-on biologics** are a new problem that neurologists are beginning to face, and the proper regulatory path for these is unclear. Should they have a smoother course through the trial maze because of similarity to other compounds? He highlighted data on:
  - **Biogen Idec's pegAvonex.** PK, PD, and safety were shown.
  - **Bio Sidus's Blastoferon**, which is approved and sold in South America, "has not made it through real clinical testing."
  - **Merck Serono's Rebif New Formulation**, with 40-week data from the IMPROVE trial.
  - **Pepgen's daily oral recombinant ovine interferon tau** failed in a Phase IIa open-label, multicenter study in RRMS.

Pipeline therapeutics

Dr. Wolinsky also commented on new information this year on drugs in the pipeline:

- **Acorda's fampridine and GW's Sativex.** Dr. Wolinsky called these "cosmetic or sympathetic therapy" but said that type of therapy is important to patients. He pointed out that their rather unusual trial designs that enrich for responders "may be new to neurologists, but they are not new to psychiatry or pain, where they are fairly well accepted."
- **Endovascular treatment for chronic cerebrospinal venous insufficiency.** He urged investigators to be careful and keep an open minded approach.
- **Genzyme/Bayer's Campath (alemtuzumab).** There is now 4-year data, and 5- and 6-year data are coming.
- **Merck Serono's cladribine.** "I'm encouraged by the durability of the response and the lack of, so far, any emergent unusual side effects or toxicity, and I hope that continues."
- **Novartis's fingolimod (FTY-720) and BAF-312.** He said, "This (FTY-720) is moving along, giving us better comfort on how long the effects might last and the range of side effects…(BAF-312) is coming faster than usual…That might eventually prove easier to use than fingolimod."
- **Roche's Rituxan (rituximab).** Dr. Wolinsky noted that off-label use is increasing "without a lot of evidence that this is really the thing to be doing."
- **Sanofi-Aventis's teriflunomide.** Dr. Wolinsky, who is an investigator, said there was added evidence that there might be some hope that the Phase III studies – which are "well underway, with one coming next year" – might be as interesting as the original Phase II study.
- **Stem cells.** There has been progress, but many questions remain before we know "whether or not we can accept and embrace this approach or reject it."
- **Teva's laquinimod.** There was some information on safety and efficacy in longer term cohorts.

Basic science

Dr. Alastair Compston of the University of Cambridge, U.K., offered some scientific highlights from ECTRIMS, including:

- **Epidemiology** studies have shown:
  - An increased frequency of the disease, especially in women.
  - A curious clustering of disease in early summer.
  - An HLA-linked Vitamin D response.
  - Additional data that trauma is not a causative agent but stress can be.
- **Genetics** gaining importance.

ECTRIMS Presentations on Pipeline Therapeutics

Product	Total presentations	Clinical presentations	Phase II-III studies	Extension studies	Notes
Genzyme/Bayer's Campath (alemtuzumab)	8	5	6	5	Longer term data reassuring
Bayhill Therapeutics' BHT-3009	1	2	0	1	---
Merck Serono's cladribine	17	7	0	7	Good durability of response and no unusual side effects yet
Acorda Therapeutics' fampridine	4	3	0	1	Responder enrichment is acceptable trial design
Novartis's fingolimod (FTY-720)	20	7	1	3	More comfort on side effects and duration of effect. **Follow-on agent, BAF-312, coming quickly**
Teva's laquinimod	11	1	0	1	More information on long-term safety and efficacy
Roche's Rituxan (rituximab)	11	7	0	0	Acceptance of off-label use growing without a lot of evidence
Stem cells	10	8	0	0	Progress but outlook still uncertain
Sanofi-Aventis's teriflunomide	N/A	N/A	N/A	N/A	Outlook for Phase III trials improving

- **Future treatments** may fall into 2 categories: those that address lymphocyte inflammation and those that axon degeneration.
- **Phenotype changes.** There seems to be "a compelling story that the phenotype of MS can change and can change quite radically in people growing up in a different environment from their predecessors – changing phenotype with changing environment."

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Neurologists were so unhappy with Biogen Idec's decision not to provide any more regular updates on the cases of PML with Tysabri at meetings, on its website, or at ECTRIMS, that this seemed to overshadow any positive Tysabri presentations.

Several doctors pointed out that PML didn't become a problem with Genentech's Raptiva (efalizumab) in psoriasis until three years of therapy, so they would like to follow the Tysabri incidence longer. Dr. Douglas Goodin of UCSF said, "With natalizumab we obviously have a concern about PML. It seems to be increasing after people are treated for >2 years. Whether that trend persists is unknown. We don't have a large enough cohort to know if it will plateau or plateau and then go down...I think there are concerns with all the new agents. Fingolimod has had two deaths – one disseminated chicken pox (which almost certainly is related to the drug) and herpes encephalitis." Dr. Richard Ransohoff of the Cleveland Clinic said, "We need to know if cases increase with time – exponentially, arithmetically, plateau? We don't know, and we need more data."

Dr. Alfred Sandrock, senior vice president of neurology research and development at Biogen Idec, defended the company's decision not to keep updating doctors on PML cases, saying, "We would like to go to a state where we report this like any other adverse event. We will not give the exact number of cases on a weekly basis. We stopped the website update. We will inform physicians and the community of any change in the safety profile of this drug." That is, if the incidence changes from 1:1,000.

The ECTRIMS Board may be considering a European registry to track PML cases in Europe, separate from Biogen.

There are now **13 cases of PML** with Tysabri, including two cases in Sweden and a sixth case in Germany. With 1,698 German patients in the TIGRIS registry, this is 1:283.

The last German woman patient was experiencing epileptic seizures, and that made doctors suspicious, so she was examined for PML and eventually proved positive. Her outlook is uncertain at this point, but she is being treated for the PML. Dr. Rolf Gold of Germany warned doctors that they need to send samples to more than one lab to test for PML because there are both false positives and false negatives. This German woman, for example, was initially a false negative until retested at the National Institutes of Health (NIH).

Swedish researchers reported that as of July 25, 2009, 971 patients had been treated with Tysabri in that country, with 216 on the drug ≥2 years. Yet, Sweden has had 2 PML cases (1:486 overall, 1:108 at 2 years of therapy). There is no explanation for this either. The researchers concluded, "With two cases of PML in Sweden, this issue continues to be a concern and needs further scientific attention to understand and options to monitor risk."

Neurologists do not know why there have been so many cases in Germany. They speculated that it could be chance, genetics, or prior immune therapy; but no one really knows. Dr. Ludwig Kappos of Switzerland, ECTRIMS secretary, said, "It could be genetics. That is being investigated, but it is very difficult to do. It could be chance, and it could be greater use of immunosuppressants."

All of the cases of PML in MS so far have been with Tysabri. However, ***PML has been seen with a number of MS drugs*** already approved in other areas (oncology, rheumatoid arthritis, psoriasis).

- 1 case of PML with **cladribine** in the oncology setting, where it is approved to treat hairy cell leukemia. This was a patient with chronic lymphocytic leukemia (CLL) who has been heavily pretreated (5 separate courses, including cyclophosphamide, for recurring leukemia). Dr. Steven Greenberg, senior medical director at Merck Serono – and project chief for cladribine – said, "There is no need for a TOUCH-type program for cladribine, but we have a strong risk management plan. We will monitor physicians, do in-service, and then re-check periodically."
- Several cases of PML with **alemtuzumab**, also in the oncology setting – generally as end-of-line therapy in leukemia patients who had been heavily pretreated with other drugs first. An alemtuzumab researcher said, "I am still hopeful we won't see any PML with alemtuzumab in MS." Another doctor predicted, "I don't think cladribine will get a black box for PML."
- Numerous cases of PML with **rituximab** in non-Hodgkin's lymphoma and rheumatoid arthritis.

In Europe, Tysabri monitoring is through the TIGRIS registry, which is not as tightly controlled as the U.S. TOUCH program. European neurologists did not think European regulators will adopt a more stringent monitoring system, something closer to TOUCH. Dr. Michel Clanet of France, the 2009/2010 president of ECTRIMS, said, "The PML is not more than expected. I don't know if the new cases will change the opinion about monitoring."

Dr. Igor J. Koralnik, a neurologist from Beth Israel Deaconess Medical Center in Boston, offered some interesting new

information and raised some new questions about PML from his studies of Tysabri patients and JC virus (JCV):

- Molecular imaging may help detect which patients are at risk of PML in the future. These analyses are not yet ready for use, but there are suggestions it may become possible.
- Tysabri is only "the tip of the iceberg," and more PML is likely to be seen as other immunomodulatory agents gain use in MS and other diseases.
- JCV does not only affect the CNS white matter, it also affects granule cell neurons. He found that up to 51% of PML patients vs. 3% of HIV positive controls have JCV infection of granule cell neurons. He called this "an important and previously overlooked aspect of JCV pathogenesis."
- It is possible PML is a cortical disease.
- Is it safer to give Tysabri to patients without antibodies to JCV? There is no clinically available assay for the antibody to JCV. If there were an assay, giving Tysabri to patients without JCV antibodies might not be safe because patients might do even worse if they had no early response to the virus but get PML.

Dr. Olaf Stüve of the University of Texas Southwestern Medical Center in Dallas also offered some new insights into possible dangers of Tysabri. He noted that the majority of patients with RRMS benefit from iatrogenic immunosuppression, with the main problem side effects, but with Tysabri there is a 14-fold decrease in leukocytes, and six months after discontinuation of Tysabri, the leukocyte level remains depressed at about the same level, "You would expect the effect to be gone in 1.5 months (but it isn't)…We currently think a drug like Tysabri probably has two separate ways of working in patients with MS…We think there is an almost instant benefit in that T-lymphocytes can no longer access the paravascular space…but we also think there is a delayed effect. If you treat patients long enough, it is quite conceivable that the number of antigen presenting cells (is decreased) …And in a disease like MS this could potentially be very beneficial…However, we think, in the setting of a viral infection, viral antigens could no longer have an effect either …The dose-duration effect is likely a contributing factor to overall risk…Alternative treatment paradigms to prolong uninterrupted exposure should be explored."

Dr. Stüve said that leukocytes do eventually return to normal, but it takes more than six months, perhaps as long as a year. He advised, "If a patient failed a disease-modifying therapy before Tysabri, then I would use a different class of agent after discontinuing Tysabri."

What are doctors doing now? Are they giving drug holidays or stopping patients after a certain time period, such as two years? Most neurologists questioned at ECTRIMS said they are not doing drug holidays and not cutting patients off Tysabri after a given length of treatment. But they are thinking about both of these ideas. The problem is that they don't know what to give Tysabri patients when they stop the drug. There are no good switching data.

Dr. Leonid Gorelik of Biogen described his company's effort to find a treatment for PML. He said they screened 2,000 compounds and found 14 "potent inhibitors" but only one had ever been shown to have any brain penetration – mefloquine. Thus, Biogen began a randomized, open-label, rater-blinded trial of mefloquine at 20 sites. So far, 13 PML patients are enrolled, with a goal of 40 patients. Biogen is continuing to screen for other agents, though, and it has "48 new hits."

A Biogen poster reported that IRIS (immune reconstitution inflammatory syndrome) would be "an expected element of recovery from PML but seems to occur more commonly in Tysabri-associated PML than AIDS-associated PML, regardless of whether Tysabri was removed rapidly (through plasma exchange, PLEX) or simply by discontinuation. Clinical deterioration consistent with IRIS occurred ~four weeks after Tysabri was removed…Management with corticosteroids early in the course of IRIS appears to lead to an improvement in most patients."

The FDA perspective

The FDA has not fully come to grips with the PML issue yet internally, and it could decide in the future to impose some type of uniform risk minimization action plan (RiskMAP) for all drugs with which PML occurs, either individually or as a group, but no action appears imminent.

In a recent interview, Dr. Robert Temple, director of the FDA's Office of Drug Evaluation I in the Center for Drug Evaluation and Research (CDER), said simply, "Three cases (of PML) got Tysabri a REMS (risk evaluation and mitigation strategy program, in this case TOUCH)."

There has been no indication that the FDA has any plans – yet – for another panel on the safety of Tysabri or on PML in general. However, if the incidence of PML becomes more frequent than 1:1,000, the FDA probably would take some action. And it is possible that the rate is near that point if you look only at patients who have been on therapy two years. According to Biogen, that's ~10,000 patients, and there have been 13 PML cases, which would be 1:769.

Just after ECTRIMS – on September 16, 2009 – the FDA issued an update on PML with Tysabri. The Agency confirmed that 13 cases of PML have been reported worldwide with Tysabri since marketing resumed in 2006, all in MS (none in Crohn's disease, which accounts for <2% of Tysabri use).

The FDA made three key points:

1. "The risk for developing PML appears to increase with the number of Tysabri infusions received. The number of monthly infusions of Tysabri in the 13 patients who

developed PML ranged from 12 to 35 infusions. The average number of infusions received before the diagnosis of PML was 25. There is minimal experience in patients who have received more than 35 infusions of Tysabri."

2. "The overall rate of developing PML with Tysabri therapy in patients who have received at least one infusion remains below one per 1,000 patients…The current rate of PML in patients who have received at least 24 infusions ranges from 0.4 to 1.3 per 1,000 patients."
3. "At this time, the FDA is not requiring changes regarding PML to the Tysabri prescribing information or to the Tysabri risk management plan."

Currently Approved Disease-Modifying Therapies

FDA-Approved MS Drugs

Drug	Company
Avonex (interferon-β1a)	Biogen Idec
Betaseron (interferon-β1b)	Bayer Schering Pharma
Copaxone (glatiramer acetate)	Teva Pharmaceuticals
Novantrone (mitoxantrone)	Merck Serono/OSI Pharmaceuticals
Rebif (interferon-β1a)	Merck Serono
Tysabri (natalizumab)	Biogen Idec/Elan

Many MS patients never take the available injectable drugs, and many of those who do either discontinue or have an interruption in therapy over time. Why? Sometimes they forget, some are needle phobic, and others are unaware of the options available. Dr. Virginia Devonshire of the University of British Columbia MS Clinic in Vancouver, Canada, said, "At our center, we found that ~33% of patients will discontinue or interrupt therapy over the years…with 13% never re-initiating therapy. The main reason for discontinuation is actually perceived lack of efficacy, the next main reason is side effects and injection-related issues…Most discontinuations occur early, ~30% discontinue in the first six months, but over time patients continually drop out…Early discontinuation (at about 5 months) is related to side effects, with discontinuation due to lack of efficacy at ~13 months." Dr. Bernd Kieseier of Germany said, "At least half of patients are non-adherent."

Neurologists are not ready to give up on the injectables, emphasizing that they have been proven, with long-term data, to be both safe and effective. However, all said they expect their use to decline as other options become available. Dr. Mark Tullman of Columbia University Medical Center noted, "The relapse rates with the interferons and glatiramer acetate (in clinical practice) are much lower than in pivotal trials… Anecdotally, many physicians find their patients are responding very well to the injectable therapies when used in their clinical practice."

Biogen Idec/Elan's Tysabri (natalizumab)

Biogen tried to get doctors to focus on Tysabri efficacy and not PML at ECTRIMS. Dr. Frederick Munschauer of the University of New York at Buffalo emphasized that Tysabri has proved to be "the most effective drug to date in reducing exacerbations," with the annualized relapse rate down 68% vs. placebo. He added, "Slowing disability is the single outcome measure of importance to MS patients…and Tysabri reduced it 42% vs. placebo at two years…More than 1 out of 3 patients are free of disease activity over 2 years with Tysabri (36.7% vs. 7.2%, $p<0.001$)."

In a poster, Biogen listed the numbers from the last official update on Tysabri, but there were no oral presentations on it, and the company said there will not be in the future unless the PML rate becomes worse than 1:1,000.

- **Overall use** as of June 30, 2009:
  - ~56,000 patients on therapy.
  - 63,900 patient-years of exposure.
  - ~30,000 on Tysabri ≥1 year.
  - ~10,000 on Tysabri ≥2 years.
- **TOUCH** as of June 30, 2009:
  - 29,500 patients enrolled.
  - ~3,800 doctors prescribing.
  - 72% of Tysabri patients changed from another disease-modifying therapy, 9.3% switched from other therapy, 14.6% were returning quitters, and 4.2% were treatment-naïve.
  - ~13% had prior Tysabri therapy.
  - On average, patients have received 13 infusions of Tysabri.
  - 16,500 patients were on Tysabri ≥1 year.
  - 6,200 patients were on Tysabri ≥2 years.
- **TIGRIS** as of May 23, 2009:
  - 5,663 patients enrolled (Germany 1,698, U.S. 1,631, France 1,101, and other 1,233).
  - Serious adverse events 4.5%: infections 1.4%, nervous system disorders 0.9%, immune system disorders 0.6%.
  - 2 cases of PML.

Another poster by Dr. Paul O'Connor of Canada et al reported on the return of disease activity after cessation of Tysabri therapy in patients from the AFFIRM and SENTINEL studies after Tysabri was pulled from the market. In the 946 patients studied, 544 were subsequently treated with either an interferon or Copaxone, and 544 did not receive any of those drugs post-Tysabri. The researchers found disease activity returned to placebo levels by 4 months, and treatment with another agent did not appear to delay the return of disease activity. However, disease activity did not rebound – did not get worse than before Tysabri therapy.

A poster by Italian and U.S. researchers reported delayed infusion reactions with Tysabri are "relatively frequent." They found:

- "Neutralizing antibody tests should be performed in these patients, and if negative, treatment ***must*** be interrupted. Otherwise, natalizumab can be continued since allergic symptoms usually tend to progressively reduce."
- "A reduction of the infusion rate and frequency (every 40-50 days) and treatment with antihistamines or oral steroids can be considered in neutralizing antibody negative patients with persistent delayed reactions."
- "Some patients (40%) with this kind of reaction showed disease activity more frequently than all other natalizumab patients."
- "Re-testing all antibody negative patients showing a reaction even after a first negative result (is a good idea)."

MERCK SERONO's Rebif (interferon-β1a)

To improve patient compliance, reduce discontinuations, and encourage more patients to undergo injectable therapy (with Rebif) will require three things, Dr. Devonshire of Canada claimed: improved patient acceptability, improved convenience, and improved drugs. Merck Serono believes that its new delivery system for Rebif New formulation, RebiSmart, meets those criteria.

RebiSmart was launched in the U.K. in May 2009, in Canada in June, in Denmark and Germany in August, and will be rolled out throughout the rest of Europe this year. A U.S. launch is planned for 2H10.

RebiSmart is fairly cool. It holds 3 doses, keeps track of dosing much like a glucose meter, reduces (but doesn't eliminate) injection pain and reactions, etc. An expert said the prime audience for the device, which is provided free to Rebif patients, is new patients. Dr. Devonshire said, "It is not as complicated as a remote or cell phone…and for the cognitively impaired patient, it is very helpful."

Asked about traveling with RebiSmart, Dr. Devonshire said, "The formula has now changed, so no refrigeration is required…There is no trouble with patients taking devices across the border. We used to supply letters, but we no longer have to do that."

A 6-week RebiSmart user study conducted by Merck Serono found >80% of patients thought the device was very useful and easy to use – and these were people already successfully giving injections.

NOVARTIS's Extavia (interferon-β1b)

Extavia, which is identical to Bayer Schering's Betaseron (Betaferon in Europe), was approved in Europe in May 2008 and in August 2009 in the U.S. There was little discussion of it at ECTRIMS. Novartis sources appeared satisfied with the roll-out so far, with pricing equivalent to Betaferon in France and ~15% less in Germany. A Belgian neurologist said, "We don't use Extavia. The immunogenicity of a new product is my concern. I've never seen the data on Extavia. It hasn't been studied. I need clear data on this first."

AGENTS IN DEVELOPMENT

A survey of 250 MS neurologists, nurses, and other healthcare professionals by the National MS Society and Merck Serono found that:

- 82% are satisfied with their current MS therapy.
- 70% said the most desired improvement in MS therapy is oral administration.
- 49% of neurologists wanted a better balance of safety and efficacy.
- 31% of neurologists wanted less frequent treatment schedules.
- 68% of neurologists believe that MS patients who initially delayed therapy would definitely have started therapy sooner if an oral medication of comparable effectiveness to existing disease-modifying therapies had been available.

When there are more options – multiple oral agents or new biologics like alemtuzumab or daclizumab – most neurologists questioned said they simply do not know how they will choose among them or which patients will get which. Many admitted that it may come down to patient preferences: "Here are the options, which do you want?" Other neurologists hope to guide their patients to the therapies they prefer – when they decide which these are. It will be a balance of convenience, efficacy, and safety. Comments included:

- *Incoming ECTRIMS President Dr. Clanet:* "Patients will want pills. (Yet) all these drugs will probably have a more severe safety profile than the drugs we use now. So, it will be a challenge to follow the patients and manage the risks."
- *Dr. Hans-Peter Hartung, the 2008/2009 president of ECTRIMS:* "(The new orals) come with apparently superior efficacy but rare but significant adverse events. This is nothing new to medicine. Our internist colleagues have been witnessing this for years. It appears that the more efficaciously or significantly you impact the immune system, the higher the risk for rare but severe side effects, and they may just be the mirror side of down-regulating immune responses. So, some aspects of normal protective immunity are compromised. It is our duty as physicians to make a judgment about the right balance. Is the yield in efficacy commensurate with the risks that may be observed with more effective treatments? I don't see that we are witnessing anything entirely new or unexpected. The neurology community is aware of the problems, and the regulatory agencies have clearly

stipulated that with any new biological agent that requires an approval, there is a legal requirement for a risk management program. It is important to be knowledgeable about risk, to minimize it beforehand, and when a patient is on hand to very elaborately monitor (the patient)."

- *Dr. Jerold Chun of Scripps Research in California, a fingolimod researcher, on whether the oral agents will compete with interferons first line or Tysabri second line:* "If the safety profile is adequate, the orals will supersede the other drugs…for compliance reasons. If you give the patient a choice of a pill vs. injecting, it is a no brainer. But one can't lump everything together just because it is oral."
- *Dr. Kappos, Switzerland:* "No one knows how to use the oral medications. At the moment, it may be driven by patients."
- *Incoming ECTRIMS president Dr. Clanet:* "Deciding how to use the orals is very difficult and challenging. They are associated with lots of bad side effects. We don't know the efficacy vs. the interferons and glatiramer acetate because there are no head-to-head trials, and there is a change in patients today. The major side effects may be after five or six years, and we don't have data on that yet…Phase IV studies, pharmacovigilance, and a lot of risk management plans will be needed for them."
- *Dr. Jeffery Cohen, Cleveland Clinic:* "The choice/place for these agents boils down to physician opinions and patient preferences of the risk:benefit…Twenty times a week patients ask me when we will have orals. Half of my patients ask how many *hours* are left until they can stop injecting. I expect the orals to be first line, but not for everyone."
- *Dr. Sibyl Wrap of Tennessee:* "Fingolimod will require a lot of monitoring…Many patients are really tired of shots. Cladribine will be a good choice for them and for newer patients who are older."
- *Ohio:* "I'll use cladribine first line in patients unhappy about injections. They won't have to fail an interferon first. I wouldn't give it to pregnant women, but I would use it in child-bearing women…Some patients will say the orals are too scary and prefer shots, but I have no idea how big this group will be."
- *Switzerland:* "I don't change things that are going well, but I would offer an oral to a new patient and to patients who fail injectables. I'll probably use orals before Tysabri. In a year after they are available, about 10% of patients will be on an oral – half on cladribine and half on fingolimod."
- *Texas:* "If an oral were covered by insurance, 70% of our patients would be on it in a year. They do ***not*** want to keep injecting."
- *Kentucky:* "How to use the orals is the $64,000 question. The CLARITY (cladribine) and TRANSFORMS (fingolimod) data indicate the efficacy looks good, and short-term safety looks good. The issue is long-term safety. Injectables have decent efficacy but excellent safety. I think there will be significant reluctance for ***MS*** neurologists to jump early into treatment with new orals, especially cladribine since it will be first, without more long-term data. It may be easier to sell the orals to general neurologists…Ideally, the orals fit early…In the first year after cladribine is approved, fewer than 5% of my patients will get it. To me, it would be the same situation as Tysabri – an option for someone not doing well on standard therapy." (It has been estimated that in the U.S. ~500 MS neurologists treat ~50% of MS patients.)
- *Belgium:* "The long-term action of cladribine is an issue. A lot of MS patients wish for pregnancy, and it is important to know long-term effects for these patients. Low-dose fingolimod is very active, and that is good because it has lower side effects (than cladribine)…It is not clear whether cladribine is better than fingolimod or vice versa."
- *North Carolina:* "If the combination of laquinimod plus Copaxone is as effective as Rituxan, then that combination will pull the rug out from under the B-cell drugs."
- *Canada:* "Alemtuzumab and cladribine will be more complicated to use than existing first-line therapies. Both will need a risk management plan that tracks them carefully."

Dr. Gold of Germany, speaking at a Biogen-sponsored symposium, suggested this treatment algorithm:

- **First line** – BG-12, pegAvonex, laquinimod, and teriflunomide.
- **Second line** – daclizumab or Tysabri.
- **Third line** – alemtuzumab, fingolimod, cladribine.

Biogen's Dr. Sandrock offered an interesting description of some of the Biogen Idec drugs in development:

- **More convenient therapies:** BG-12, pegAvonex, S1P1.
- **More effective therapies:** anti-CD20, daclizumab, S1P1.
- **Inhibitor of neurodegeneration/enhancing repair:** BG-12, anti-Lingo.
- **Improve physical symptoms:** fampridine.

ORAL AGENTS IN DEVELOPMENT

Neurologists are expecting strong demand for oral agents from patients. In fact, patients are already asking about them at every visit. Many doctors expect to take a conservative approach to use of the new agents and think their patients will do what they recommend. Others, perhaps more realistically, acknowledge that patients more than neurologists have driven the adoption of other therapies and predicted the same will occur with the oral agents.

Where the oral agents fall in the tier of options – first, second, or third line – will depend on the final safety profile, most neurologists agreed. They do not expect patients doing well on injectables to switch to an oral, but other neurologists – and some MS nurses – insisted that there are significant numbers of patients on injectables who want to get rid of the needles and, for interferon users, the flu-like side effects.

Most doctors believe that a safe oral agent will expand the number of MS patients on treatment. They also generally believe that a significant percentage of patients will switch from an injectable to an oral. A year after the first oral drug is approved, doctors estimated that 23% of their MS patients would be on it, but the range was from 5% to 70%, and no one was very confident in the estimate.

BIOGEN IDEC's BG-00012 (dimethyl fumarate)

BG-12 is almost a sleeper drug among the orals. Speakers sometimes even left it off the list of oral agents in development. Partly, this may be because there was no real news about it at the meeting. But it is in Phase III trials and has fast-track designation from the FDA.

- **DEFINE** trial of BG-12 vs. placebo in RRMS . It is fully enrolled.
- **CONFIRM** trial of BG-12 vs. placebo and vs. Copaxone. This trial also is fully enrolled.

Biogen's Dr. Sandrock emphasized that BG-12, an enteric coated microtablet, is actually well-known in Europe – as Hemoderm, a treatment for psoriasis – and that, therefore, it has a long track record for safety.

BG-12 appears safe; the issue is dosing. It currently has to be taken TID. BID dosing is being explored, but an expert predicted that the BID won't work, at least on a MRI basis, or the dose will have to be too high to tolerate.

Dr. Giancarlo Comi of the University Vita-Salute in Milan, Italy, commented during his review of oral agents, "The drug probably has some neuroprotective possibility because of the interaction with the Nrf2 pathway which is important for removal of products of the metabolic activity of the brain, and I think the antioxidant possibilities for neuroprotection…Only the high dose showed a significant drop in lesions…The annualized relapse rate was difficult to establish because of the short duration of the trial. Safety is not a real problem."

DAIICHI SANKYO's CS-0777

This S1P1 competitor to Novartis's fingolimod is still in early development; it's just starting a 12-week, Phase I, dose-finding study. It can't be differentiated yet from fingolimod, but the strategy is in the dosing; Daiichi Sankyo is starting with very low doses (0.1 mg and 0.3 mg ***weekly***) and working up to find the right dose, while Novartis started with a high dose (5 mg) and has worked down to 0.5 mg. Daiichi Sankyo hopes that its lower – and less frequent – dosing may reduce the level of side effects, though the types of side effects are the same – lymphopenia, bradycardia, and the potential for liver injury. A CS-0777 researcher said Novartis is seeing the same side effects with its follow-on S1P1, BAF-312. CS-0777 also appears to be safe in healthy males up to 2.5 mg.

Oral Drugs in Development

Drug	Company	Type of drug	Status	Efficacy	Safety/usage issues
BAF-312	Novartis	S1P1 receptor modulator	Phase II	Unknown	Unknown
BG-00012	Biogen Idec	Immuno-modulator	Phase III	Comparable to laquinimod	Difficult to tolerate at first, TID
Cladribine	Merck Serono	Cytotoxic	Submitted to FDA	Comparable to interferons; ~80% of patients free from relapse	Teratogenicity, long-term immunosuppression, cancer risk, can't switch to Tysabri. 1 case of PML in CLL. Convenient with only 2 courses per year
CS-0777	Daiichi Sankyo	S1P1 receptor modulator	Phase I starting	No data yet but likely similar to fingolimod	Lymphopenia, bradycardia, potential for liver injury (same as fingolimod) but perhaps less frequent due to lower dosing
Fingolimod (FTY-720)	Novartis	S1P1	Phase III ongoing, expected to file with FDA by end of 2009	Very good; superior to Avonex; ~77% of patients free from Gd+ lesions	Multiple issues but mostly manageable. Most concerning: skin cancer and herpes
Laquinimod	Teva/ Active Biotech	Immuno-modulator	2 Phase III trials ongoing	Good (tested in sicker patients than fingolimod or cladribine)	Very safe. May be able to be combined with other therapies
Teriflunomide	Sanofi-Aventis	Immuno-modulator	Phase III	Almost as good as interferons	Teratogenicity, long-term immunosuppression, liver toxicity; can't switch to Tysabri
(Unnamed)	Biogen Idec	S1P1 receptor modulator	Early development	Unknown	Unknown

MERCK SERONO's cladribine

There were numerous posters on cladribine but only a little new data. The key finding was that the higher dose was not better than the lower dose on annualized relapse rate (ARR) or on MRI lesions, though the higher dose may have an incremental benefit in the subgroup of patients with ≥1 T1 Gd+ lesions at baseline. This is confusing since the lower dose in CLARITY failed to show significant activity in an earlier trial. An oral presentation on safety from the 96-week Phase III CLARITY trial raised no real issues. The full CLARITY results are expected to be published in a major medical journal very shortly.

An investigator, Dr. Stuart Cook of the University of Medicine and Dentistry in New Jersey, said:

- The lymphopenia was expected, given the method of action of this drug.
- 20 patients had 21 herpes zoster events in the cladribine groups. All 21 cases were self-limiting and dermatomal. None were disseminated.
- 3.2% of the patients developing Grade 3-4 lymphopenia at any time during the study developed herpes zoster vs. 1.8% of those that did not develop Grade 3-4 lymphopenia. 70% of patients with herpes zoster had normal lymphocyte counts or lesser grade lymphopenia at the approximate time the herpes zoster appeared.
- Giving this drug to pregnant women will likely be contraindicated (Pregnancy Class D), and there may also be a warning about men wanting to father children. Dr. Douglas Jeffery of Wake Forest University in North Carolina said women will have to be off cladribine for two years before getting pregnant.

Asked about the cancer cases with cladribine, Dr. Cook said, "Obviously, cancer is a concern…There were too few cancers to be certain this has a relationship to the drug. Obviously, this is something that needs to be observed…We looked at the relative risk of having cancer based on age, sex, geography, and we didn't find a difference. That isn't to say there isn't a difference, but at this point there are too few cases to say."

The key posters on cladribine and CLARITY showed:

1. The **annualized relapse rate** was comparable for both doses tested.
2. The **high dose** may have incremental benefit in patients with ≥1 lesion at baseline. In these patients, the odds ratio for disease-free activity with cladribine was 8 with the low dose, 16 with the high dose.

96-Week CLARITY Trial Results of Cladribine in RRMS

Measurement	Placebo n=435	Cladribine 3.5 mg/kg n=430	Cladribine 5.25 mg/kg n=454	Cladribine overall n=884
Efficacy				
Change in T2 lesion volume (by ITT)	- 4.1%	- 9.5%	- 14.2%	---
Patients free of T1 Gd+ lesions	48.3%	80.8%	91.0%	---
Patients free of active T2 lesions	28.4%	61.7%	62.6%	---
Patients with no lesions at baseline who were free of disease activity at 96 weeks	21%	51.5% (OR 3.99)	46.6% (OR 3.28)	---
Patients with ≥1 lesion at baseline who were free of disease activity at 96 weeks	3.9%	24.6% (OR 8.04)	39.5% (OR 16.03)	---
Any treatment-emergent adverse event	73.3%	80.7%	83.9%	82.4%
Adverse event leading to discontinuation	2.1%	3.5%	7.9%	5.8%
Adverse event leading to withdrawal	1.1%	1.2%	2.2%	1.7%
Serious adverse event	6.4%	8.4%	9.0%	8.7%
Deaths	0.5% (2 patients)	0.5% (2 patients)	0.4% * (2 patients)	0.4% (4 patients)
Adverse events				
Headache	17.2%	24.2%	20.7%	22.4%
Lymphopenia	1.8%	21.6%	31.5%	26.7%
Nasopharyngitis	12.9%	14.4%	12.8%	13.6%
Upper respiratory infection	9.7%	12.6%	11.5%	12.0%
Leukopenia	0.7%	5.6%	8.6%	7.1%
Neutropenia	0.5%	1.9%	2.2%	2.0%
Alopecia	1.1%	3.5%	3.1%	3.3%
Uterine leimyomas	0.2%	1.2%	0.9%	1.0%
Adverse events of special interest				
Any infection/infestation	42.5%	47.7%	48.9%	48.3%
Serious infection/infestation	1.6%	2.3%	2.9%	2.6%
Herpes zoster	0	1.9%	2.4%	2.1%
Herpes zoster oticus	0	0	0.2%	0.1%
Varicella	0.2%	0.2%	0.2%	0.2%
Malignancies				
Malignant melanoma	0	0.2%	0	0.1%
Ovarian cancer	0	0.2%	0	0.1%
Metastatic pancreatic cancer	0	0.2%	0	0.1%
Choriocarcinoma during post-study surveillance	0	0	0.2%	0.1%

*** One of these was related to TB-reactivation, so patients are now screened for TB.**

3. An 8-year, observational, prospective **safety registry** is planned at ~500 sites. As many patients as possible from all of the cladribine Phase I, II, and III studies will be enrolled (~2,000), starting in October 2009. In particular, patients will be monitored for death, severe infections, malignancies, pregnancies and pregnancy outcomes, myelodysplastic syndromes (MDS), and hematologic toxicity.
4. The **higher dose** showed a slightly better improvement on MRI lesion numbers. An investigator said, "The higher dose is more immunosuppressive on cells, so maybe there are individual patients who will need the higher dose." Merck Serono's Dr. Greenberg said, "Our recommendation is the low dose…There are some signals and trends to a slight potential benefit to the higher dose (T2 volume data)." And he pointed out that the failure of the low dose in a prior trial was in a different patient population – progressive MS patients, not RRMS. He said the company is continuing the high dose because "at baseline we identified patients with more disease activity who might benefit…We are suggesting physicians may reserve the high dose for patients with more disease activity."

Merck Serono has a crossover trial underway which may definitively answer the question of the value of high vs. low dose. Patients initially divided into high vs. low dose vs. placebo are being re-randomized at the end of that period into five groups. The data should be available at the end of 2010 or early 2011, though there may be an interim analysis:

- Low dose continued on low dose.
- Low dose switched to placebo.
- High dose switched to low dose.
- High dose switched to placebo.
- Placebo switched to low dose.

At a Merck Serono-sponsored session, Dr. Gavin Giovannoni from London emphasized how effectively and quickly this drug works, concluding, "These (CLARITY) results were achieved with only 8-20 days of oral therapy in the first 48 weeks and only 8-10 days of therapy in the second 48 weeks…Short-course oral therapy with cladribine may provide an important new option in MS.

Asked about the need for a comparator-controlled study, Dr. Giovannoni said, "We would like comparative data…There is an add-on study ongoing, mainly for safety. There are a lot of additional questions to be addressed in future studies. For right now, the efficacy is robust…and my personal opinion is I don't think we need more efficacy data to start using this, but we do need long-term safety data…At the end of the extension study we will have information on what to do long term. It is unclear how long we can give this. Hopefully, the extension study will answer that."

Asked how far lymphocyte counts go down, Dr. Cook said CD3 T-cells drop to ~600 with low dose and ~500 with high dose and stay low through 96 weeks. CD19 B-cells drop but also rapidly come back to close to normal over 48 weeks then drop again on re-treatment. The CLARITY protocol was amended to say that re-treatment should be delayed if one or more of these occur:

- Lymphocytes <500
- Leukocytes <2,000
- Neutrophils <1,000
- Hemoglobin <8.0 g/dL
- Platelets <50,000

Asked where and how cladribine should be used, Dr. Giovannoni said, "I suspect this will be used first, second, and third line. I can see patients on injectables switching. Even Tysabri patients who have had enough infusions or have questions about the risk. We have to be open about the fact that this is a new treatment, and we don't have long-term data, and the patient who takes it must be aware there could be risks down the line."

Asked what to do with patients who fail on cladribine, Dr. Peter Rieckmann of Germany and Canada said that is difficult to determine at this point. Dr. Cook said, "One could look at the risk:benefit ratios of other drugs, and I think that we have to see if it is safe to add other drugs or if you have to wait until the CD4 count comes up. We will have to experience that as time goes on." Another U.S. neurologist said, "If a person relapses on cladribine, you could go with any injectable, though Copaxone is probably the safest. A patient could fail Copaxone, take cladribine, then go back to Copaxone and respond."

Asked why cladribine couldn't be given monthly instead of yearly, Dr. Rieckmann said, "The mechanism of action is that the drug targets stem cells, so the return is very, very slow. It doesn't matter how you give it; the effects are long term. It is what I call an immune system re-booter. Alemtuzumab is a similar philosophy."

Asked if there is a "simple" dose of cladribine, Dr. Fodor Heidenreich of Germany said, "There is not a simple dose. It needs a lot of thinking and cooperation with the neurologist to find the appropriate dose and handle it. It isn't the case that the patient is seen for five days and then a year later. The patient needs close counseling with apparently simple drug." Dr. Giovannoni added, "I see us having to use this drug intelligently…It won't be fixed dosing."

Merck Serono also is running a global trial in clinically isolated syndrome (CIS) patients, ORACLE-MS. An official said, "We don't know if a drug like cladribine, offered early, could change the course of the disease and have the best chance of putting the disease into sustained remission. About 120 patients have been enrolled so far out of a planned 642 patients.

NOVARTIS's fingolimod (FTY-720)

The fingolimod Phase III program includes three trials:

1. **TRANSFORMS** – 0.5 mg and 1.25 mg fingolimod vs. 30 µg Avonex in RRMS. This 1,292-patient, one-year, double-dummy (sham injection) trial is completed, and some data have been released, including some additional details at ECTRIMS. An extension study is ongoing.
2. **FREEDOMS** – 0.5 mg and 1.25 mg fingolimod vs. placebo in RRMS. Top-line data from this two-year trial in 1,272 patients will be released in 4Q09, and Novartis expects to file on fingolimod with the FDA by the end of 2009, but the FREEDOMS data won't be presented until the American Academy of Neurology meeting in 2010 or ECTRIMS 2010. An extension study will be conducted.
3. **FREEDOMS-II** – 0.5 mg and 1.25 mg fingolimod vs. 30 µg Avonex in RRMS. This 2-year, ~1,080-patient trial is fully enrolled and ongoing.

There were some additional details from the TRANSFORMS trial at ECTRIMS, but Novartis was "not promoting" the results of this trial, ostensibly because it expects journal publication (***New England Journal of Medicine***) in 1H10. The key issues in these data are:

- The **higher dose** (1.25 mg) did ***worse*** on efficacy – at least in terms of relapses – than the low dose (0.5 mg). There was no statistically significant difference between the 2 doses, but the higher dose clearly wasn't better and actually was numerically worse. Thus, there isn't any difference between the two doses on efficacy.
- The **lower dose** (0.5 mg) was safer than the higher dose. This raises a question whether the FDA will want another trial of an even lower dose since there now is no dose-response curve. The principal investigator, the Cleveland Clinic's Dr. Cohen, predicted that the lower dose would be the dose approved. He thinks it is unlikely the FDA will require a pre-approval lower dose study, but the FDA may stipulate it wants a lower dose study post-approval. There were some hints at the meeting that it may be technically difficult for Novartis to take the dose lower than 0.5 mg, but investigators reportedly have been pushing for a lower dose. However, Dr. Jeffery of North Carolina said the higher 1.25 mg dose was more effective on MRI measures but not on relapses.
- To enter this trial, patients had to have had MS activity recently, but patients could enter this trial if they were **Avonex failures**, and it is not clear how that affected the results. Dr. Cohen said he has asked the company for information on what percent of patients had trial-qualifying activity while on Avonex, but the company hasn't provided that information yet. He doubts the number is high, but it is a detail that needs to be nailed down. In the trial, the Avonex relapse rate was lower than would have been expected, which might argue against the trial having too many Avonex failures in it, but, again, this needs to be examined.

Novartis experts wouldn't speculate on what the FDA advisory committee issues are likely to be until they see the results of the Phase III trials. Dr. Chun from Scripps said that the 0.5 mg (low dose) "will be really interesting to watch." However, neurologists expect the lack of a dose-response curve to be an issue – along with all the myriad safety issues. On the safety issue, Dr. Comi commented, "It is almost impossible to have an effect on the immune system without accepting some cost."

TRANSFORMS Phase III Trial Results with Fingolimod

Measurement	Avonex 30 µg	Fingolimod 0.5 mg	Fingolimod 1.25 mg
ARR	0.33	0.16 (<0.001 vs. Avonex)	0.20 (<0.001 vs. Avonex)
Adverse events			
Any adverse event	91.6%	86.0%	90.5%
Adverse event leading to discontinuation	3.7%	5.6%	10.0%
Serious adverse event	5.8%	7.0%	10.7%
Death	0	0	2 patients
Any infection	50.8%	51.7%	52.6%
Any serious infection	1.4%	0.2%	1.7%
Any bradycardia	0	0.5%	2.4%
Symptomatic bradycardia	N/A	0.7%	1.0%
Herpes viral infections	0.2% (1 patient)	0.2% (1 patient)	0.7% (3 patients)
Macular edema	0	2 patients	4 patients
ALT 3xULN	2%	8%	7%
Basal cell carcinoma	0.2%	0.7%	0.5%
Squamous cell carcinoma	0.2%	0	0
Malignant melanoma	0	0.7%	0
Breast cancer	0	0.5%	0.5%

60-Month Phase II Extension Study with Fingolimod

Measurement	Placebo	Fingolimod 0.5 mg	Fingolimod 1.25 mg
Still on therapy at Month 60	N/A	50%	
Relapse-free	N/A	2/3 of patients	
Free of GD+ lesions	N/A	>92%	
ARR	0.23	0.17	0.19
Adverse events			
Nasopharyngitis	31%	39%	45%
Headache	31%	37%	27%
Flu	16%	29%	23%
Back pain	20%	17%	18%
Lymphopenia	13%	17%	17%
Serious adverse events			
Bradycardia	1 patient	0	3 patients
Chest pain	0	1 patient	2 patients
Macular edema	0	2 patients	1 patient
Anxiety	0	2 patients	0
Asthma	0	0	2 patients
Cholelithiasis	0	2 patients	0

On specific fingolimod safety issues:

- **Deaths** in TRANSFORMS:
  - **a.** Two deaths occurred during the trial, both on the 1.25 mg dose, and both were due to herpes infections.
  - **b.** Two deaths occurred after the end of the study in patients who had taken 1.25 mg fingolimod:
    - → A man with rapid neurological progression prior to study entry who developed a respiratory tract infection after 11 months of fingolimod therapy. Upon discontinuation of fingolimod, the man's neurological deficit progressed, and he died of aspiration pneumonia six months after discontinuation. PML was excluded.
    - → A woman who died of metastatic breast cancer 10 months after discontinuing fingolimod.
- There is a rare but serious increase in the risk of **infection**, especially herpes.
- The **heart rate elevation** with fingolimod is apparently a first-dose effect and "common but not serious." A poster looked at the effect on heart rate when fingolimod is combined with atenolol, diltiazem, atropine, or isoproterenol. The study found adding fingolimod to the beta blocker atenolol results in a moderately lower mean heart rate vs. fingolimod alone, but adding fingolimod to the calcium channel blocker diltiazem did not further lower heart rate compared to fingolimod alone. Atropine and isoproterenol were effective in reversing the transient negative chronotropic effects associated with initiating fingolimod therapy.
- There may be an increase in **skin malignancies**.

Novartis was emphasizing the "unique" method of action of fingolimod. Dr. Kappos of Switzerland reviewed the scope of the whole fingolimod program, highlighting:

- >5,300 patient-years.
- 975 patient-years in Phase II (146 with >4 years and 70 with >5 years).
- ~4,930 patient-years in Phase III, with 953 patients on drug ≥2 years.
- The effect on Gd+ lesions is maintained out to 60 months, and patients who continued in the study long term had only minimal disease activity.

NOVARTIS's BAF-312

This is Novartis's follow-on to fingolimod, and it is already in Phase II development. The reported goal is a safer S1P1 receptor modulator.

There were 3 posters on BAF-312 at ECTRIMS:

1. **Phase I study** characterizing the transient heart rate reduction seen with initiation of BAF-312 (at doses of 0.3 mg, 1 mg, 2.5 mg, 10 mg, and 20 mg). The study found the heart rate decrease peaked at 2 hours after the first dose, concluding it could be well monitored.
2. **Preclinical study results and a multiple ascending dose study in healthy volunteers.** Researchers found the clinically relevant half-life is ~30 hours. The most common adverse events were headache (28%) and dizziness (6%), with a transient dose-dependent decrease in mean ventricular heart rate on Day 1, but only sporadic, non-dose-dependent heart rate changes were noted after that first reaction. After stopping treatment, lymphocyte levels turned to steady state levels in 98 hours.
3. **Phase II BOLD trial adaptive study design.** This dose-finding trial is underway comparing 0.5 mg/day, 2.0 mg/day, and 10.0 mg/day to placebo over 180 days, with an interim analysis after the first 90 days to determine the doses to be used in the second 90 day period.

SANOFI-AVENTIS's teriflunomide

A poster reported on the combination of safety and efficacy of teriflunomide (7 mg/day or 14 mg/day) plus interferon-beta vs. interferon-beta alone in a 6-month, placebo-controlled study which randomized 117 patients. The study found both doses of teriflunomide had acceptable tolerability and safety when combined with interferon-beta, and teriflunomide improved disease control beyond the level with interferon-beta alone.

Dr. Comi commented that teriflunomide appears to be a potent oral immunomodulator, with no effect on resting lymphocytes and perhaps some protection against the risk of infections.

Safety and Efficacy of Teriflunomide

Measurement	IFN-β n=41	IFN-β + teriflunomide 7 mg n=37	IFN-β + teriflunomide 14 mg n=38
Gd+ T1 lesions	0.743	0.337 * (56% reduction)	0.139 * (81% reduction)
Patients free of Gd+ lesions	57.9%	69.4%	81.6%
Safety			
Any treatment-emergent adverse event	85.4%	89.2%	84.2%
Serious treatment-emergent adverse events	2.4%	5.4%	0
Infections/infestations	29.3%	35.1%	34.2%
Neurological symptoms	17.1%	16.2%	31.6%
Skin	4.9%	18.9%	13.2%
Musculoskeletal	9.8%	16.2%	15.8%
Respiratory disorder	14.6%	8.1%	10.5%
GI	17.1%	10.8%	18.4%
Psychiatry (e.g., anxiety/sleep disorder)	0	8.1%	5.3%

* $p<0.001$

TEVA/ACTIVE BIOTECH'S laquinimod (ABR-215062)

Like the other companies with a new agent in late-stage development, Teva sponsored a session on laquinimod at ECTRIMS. It was very well attended, and the speakers made a strong case for this once-daily oral drug, which is currently in two Phase III trials. A speaker said it has a half-life of ~72 hours, does not accumulate in the body following long-term (36 week) exposure, is metabolized by CYP3A4 (so inhibitors of CYP3A4 are contraindicated), and there is no effect on cardiac repolarization or any other ECG parameters. Dr. Wolfgang Brück of the University Medical Centre Gottingen in Germany called laquinimod a "safe oral drug…This has an excellent risk:benefit ratio."

- **ALLEGRO** – a >1,100-patient, open-label, extension study in RRMS comparing 0.6 mg laquinimod to placebo over 24 months.
- **BRAVO** – a ~1,300-patient trial of 0.6 mg laquinimod vs. placebo and vs. Avonex 30 mg/week for 24 months in RRMS. The trial will be followed by an open-label extension study.

One of the questions overhanging laquinimod – a derivative of linimone, which was developed as an anti-angiogenic agent for oncologic use but was associated with cardiotoxicity – has been its method of action. At ECTRIMS 2007, the lack of information on method of action was a topic of discussion. At ECTRIMS this year, Dr. Brück provided a detailed look at the method of action of laquinimod. He said laquinimod is an immunomodulator with both anti-inflammatory and neuroprotective properties, shifting the cytokine balance toward a Th2/Th3 profile, reducing immune cell infiltration into the CNS, and inducing myelin and axonal preservation.

Among the points Dr. Brück made were:

- Laquinimod does not affect cell viability or cell proliferation in high doses (10-20 times the human dose) or with long-term exposure.
- It is not an immunosuppressive agent; it is an immunomodulator that is not toxic to peripheral monocytes or lymphocytes.
- It has an effect on inflammation, demyelination, and axonal neurodegeneration with:
  - Effect on acute and chronic EAE (experimental autoimmune encephalitis, a model of MS) in preventive and therapeutic approaches.
  - Effects on cytokine production in mice and *in vitro* (healthy volunteers).
  - Effect on PPMS (primary progressive multiple sclerosis) from RRMS patients.

The animal data, which Dr. Brück contended can be transferred to humans, was summarized as follows.

In ***mice***, laquinimod:

- Reduces T-cell infiltration into the spinal cord and reduces leukocyte infiltration into the CNS.
- Reduces the product of the pro-inflammatory cytokine IL-17.
- Dose-dependently inhibits disease development in IFN-β knockout mice and in wild type mice. Its efficacy is independent of IFN-β.
- Reduces spinal cord demyelination and axonal loss. The lesions are smaller and the amount of demyelination is considerably less than control animals. If axonal densities are compared by electronic microscopy, there "is a clear axon preservation in demyelinated lesions. Axons are better preserved in laquinimod-treated animals than control, indicating an effect beyond the immunomodulatory effect."
- Reduces axonal loss and demyelination in optic neuritis, reducing disturbances of axonal transport and providing a protective effect.

In ***rats* with EAE**, laquinimod:

- Induces a cytokine shift from Th1 to Th2.
- Inhibits expression of IL-12 and TNF-α mRNA and up-regulated expression of TGF-β mRNA in the spinal cord.
- Reduces inflammation in the sciatic nerve.
- Reduces inflammation and demyelination in the peripheral nervous system.

Dr. Comi of Italy reviewed the clinical data on laquinimod. He pointed out that the Phase II data showed that the high dose (0.3 mg) had "some evidence of activity and reduced MRI activity," but that activity was "not very high," and the lowest dose (0.1 mg) was no different from placebo. The effect was apparent early in treatment (after the first 8 weeks of therapy). A second Phase II trial, published last year in ***The Lancet***, found no significant effect with the 0.3 mg dose either – but the 0.6 mg dose was effective on the primary endpoint of Gd+ T1 lesions and trended positive on annualized relapse rate (ARR), p=0.0978. Dr. Comi said Teva is exploring a 0.9 mg dose in a Phase II trial. Dr. Comi commented, "It's not as effective as Tysabri, but it is safe."

Bottom line, sources here agree, is that laquinimod is likely mildly effective – but very, very safe, with no excess of infections or side effects as seen with other agents. Can Teva sell it? Sources think so. After all, they sold Copaxone when no one thought patients would use it. The adverse event to watch is liver enzyme elevation, but there has been no liver failure, and the ALT elevations were transient and normalized on drug and reversed upon discontinuation.

In new data from Phase II extension studies, Dr. Comi noted that:

- Patients who moved to active treatment from placebo responded to both doses (0.3 mg as well as 0.6 mg).
- The effect seen in the first 9 months is not lost in the next 9 months.
- With increased exposure, there was a ***decrease*** in the incidence of liver elevations.
- There were no opportunistic or life-threatening infections, no cardiac events suggestive of MI, and no increased rates of specific malignancies.
- Further reduction in MRI activity over 3.5 years of exposure to the drug, which might be explained by regression to the mean. "We can say this drug in >3 years of treatment doesn't lose any effect."

Asked if there was any effect on lesion evolution (an increase in BDNF), Dr. Comi said, "This is something possibly to look at, and I see (Teva officials) nodding their heads."

NON-ORAL AGENTS IN DEVELOPMENT

Dr. Tullman of Columbia University commented, "So far we have not been able to improve efficacy (over the injectables) without sacrificing safety. One of the lessons we learned from rituximab is that it was on the market for 9 years for non-Hodgkin's lymphoma and rheumatoid arthritis, with ~300,000 patients treated before there was a concern about an increased risk of PML. Currently, there have been 57 cases of PML (with rituximab)…but the overwhelming majority of these (52) had lymphoproliferative disorders."

Genentech's withdrawal of Raptiva (efalizumab), a psoriasis therapy, from the market due to several (3 and maybe 4) cases of PML, has made neurologists more nervous about new biologics. The Raptiva cases occurred in patients treated for more than three years. At the time 5,100 patients had been treated with Raptiva for more than 2 years, so the rate was 1:1,275 or 1:1,700. Neurologists now are concerned that the rate of PML with Tysabri – or other investigational agents – could escalate with time.

Until there is more information on PML and other side effects with the new agents, Dr. Tullman said doctors will have to consider many things in making a treatment decision: safety, tolerability, convenience, monitoring requirement, pregnancy issues, cost, patient preference, physician experience, response, and method of action. Dr. Hartung said, "I think the monoclonal antibodies carry the advantage of providing exquisite specificity. It appears they also have increased efficacy, and they would offer the advantage that they need to be administered only infrequently. However, there are a number of caveats: B-cell depletion or silencing may interfere with the protective immune response, the long-term effect on immune response needs to be determined…and there are appearances of rare but serious side effects…Nevertheless, I think this is a very exciting part of the evolving exploration of novel agents. We clearly need to be aware of the potential side effects and to balance the risks and benefits."

BIOGEN IDEC's "pegAvonex" (BIIB-017, pegylated interferon-β1a)

The biologic activity and tolerability of pegAvonex is similar to Avonex. The only real difference is less frequent dosing – every other week or monthly – and subcutaneous injections instead of intramuscular injections.

Non-Oral Investigational Agents

Drug	Company	Type of drug	Status	Efficacy	Safety/usage issues
Anti-Lingo	Biogen Idec	Anti-Lingo antibody	IND to be filed in 2009, Phase I to start in 2010	Unknown	Unknown
Atacicept	Merck Serono/ ZymoGenetics	B-cell inhibitor	Failed in Phase II for toxicity	Unknown	Toxicity
Campath (alemtuzumab)	Genzyme/Bayer	Anti-CD52 Mab	Phase III trials fully enrolled	Excellent	ITP, thyroid, Goodpasture's, PML cases in oncology
Ocrelizumab	Roche/Genentech	Humanized anti-CD20 Mab	Phase II to be completed in 2009	Unknown	Unknown
Arzerra (ofatumumab, formerly HuMax-CD20)	GlaxoSmithKline/ Genmab	Anti-CD20 Mab	Failed for toxicity, on hold	Unknown	Unknown
"pegAvonex"	Biogen Idec	Pegylated-interferon-β1a	Phase II	Similar to Avonex	Similar to Avonex but less frequent dosing (Q2W or Q4W) and subcutaneous rather than IM injections
Rituxan (rituximab)	Roche	anti-CD20 Mab	Failed Phase III trial in PPMS	Uncertain	PML, infections, infusion reactions
Zenapax (daclizumab)	Facet Biotech/ Biogen Idec	anti-IL-2 hMab	Phase II registration study ongoing; Phase III pivotal study to start in 1H10	Very good	Very good; extensive experience in transplant rejection
Stelara (ustekinumab, CNTO-1275)	Johnson & Johnson	Anti-IL-12/23 Mab	Failed Phase II. No efficacy in RRMS vs. placebo	No efficacy in RRMS	Infections, possible cancer link

Because it has fast-track status from the FDA only a single trial is required, ADVANCE. This ~1,260-patient, parallel-group, placebo-controlled study of two dosing regimens (125 µg Q2W and 125 µg Q4W) is still enrolling patients.

Asked why the control was placebo and not Avonex, Dr. Sandrock said, "Regulators do not accept non-inferiority or bioequivalence trials for approval. It is difficult to demonstrate efficacy. There are methodological reasons for that. We discussed this with multiple European regulators and the FDA. The only way to demonstrate efficacy today is by doing a superiority trial either vs. placebo or another drug. In this case you can't demonstrate superiority over Avonex, so we are doing a one-year efficacy trial."

He said the FDA restriction on non-inferiority trials "is a restriction in MS…because the placebo rate has changed dramatically over the years…If a drug has a low rate, it could be like placebo. That is why the FDA and European regulators shy away from non-inferiority trials (in MS)."

FACET BIOTECH/BIOGEN IDEC's Zenapax (daclizumab)

At ECTRIMS, Facet, which Biogen Idec is buying, presented the results of a subanalysis of data from the Phase II CHOICE trial, looking at CD56^{bright} NK cell expansion. Investigators believe the expansion of CD56^{bright} NK cells may be a biomarker of daclizumab activity and may contribute to its mechanism of action. A researcher said, "This is a potentially extremely valuable biomarker." He said the test is a standard assay by flow cytometry measuring CD56^{bright} NK cells in peripheral blood.

(Remember, CHOICE met its primary endpoint at the 2 mg/kg dose + interferon vs. interferon alone, showing a 72% reduction in ARR with 2 mg/kg subcutaneous). The key findings of the subanalysis were:

- Daclizumab rapidly and significantly expanded CD56^{bright} NK cells in a dose-dependent manner, and expansion of CD56^{bright} NK cells correlated with a reduction in new or enlarged Gd+ lesions.
- Daclizumab-treated subjects in the top 25% in terms of CD56^{bright} NK cell expansion had a statistically significant 87% reduction in new and enlarged Gd+ lesions vs. interferon alone.

The Phase II/III SELECT trial, the first of two registration trials, is currently enrolling RRMS patients in Europe. The second registration trial, the Phase III DECIDE study, is expected to start in 1H10, and it will be an active comparator study.

GENZYME/BAYER's Campath (alemtuzumab)

At a Genzyme/Bayer-sponsored session, Alisdair Coles, Ph.D., of the U.K. said the four-year data on the original alemtuzumab patients indicates both that alemtuzumab is "profoundly effective" but also that the risk of accumulating disability remains 73% less than in patients on Rebif out to three years after the last dose, "The annualized relapse rate doesn't change over the four years, which is evidence for continued and durable efficacy."

In terms of safety, Dr. Coles said there were "remarkably very few infections and those that occur are predominantly mild/moderate in severity…We continue to see thyroid autoimmunity (28%), but these all respond in a conventional way to thyroid medication…The total of Goodpasture's syndrome is now two…There are delayed autoimmune disease, which require a robust risk management program, but so far that appears to be successful. The recent Goodpasture's case was picked up early, treated, and now has near normal renal function." Dr. Eva Havrdova of the Czech Republic said the monitoring program for the two CARE-MS studies was not difficult, "Laboratory monitoring is easy. It's a blood test that can be done at any lab – a CBS plus quarterly TSH screening. Then, there is clinical follow-up by phone or office survey of patients to ask for signs and symptoms."

ITP (idiopathic thrombocytopenic purpura), thyroid disorder, and Goodpasture's syndrome are the concerning side effects with alemtuzumab. Neurologist comments included:

- "The great excitement, in my opinion, is the question this drug asks: If you induce a strong immune modulation at the beginning of the disease, will we have a long-term effect? Alemtuzumab blocks the activity of the disease and relapses for three years…It's a big gun used early in the disease."
- "I don't know how to put (the safety profile or the Goodpasture's case) in context yet."
- "Alemtuzumab will be a rescue drug of last resort. No question the efficacy is fantastic, but the issue is when the risk is worth it. Goodpasture's is rare (<1%), but there have been several cases, and it is a deadly disorder with high mortality…Community neurologists won't do alemtuzumab; it will be special referral centers."

Bruce Roberts, Ph.D., of Genzyme said a transgenic mouse has been developed, and it has produced some mechanistic insights, including:

- There is a dose-dependent, prolonged depletion of CD4 and CD8 T-cells and B-cells in tissue.
- T- and B-cell depletion is less complete in lymphoid organs than in blood, so reservoirs of lymphocytes are spared, which may explain the low rates of infection with alemtuzumab.
- B-cells recover more rapidly than CD4 or CD8 T-cells.

- There is limited depletion of neutrophils and NK cells (in the mouse).

Asked if there is need for more than 2 alemtuzumab treatment cycles, Dr. Havrdova said, "Alemtuzumab is not a cure, so we can expect that in some patients disease activity may recur. For those responding, additional treatment cycles might be offered, but on a different basis. We won't offer a 3rd cycle at 24 months…If a patient develops a relapse or 2 MRI lesions, then another alemtuzumab cycle will be offered, but not earlier than 12 months after the last alemtuzumab dose."

Asked how many cycles can be given, Dr. Havrdova said, "These are important practical questions and important academic questions…but it is fair to say that there is clear evidence or a strong hint that three cycles is superior to two cycles in terms of efficacy with no obvious difference in risk, though the number of patients who got three cycles in formal trials is still small…We are very much exploring this…as to what is the preferred protocol...but I personally think it will be more than two cycles."

Asked if Copaxone could be started concomitantly or after two years of alemtuzumab therapy, a speaker said, "Certainly, one could speculate that it might be possible to steer the reconstituting immune system into a beneficial direction. To park the reconstituting cells in an area with a…substance like glatiramer acetate…That is slightly different from the concept of combination therapy in which you are hammering the disease process from two angles simultaneously…We don't rule out combinations."

Asked how many of the 22 patients with 8 years of follow-up from the initial alemtuzumab study have developed progressive disease, a speaker said, "We have 54 patients with early RRMS for 10 years, and none have yet gone to SPMS (secondary progressive multiple sclerosis)."

Asked what happens if alemtuzumab patients get the swine flu, a speaker said, "We've had several patients get the swine flu (and there were no issues)."

ROCHE's Rituxan (rituximab)

A poster by German researchers reported on the use of Rituxan in 8 patients with neuromyelitis optica (NMO) who did not respond to standard immunotherapy. 2 g Rituxan was administered in two bi-weekly infusions. The results were:

- Clinical stability in 4 of 5 patients treated >2 years. But they noted that the observation period is not long enough to draw a final conclusion.
- 1 patient died a few days after the first course.
- 1 patient had no clear benefit.
- 1 patient had no clear data.

The researchers noted that disease activity may be associated with the reappearance of even a small number of circulating B-cells, adding, "Due to the severity of relapses, which were associated with the reappearance of B-cells, it may be advisable to administer Rituxan at fixed intervals of 6-9 months rather than waiting until B-cells become detectable again."

SYMPTOMATIC THERAPIES

While exacerbations, relapses, and disability progression are the No. 1 concern of MS patients, they also have other disease-related conditions that are getting increasing attention, including:

➢ **Depression.** Dr. Maria Ron of the U.K. said it is "quite clear" that major depression is higher with MS than in the general population (15.7% vs. 7.4%). While depression doesn't occur at the same time in all patients, the prevalence of depression is much higher in younger MS patients, particularly one year after diagnosis. SSRI antidepressants are often helpful.

➢ **Fatigue.** Speakers were emphasizing that fatigue is different from depression and the most commonly reported symptom of MS, affecting from 65%-90% of patients and occurring in all MS subtypes. Dr. Lauren Krupp of Stony Brook University in New York defined it as "an overwhelming sense of tiredness, lack of energy, feeling of exhaustion. It is distinct from weakness and depression. Fatigue can be divided into primary (intrinsic to MS) and secondary (due to chronic illness factors)."

Current medications to treat MS fatigue are not fully effective, but amantadine and modafinil (Cephalon's Provigil) are sometimes used. Dr. Krupp said that, in carefully selected patients, methylphenidate may help.

➢ **Cognitive impairment.** From 45%-65% of all MS patients reportedly suffer from cognitive impairment, and it is currently impossible to predict early whether patients will suffer from cognitive problems in the long run or not. Dr. Kappos of Switzerland said cognitive function correlates poorly with depression, fatigue, or conventional MRI measures, and assessments by the treating physician/neurologist are frequently wrong. A French neurologist said, "I've given donepezil (Pfizer's Aricept) in some trials with interesting results."

The most frequent cognitive impairments are: **s**hort-term and working memory impairment (long-term memory is relatively spared), attention impairment, slowed information processing, and executive dysfunction. The best predictors of clinically-apparent cognitive deterioration in MS are reported to be: global brain atrophy and third ventricular width. Currently, the therapy thought to be most useful is Aricept. The value of Forest Laboratories Namenda (memantine) remains debatable.

➢ **Walking ability.**

➢ **Sexual dysfunction.**

➢ **Spasticity.** Spasticity is not only a problem itself, but it also triggers infections (especially urinary tract infections), pain, menstruation, constipation, wounds (from ingrown toe-nails to decubitus ulcers), and disease progression. Speakers generally agreed that the most effective current therapies are baclophen, tizanidine, and diazepam (usually restricted for night time use). The following are usually not useful: gabapentin, pregabalin (Pfizer's Lyrica), clonazepam, diaze-pam, cannabinoids, and dantrolene. In some cases, injections of botulinum toxin can be helpful for large muscles. The speakers pointed to the new therapy on the horizon: fampridine.

ACORDA THERAPEUTICS' fampridine-SR (4-aminopyridine sustained release tablet) – improves walking ability and maybe cognition

Fampridine is a BID potassium channel blocker which is aimed at improving walking ability in MS patients. The method of action is thought to be by improving nerve conduction in demyelinated nerve fibers. Biogen will market it outside the U.S. and is responsible for OUS regulatory filings. Biogen's Dr. Sandrock said it is expected to file an MAA (Marketing Authorization Application) in Europe in 1H10, adding, "We are excited about fampridine…It will be used not just by RRMS patients but also by SPMS and perhaps PPMS patients."

Fampridine got a lot of mentions at ECTRIMS; speakers at a variety of sessions referred positively to it. In fact, for a small company, Acorda – perhaps with some guidance from Biogen – had a big presence at the meeting.

The FDA PDUFA date is October 22, 2009, and there is an FDA advisory committee scheduled for October 14, 2009.

Many neurologists are already using a generic version of fampridine – 4-AP – by having a pharmacy compound it. However, all the neurologists questioned at ECTRIMS who are doing this said they will switch to the brand when it is approved – provided there is insurance reimbursement – because of side effects with compounded 4-AP. Comments about fampridine included:

- *France:* "We knew this drug a long time ago, but it was not stable. There is probably a window for this drug in patients with fatigue, but I am not waiting for it. Patients can't run again (with it)…If it is approved, I would use the brand because the brand may be more stable."
- *Belgium:* "We've used 4-AP for 15 years, but it is TID…Fampridine may work longer, but it only works in one-third of patients. I'll prescribe it, but only for progressive patients, not RRMS. In a year, ~10% of my patients might be on it."
- *Austria:* "If fampridine is approved, it might be an option in cognition."
- *Germany:* "We compound 4-AP and get a response of 25%-30%. I'll try fampridine in progressive patients, which is ~30%-50% of patients."
- *Switzerland:* "We already use 4-AP compounded. I would use the brand because of the epileptic seizures in wrongly compounded 4-AP. In a year, about 10% of my patients would probably try it."
- *U.S.:* "Seizure is an issue. The question is whether the therapeutic window is too narrow. Is the difference between efficacy and toxicity predictable? To discontinue fampridine, you will probably have to titrate people down."
- *Texas:* "About 10% of our current patients are taking compounded 4-AP. Branded fampridine will increase that, but we will still not offer it to all patients. We offer it based on core body temperature and to progressive patients…We would use the brand if the patient couldn't get to the compounding pharmacy or if the patient had insurance coverage for the brand."
- *Kentucky:* "It is hard to decide which patients to give it to based on the study. 4-AP was for fatigue, so I think there may be a lot of interest in fampridine off-label in fatigue, though reimbursement will be an issue…I would give fampridine to patients who don't respond to other drugs for fatigue and to patients not responding to anti-spas-motics…In one year, more than 25% of my patients might be on it…Compounding has been available for years, but there is a significant risk of seizure with that, which dissuades neurologists from using it. Fampridine SR doesn't seem to have that risk."

Asked why the trial retention rate was higher than the response rate, Dr. Andrew Goodman, a fampridine investiga-tor, said, "Patients perceive some benefit."

Dr. Goodman presented new results from an open-label Phase III extension study, MS-F203-EXT. Of the 283 patients eligible for the extension study, 269 enrolled, and at the time of data cutoff (November 30, 2008), ~70% were still enrolled (187 patients). In the trial, patients were given 10 mg fampridine SR BID. The study showed:

- Of the 30.5% of patients who **discontinued**, 10.4% were due to adverse events and the remainder for a variety of reasons including the perception of loss of efficacy.
- **Responders** had a 25% mean change from baseline in the primary endpoint of 25 foot walking speed at 1 year, and that only dropped to 22% at 2 years.
- Most common **treatment related adverse event** was urinary tract infection (34.6%), and 31.2% of patients had a MS relapse.
- **Serious adverse events:** MS relapse 4.1%, cellulitis 1.9%, convulsion 1.1% (3 patients), and 0.7% for each of these: fall, injury, back pain, suicide attempt.

- 4 **deaths** occurred – none believed related to the drug.
- On **seizures** specifically, there were 4 patients – 3 convulsion and one partial seizure. Dr. Goodman said the incidence of seizures across all 3 extension studies is 0.41 per 100-patient-years. He said this compares to an expected incidence of a first seizure in the MS population of 0.35, with this increasing for older patients and more advanced disease. His conclusions: "The incidence of seizure at 10 mg BID is difficult to distinguish from background and other MS trial experience." There were no seizures in the placebo group, though there was one placebo patient who was "suspicious" for partial seizure.

The FDA issues are likely to be: seizures and MS relapse side effect (rebound?). In 4.5% of patients, their MS worsens as a side effect of the drug. Dr. Jeffrey Cohen of the Cleveland Clinic, one of the largest MS Centers in the U.S., described the MS relapse side effect more as rebound than relapse. However, Dr. Goodman speculated that this MS relapse is a consequence of patients going off the drug and insisted these were relapses and not rebound, "I think when people stop taking fampridine, there is loss of effect, and it gets categorized as relapse, but not a relapse in the traditional sense. It doesn't make the disease worse. Most of the patients have progressive disease, so it is harder to beat their timed walk over time…I don't accept the term 'rebound.' It is a discontinuation effect." Biogen's Dr. Sandrock agreed with Dr. Goodman, "There is no evidence of rebound."

A poster on cardiac toxicity showed no really concerning QT prolongation and no QTc >500 ms with fampridine. However, it is curious that across the board, at all the time except the last (23.5 hours), there is more cardiac effect with the lower dose than the higher dose. A company official said the numbers are correct, not reversed, and he had no explanation for this.

Fampridine appears to work in only about half the patients who take it, but in the patients with a response, it really seems to work. And there were some early data at ECTRIMS suggesting it may have a benefit on cognition. A retrospective analysis of 10 patients with cognitive impairment from an open-label fampridine study found 6 had improved cognition, 2 remained the same, and 2 worsened. Overall, there was a statistically significant (p=0.05) improvement in cognition in those 10 patients. U.S. neurologist Dr. Keith Edwards concluded, "Fampridine may increase neuropsychological functioning, but we need a large study and an analysis of subsets most likely to respond. Maybe there is hope here."

Dr. Edwards recommended that a placebo-controlled, double-blind, prospective trial be conducted to examine the effect of fampridine on cognition, perhaps allowing concomitant SSRI use (for depression) and concomitant use of disease-modifying therapies."

Asked how he thinks fampridine helps cognition, Dr. Edward said, "We know this drug can cause seizures. Is it increasing the speed of connections? It does increase the velocity through demyelinated sections. Signals move quickly from the language area to the occipital area. Think of integrated circuitry. I think it increases processing speed and makes increased connections."

Asked if the cognitive improvement overlaps with an improvement in walking time, Dr. Goodman said, "That assessment hasn't been done, but there are a spectrum of responses to this drug – more stamina, better on this or that."

Cardiac Safety of Fampridine

Measurement	Fampridine SR 10 mg	Fampridine SR 30 mg	Placebo	Moxifloxacin 400 mg
QTc >500 ms	0	0	0	0
QTc >450 ms	0	0	4%	0
Mean QTc interval increase				
0.5 hours	3.3	1.6	---	- 0.5
2 hours	3.4	- 0.1	---	5.5
4 hours	3.1	0.5	---	8.2
6 hours	1.3	1.1	---	6.4
10 hours	2.5	- 0.2	---	7.3
14 hours	0.6	-1.3	---	4.3
18 hours	0.6	- 1.4	---	4.7
23.5 hours	- .5	- 1.7	---	2.2
Adverse events				
Serious treatment-emergent adverse events	0	2%	0	0
Treatment-related adverse events	25%	66%	21%	18%
Dizziness	0	55%	0	4%
Headache	15%	34%	17%	10%
Insomnia	4%	21%	0	0
Nausea	4%	19%	2%	4%
Tremor	2%	13%	0	0

GW PHARMACEUTICALS' Sativex (nabiximols), a cannabinoid-based oromucosal spray for MS spasticity

Previous studies had conflicting results, and data at ECTRIMS didn't resolve the conflict, but the data did suggest that Sativex is effective and well tolerated in MS patients with refractory spasticity. A new study of Sativex found that if the drug is only used in responders, it is significantly better than placebo. In this study (with 71% of the patients having some form of progressive MS), investigators used a 4-week test period to identify responders (≥20% response), and only those responders were entered into the 12-week, randomized, placebo-controlled phase (Phase B) of the trial. Interestingly, almost half the non-responders showed a response <5%, so it would appear patients either have little/no response to Sativex or respond pretty well.

In the randomized Phase B, 74% of patients had a ≥30% improvement from baseline, which was more than double the placebo response (35%). Tolerability was good, with the major side effects dizziness (14%), fatigue (6%), somnolence (5.1%), and 4.2% each for dry mouth and nausea.

Dr. Xavier Montalban of Spain concluded, "What we should tell patients is that we will try a drug that may or may not work, and after trial period we will assess whether it is worthwhile. It seems the differentiation between responders and non-responders shouldn't be that difficult."

MISCELLANEOUS

PFIZER's Lipitor (atorvastatin) – failed in CIS

In the STAyCIS trial, an 80 mg dose of Lipitor failed to show a benefit in patients with CIS. Dr. Emmanuelle Waubant of France reported that it did not significantly reduce T2 lesions or Gd+ lesions from baseline and did not significantly improve the odds of remaining relapse free. There were some positive secondary endpoints – e.g., patients free of new T2 lesions, but the question is if anyone would conduct a larger trial now. Dr. Waubant commented, "We think that what has occurred in the study is that the conversion rate to CIS or exacerbation was actually much less frequent in placebo than in the CHAMPS study…so that has decreased the power of trial to detect a treatment effect. Only a few secondary endpoints have been analyzed so far, and some suggest an effect on disease activity. I think a larger trial is needed."

Asked what she tells patients now, Dr. Waubant said, "There is likely a modest effect on MRI, and we don't know if there is a larger effect. There is a lot unknown in terms of combination therapy – combining a statin and a disease-modifying therapy…There are a lot of unknowns. That is what I tell my patients."

12-Month Results of STAyCIS Trial of Lipitor in CIS

Measurement	Lipitor 80 mg n=49	Placebo n=32	p-value
Primary endpoint: ≥3 new lesions or new clinical exacerbation	49%	56.3%	Nss, 0.65
Secondary endpoint #1: Patients free of new T2 lesions	55.3%	27.6%	0.032
Secondary endpoint #2: Patients remaining T2-free	OR 3.93	---	0.012
Safety			
Adverse event leading to study drug discontinuation	18.4%	12.5%	---
Serious adverse event	4.1%	3.1%	---
Grade ≥3 adverse event	16.3%	12.5%	---
Nausea	28.6%	9.4%	---
Myalgia	10.2%	12.5%	---
ALT increase	18.4%	3.1%	---
AST increase	16.3%	3.1%	---
CPK increase	8.2%	6.3%	---

LILLY's dirucotide – failed in SPMS

Dr. Mark Freedman of the University of Ottawa, Canada, reported on a 24-month, double-blind, placebo-controlled, multicenter Phase II study of dirucotide in SPMS – the largest study ever in SPMS – which found no significant treatment effect with the drug on EDSS (disability) progression. Dirucotide is a synthetic peptide with an amino acid sequence identical to human myelin basic protein (MBP). It was administered 500 mg IV push four times over 18 months.

24-Month Results of Dirucotide in SPMS

Measurement	Placebo	Dirucotide	p-value
Baseline mean EDSS	~5.5	~5.6	---
Primary endpoint: Time to 1 point EDSS progression sustained for 6 months	27.8%	30.7%	Nss, 0.527
Secondary endpoint: EDSS progression	35.8%	28.3%	Nss, 0.324
EDSS progression in DR2/4+ patients	0.17	0.22	Nss, 0.428
EDSS progression in DR2/4- patients	0.45	0.32	Nss, 0.439
Brain atrophy by MRI	N/A	N/A	Nss
Affect on quality of life	N/A	N/A	Nss
Safety			
Injection site reactions	13.4%	4.5%	<0.001
Flushing	2.0%	8.1%	<0.001
Back pain	15.4%	6.8%	<0.001

♦