Trends-in-Medicine

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by Lynne Peterson

SUMMARY

The European launch of Biogen Idec/Elan's Tysabri has gotten off to a slow start. Neurologists plan to use it, but very selectively until they see if more cases of PML develop. ♦ A 16-year study of Schering AG's Betaseron had a surprising finding: lower all-cause mortality with Betaseron than placebo. Researchers aren't sure why, but the finding was intriguing. ♦ Serono's new formulation of Rebif has fewer injection site reactions and neutralizing antibodies, but flu-like symptoms are increased. ♦ A trial of a double dose of Teva's Copaxone missed its primary endpoint, failing to significantly reduce Gd+ lesions. ♦ The early benefits of Novartis's oral fingolimod held up at 24 months in a Phase II extension study. The drug looks very promising, but there are still several safety issues that need to be watched in the ongoing Phase III trials. ♦ Schering AG continues to work on development of IV Campath and is optimistic that the efficacy will be excellent with a manageable risk management plan. ♦ Numerous other drugs, both oral and IV, are in development.

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EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS)

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More than 4,500 doctors from 78 countries attended ECTRIMS, making it a record year for the meeting. What attracted them? New therapies, particularly Biogen Idec/Elan's Tysabri (natalizumab) which was just launched in Europe, and new oral medications on the horizon.

About 400,000 Americans and one million people worldwide are affected with MS. From 30,000-40,000 new MS patients are diagnosed worldwide annually. Of those, about 225,000 in North America and Europe are undergoing treatment and considered stable, and <175,000 are experiencing relapses and disability and are not stable. Another 100,000 have quit therapy.

MS is a progressive disease. There is a 5-7 year decrease in life expectancy with MS, a 2- to 7-fold increase in suicide risk, and ~50% of MS patients die of disease-related causes. The median time to use of a cane/crutch is 15 years, and the median time to wheelchair confinement is 25 years. Cognitive disability occurs in 43%-65% of patients, and often goes under diagnosed. The most common deficits are impaired learning and memory and slowed information processing speed. Cognitive impairment was described by a speaker as "inability to follow more difficult sequences of arguments and an inability to interact with many people at the same time. It is not a direct cortical effect, so there is no aphasia, no inability to speak, and memory deficits do not occur early or are not pronounced."

From 80%-90% of MS patients present as relapsing remitting (RRMS). Within 10 years, 50% of patients move to the secondary progressive (SPMS) phase where they chronically progress.

Currently, an average of 28% of MS patients in Europe are on a disease modifying drug (DMD) vs. 47% in the U.S., but in some European countries very few patients are on any DMD. For example, in Poland, <2% of MS patients are taking a DMD, and in Czechoslovakia the government has been tightening the restrictions on who can get a DMD, not loosening them.

Besides getting more patients on therapy, a key topic at the meeting was encouraging earlier treatment in MS. Several hurdles to treating MS early were outlined:

- Especially at the CIS (clinically isolated syndrome) stage, the disease may still be in question. A speaker said, "We are safe in ~95% of cases with our diagnosis…In 2%-3% of cases we may fail, but we are correct in 97%."

Approved MS Drugs

Company	Brand name	Generic name	Dosing	Dosage	Type of MS treated
Immunomodulators					
Biogen Idec	Avonex	rhu interferon beta-1a	IM	30 µg QW	Relapsing remitting
Schering AG/Berlex	Betaseron	rhu interferon beta-1b	SC	250 µg EOD	Relapsing remitting (In Europe: secondary progressive)
Teva Pharmaceuticals	Copaxone	Copolymer-1, glatiramer acetate	SC	20 mg QD	Relapsing remitting
Serono	Rebif	rhu interferon beta-1a	SC	44 µg 3xWeek	Relapsing remitting
Immunosuppressants					
Serono	Novantrone	mitoxantrone	IV	12 mg/m^2 Q3M (with maximum lifetime limit)	Relapsing remitting, secondary progressive, progressive relapsing
Johnson & Johnson	Leustatin	cladribine	IV	90 µg/kg daily	Relapsing remitting, secondary progressive, primary progressive
Bristol-Myers Squibb	Cytoxan	cyclophosphamide	Oral	1-5 mg/kg daily	Relapsing remitting, secondary progressive, primary progressive
GlaxoSmithKline	Imuran	azathioprine	Oral	3-5 mg/kg daily	Relapsing remitting, secondary progressive, primary progressive
Wyeth	Rheumatrex	methotrexate	Oral	15-20 mg weekly	Relapsing remitting, secondary progressive, primary progressive
Antibodies					
Biogen Idec/Elan	Tysabri	natalizumab	IV infusion	300 mg monthly	Only patients enrolled in the TOUCH risk management program

- Some patients may be destined to have a disease course with minimal disability and impairment. An expert said, "We know only a few patients – 7%-8% – will have this label at the end of their life, and even those without obvious effects may have cognitive disability."
- When considering 15-20 years of therapy, using a partially effective agent with known side effects, they may ask, "Why not wait to be sure the disease is active?" The speaker said, "What is lost is lost. This is very simple to understand. If there is even one more lesion in the brain, there is more damage. Patients with early treatment have a better outcome than those who delayed."

Comparison of MS Therapies

Drug	Relapse rate	Reduction in disability progression	Side effects
Interferon beta	29% - 32%	30% - 37%	Injection site reactions, flu-like symptoms, depression, liver toxicity
Copaxone	29%	Nss	Injection site reactions, lipoatrophy, acute systemic reaction
Tysabri	68%	42% - 54%	Headache, fatigue, injection site reactions, PML

Finnish Study of Safety and Tolerability of IFN-βs

Side effect change from baseline to 6 months	Betaseron n=45	Avonex n=18	Rebif 22 µg n=33	All n=96	p-value
Injection site reactions	-27%	-6%	-24%	-22%	0.06
Flu-like symptoms	-33%	-28%	-33%	-33%	0.03
Headache	-9%	-16%	-5%	-10%	0.19
Depression	+7%	-6%	-8%	-1%	0.78
Elevated transaminases	-5%	-5%	+13%	+1%	0.17
All	-33%	-22%	-28%	-29%	0.60

- Lack of really long-term data. A speaker said, "This is the most reasonable objection. There are not enough long-lasting observations."
- Keeping patients on therapy to give them the best chance for the future.

Choosing among available therapies

A Finnish study found that IFN-βs are well-tolerated and efficacious, with a 66% reduction in the annual relapse rate and a 58% reduction in the total number of new relapses. However, one-third of patients obtained no benefit from the treatment, and adverse effects were common (80% of patients). During the study, 28% of patients switched from one to another IFN-β, generally for lack of efficacy. They recommended that the value of therapy should always be individually assessed.

Dr. Mark Freedman, neurologist and director of the MS clinic at the University of Ottawa, Canada, suggested a new way to look at risk:benefit of different therapies. He said, "The concept is spreading of an evidence-based approach to evaluating risk:benefit. It is difficult for clinicians – because each study is unique and there are enough differences in the study populations – to make direct comparisons (between drugs). We doctors need a way to reduce the numbers to a common playing field."

He offered these definitions:

- Optimal therapy: best benefit:risk.
- Maximal benefit: lowest NNT (number needed to treat) in order to obtain a treatment effect.
- Minimal risk: a high NNH (number needed to harm) – a high number of patients treated before any side effect.
- Maximum benefit:risk:
  low NNT divided by high NNH = $\frac{\text{Low NNT}}{\text{High NNH}}$
- Likelihood of help vs. harm (LHH) = 1/NNT vs. $1/NNH^2$

A speaker at a Teva-sponsored satellite symposium said the initial choice of therapy for RRMS should take into account:

- Stage of disease (CIS early RRMS, late RRMS, SPMS, PPMS).
- Risk factors for near-term attacks and accumulating disability.
- Gender. Some trials have suggested the therapeutic effect may be different in males and females.
- Reproductive potential and family planning.
- General medical status.
- Doctor *and* patient aversion to risk.
- Likelihood of compliance with therapy.
- Preconceived biases.
- Cost.
- Genetics and expression genomics. Genetic tests are being developed that may determine the likelihood of patients to respond to therapy.
- Evidence-based comparative data. He said, "This is limited and to some extent may be biased."

His suggestions on when to change therapy were:

- Continued frequent relapses or non-relapse associated with excessive MRI activity may justify the selection of an alternative immunomodulator, but there is no Class 1 data to support a change.
- Treatment failure due to continued frequent and severe relapses may justify escalation to Novantrone or Tysabri.
- MRI activity may justify combination therapy with different classes of approved drugs, not non-approved drugs.
  - Copaxone combinations include:
    - Copaxone + methylprednisolone. A speaker said, "A study of this combination looked safe, but the efficacy was totally ambiguous."
    - Copaxone + Novantrone. An expert said, "A study showed a very rapid reduction in Gd+ frequency which was not seen with the same magnitude with Copaxone alone, and it was sustained over the follow-up period…The relapse rate fell but not significantly. Safety was acceptable and efficacy possible."
    - The ongoing three-year ASSERT trial in the U.S. and Canada is testing the combination of oral Copaxone ± oral prednisone.
  - Combination therapy assumes:
    - Both therapies provide incomplete disease control.
    - The two treatments have different but complementary mechanisms of action.
    - The effect is additive if not synergistic.
    - There are no antagonistic interactions.
    - There are no or modest additive adverse events.
- Patients failing therapy should be considered for well-designed, IRB-approved trials.

Benefit:Risk with Serono's Rebif *(Freedman analysis)*

Ratio	Avoid
22:1	For avoiding one relapse
5:1	For maintaining one patient relapse free
3:1	For maintaining one patient free from disability progression
6:1	For maintaining one patient with no new T-2 activity

Comparison at 2 Years with Current MS Therapies

Drug	NNT clinically			NNT by MRI			NNH
	Relapse rate	Relapse free	Sustained disability progression	Free of T-1 Gd+ lesions	Free of T-2 active lesions	Free of T-1 active lesions	
Avonex	7	9	8	1.4	N/A	8	33
Betaseron	2	7	9 (Nss)	N/A	5	N/A	14
Copaxone	4	15	33 (Nss)	0.09	N/A	14	21
Novantrone	2	5	8	---	---	---	---
Rebif	2	6	8	0.11	4	3	27
Tysabri	2	4 - 5	8 - 17	---	---	---	---

Neutralizing antibodies (NAbs)

An expert said "It is a big hurdle for almost all biological compounds." Biogen Idec CEO James Mullen said the difference in neutralizing antibodies (NAbs) in various IFN-βs comes from the way the products are made.

Do NAbs impact the clinical course of MS? Yes, Dr. Bernd Kieseier of Austria said, "Those patients with NAbs have the greatest probability of disability progression over four years. You do have a risk with IFN-β, and this does have a clinical effect on the course of the disease, so you have to consider this when you treat patients long-term with IFN-β."

Canadian researchers tested all 111 MS patients who received an IFN-β for more than one year at their center since July 2004 for antibodies. They reported a lower than expected incidence of neutralizing antibodies and no impact on clinical evolution.

Canadian Study of Neutralizing Antibodies in a Clinical Setting

Measurement	Betaseron n=45	Avonex n=18	Rebif 22 µg n=33	Rebif 44 µg n=33	Overall
Persistent neutralizing antibodies	4.4%	5.5%	12.5%	28.6%	14%

Treatment adherence

An expert said that, on average, only 70% of patients are on therapy after 12 months, and in non-specialist MS centers <50% are on therapy at one year. However, in combination with an expert patient program, >90% are on therapy. Another expert said, "To optimize adherence, especially over the first 6-12 months, patients need: injection supervision, more frequent physician and nurse visits, direct contact, etc."

A Czech study retrospectively examined why RRMS patients discontinued DMD therapy over 10 years (1996-2005). Of the 303 patients examined, 7.6% stopped treatment.

- 4.3% suicide.
- 4.3% accidental death.
- 21.8% psychological problems with injection therapy or doubts about the efficacy of the therapy.
- 65.3% RRMS and SPMS conversion.
- 4.3% cutaneous adverse events.

The Biogen Idec-sponsored Global Adherence Project (GAP) study, which was presented at ECTRIMS, looked at adherence issues. It found that patients on Avonex adhered to treatment more than patients taking other approved DMDs. Adherence was defined as compliance in the long-term. GAP was a 2,566-patient, multicenter (176 sites in 22 countries) survey. The primary endpoint was adherence to disease modifying therapy for RRMS at 31 months, which meant not missing more than one injection or not changing dose within 4 weeks prior to the survey.

GAP Primary Endpoint Results

Drug	Patients not missing >1 dose and not changing dose within 4 weeks prior to the survey
Avonex	85%
Rebif 22 µg	78%
Rebif 44 µg	73%
Betaseron	70%
Copaxone	66%
Overall	75%
Reasons for non-adherence	
Forgot to administer	50%
Tired of taking injection	20%
Fatigue	15%
Flu-like symptoms	15%
Pain at injection site	12%
Headache	10%
Dosing schedule difficulty/inconvenience	10%
Injection anxiety	10%
Skin reaction	9%

A study from Argentina in RRMS reported on 784 RRMS patients treated with an immunomodulatory drug (IFN-β or Copaxone). It found that the main reason for treatment discontinuation was lack of efficacy and side effects.

Argentine Study on DMD Discontinuations

Reason for dropout	All	Interferons	Copaxone
Lack of efficacy	44%	41.2%	2.8%
Side effects	16.3%	15.8%	0.56%
Pregnancy	3.9%	0.56%	3.3%
Lost insurance	12.9%	8.4%	4.5%
Patient decision	6.2%	3.9%	2.2%
Medical decision	2.8%	0	2.8%
Death	1.7%	0.56%	1.12%

ALREADY APPROVED MS DRUGS

BIOGEN IDEC/ELAN'S Tysabri (natalizumab)

Tysabri was approved for re-introduction in the U.S. on June 5, 2006, with a comprehensive risk management program (TOUCH), and the drug was re-launched there in July. The EMEA approved Tysabri for the first time for use in Europe in late June 2006, but it has gotten off to a ***very*** slow start there. So far, it is available in Germany, Austria, Ireland, and the U.K., but only about 400 patients have gotten it yet. The company plans to launch Tysabri in Italy and Canada in 4Q06 and in other major European markets in 1H07.

Current European reimbursement and usage

Except for the U.K., it appears Biogen Idec/Elan is only launching Tysabri in countries where they've worked out some reimbursement. Even though the EMEA has approved Tysabri, each country must act on it with respect to reimbursement, and there is ***no*** use in countries where the government has not yet approved reimbursement. This is in contrast to other drugs which have found some usage among private pay patients prior to a government decision on reimbursement.

Reimbursement is a major issue in most European countries, but doctors in many countries are optimistic that it will get worked out. In Germany, Ireland, and Austria, the government is covering the cost. German doctors said there is no problem with reimbursement, but the insurance companies want the safety measures met. One doctor said, "There are no insurance restrictions on Tysabri use as long as I follow the indications. There are rules, but I don't have to register, and neither does the patient."

Nearly every neurologist questioned plans to use Tysabri, but selectively. The outlook is for European usage to peak at <10% of MS patients (and perhaps <5%) during Year 1, ***even if reimbursement is made available***. In some countries, where MS patients are treated exclusively or almost exclusively at MS centers, these centers have been talking about it, and there appears to be a consensus on how much Tysabri they expect to use. While there are individual doctor variations, those are mostly in the U.K. and Germany. In other countries, there appears to be a more "national" approach.

➢ **Germany** – *reimbursement approved:* Even though this is the first country to use much Tysabri, the outlook, as noted before, is for <10% of patients to be on it within a year, and use will vary from hospital to hospital, depending on local restrictions on use. A German expert said there are 130,000 MS patients in Germany, and about 50,000 of these are on a disease modifying drug. Currently, he said there are 380 patients on Tysabri, and he believes the nationwide outlook is for 1,200 patients (2.5% of treated patients or 0.9% of all MS patients) to be on Tysabri in a year.

If there are no cases of PML over the next couple of years, he believes usage could increase, depending upon hospital budgets, to a peak of 20% of patients. The cost of high dose Rebif there is €18,000, and Tysabri costs €26,000. A German doctor said, "Patients are excited about Tysabri. It is a big thing. They want to know about it. They ask for it, but when we say there are special requirements, they accept that. It is usually the chronic progressive or secondary progressive patients who ask, and they don't qualify."

➢ **Austria** – *reimbursement approved:* The outlook is for ~10% usage (300 of the 3,000 MS patients there). The Austrian Neurological Society plans its own registry of Tysabri patients. The experience of the first patients will be carefully watched and will determine any expansion of use.

➢ **Ireland** – *reimbursement approved:* A Biogen Idec sales rep from Ireland said it "is doing well" there.

➢ **U.K.** – *launched but zero usage so far.* U.K. neurologists insisted there will be no use there until NICE issues its recommendations in spring 2007. Sources were hesitant to try to predict what NICE will do. They estimated that even if NICE approves Tysabri, a year after approval, <5% of patients, on average, would be on it. One doctor said, "It would be just for interferon failures. I'd use it like Novantrone." Another said, "If you look at the cancer drugs and the disease modifying drugs (DMDs for MS), then the determinants for NICE are (1) Efficacy, and that's no problem; and (2) Cost. I'm assuming Biogen will do the best it can to show cost-effectiveness."

There is no private pay market for Tysabri in the U.K. One doctor said, "I'm not aware of any use in private patients." Even with a NICE blessing, doctors predicted U.K. usage would be <10% in a year.

➢ **Belgium** – *reimbursement not approved yet:* Use will depend on reimbursement, but Belgium was described as "slow on adoption of new drugs." An expert from there said, "Tysabri efficacy is really strong, but it is useful in only a fraction of patients."

➢ **Italy** – *reimbursement not approved yet:* An expert said reimbursement is under negotiation right now and a decision could come any day. What has been proposed and he thinks will be agreed upon is an initial restricted access program under which only ~20 of the more experienced, Level 2, regional MS centers (out of the country's 200 MS centers) will be allowed to use Tysabri at first until there is more experience with the drug. He said there are 10,000 patients under treatment in Italy, and 5%-10% of those will get Tysabri the first year, which means ≤50 patients per center, which he described as a good number. After a couple of years, depending not only on safety (no PML) but also general tolerability in clinical practice (vs. trial experience), usage could be allowed to expand to other MS centers. If everything went ***perfectly***, usage could eventually get to 40% of treated patients, but that will take several years.

➢ **Norway** – *reimbursement not approved:* The outlook is for usage to be <10% of MS patients in one year and to stabilize at that level. Right now about 2% of patients are on Novantrone, and the expectation is that Tysabri will be perhaps double that.

➢ **Spain** – *reimbursement not approved yet:* The outlook for usage in this country is the highest in Europe, but the estimate is for a peak of 12% (of the ~4,000 patients there who are followed regularly), perhaps a year after it is reimbursed. An expert said, "Usage beyond one year is a mystery. It

depends on whether there are new cases of PML. If there are any cases, usage would slow."

➢ **Switzerland** – *reimbursement not approved yet:* A Biogen speaker claimed there has been usage in Switzerland, but an EASD official from Switzerland said there has been no usage outside of clinical trials yet.

➢ **Denmark, Finland, France, Netherlands, Portugal, and Sweden** – *no use yet.*

Future European usage outlook

Doctors generally had a difficult time estimating what Tysabri usage will be in two or three years – because it depends on how the drug performs in clinical practice and whether additional PML cases occur. Two years after Tysabri is available, doctors estimated that Tysabri would still be used by <10% of patients, on average. A U.K. doctor said, "It is too early to say how Tysabri will do in Year 2 because that depends on the safety and long-term efficacy we see when we use it in clinical practice. The real concern is whether DMD failures will respond." Several neurologists suggested that if there are 2-3 PML cases over the next two years, it would almost kill Tysabri use.

(NOTE: U.S. usage and outlook will follow in a separate report.)

Risk management

European monitoring requirements are not as strict as in the U.S. Mostly, this is being left to either the hospital or the doctor, but doctors are being encouraged by the companies to consider risk management issues. No European doctors have encountered restrictions anywhere near what doctors in the U.S. face. A U.K. doctor said, "Monitoring is left to doctors mostly. There is heightened awareness of safety concerns."

Risk management programs in both Europe and the U.S. contain educational tools for patients and physicians as well as studies to better understand the risk of PML. No mandatory registry is required in Europe as in the U.S. Biogen officials outlined their European risk management objectives:

1. **Risk minimization:**
   - To promote informed risk:benefit decisions regarding Tysabri use.
   - To minimize the risk of PML and the health consequences of PML.
2. **Risk assessment:**
   - Determine the incidence and risk factors for PML.
   - Assess the overall safety profile.

Biogen is not ignoring the PML issue or downplaying it, but their experts were characterizing PML as a rather routine but very rare side effect, something for which neurologists can monitor, and something easily identified by neurologists – clinically, with MRI, and with cerebrospinal fluid (CSF). Neurologists are generally accepting that message. They are taking a cautious approach to Tysabri, but they are not overly worried about its safety, and they believe the efficacy is very good.

Patient selection

Use of Tysabri is restricted to: Single disease modifying therapy in RRMS in patients with high disease activity despite treatment with IFN-β or with rapidly evolving severe RRMS.

Factors to consider prior to Tysabri use:

- MS diagnosis and disease status.
  - Comorbidities, such as HIV and hematologic malignancy.
  - Treatment history, especially immunosuppressant and anti-neoplastic use.
  - Lab values.
- Reference MRI is recommended (but not required in Europe)
  - To confirm RRMS diagnosis.
  - To provide reference for comparison with subsequent scans in the event of new or worsening neurological symptoms.
- On therapy, ensure timely assessments of new or worsening neurological symptoms to differentiate MS relapse from PML (clinical evaluation, MRI, CSF).

Most doctors agreed that Tysabri will be reserved for patients (1) who fail on an interferon, (2) where the prognosis is bad, or (3) present for the first time with serious disease. Except for one German doctor, all neurologists questioned plan to do a baseline MRI before starting Tysabri. A German neurologist said, "My first patient is first-line treatment for someone with progressive relapsing remitting MS with strong progression." Another German neurologist said, "My first patient is a 25-year-old woman with a lot of Gd+ T-2 lesions who has had three relapses in the past year. She was on Avonex for 3-4 months but still relapsed. In the beginning, at least, that is the typical patient who will get Tysabri – someone with a bad situation in the beginning (of treatment)." A Danish doctor said, "Tysabri will be for patients who fail interferon therapy, and a few first-line patients who present badly."

Monitoring patients on Tysabri

There were also several discussions of monitoring algorithms to use with Tysabri. Dr. Oscar Fernandez of Spain characterized PML as a "rare, progressive, demyelinating disease of the central nervous system (CNS) that is well-known to neurologists," recommending:

- Vigilance for the appearance of PML.
- MRI when in doubt.
- CSF assessment if the MRI is not clear.

It was interesting that PML was not presented by most speakers as a "doom and gloom" crisis or a death sentence but as something that could be treated. A speaker emphasized, "Single case observations suggest immune reconstitution may improve the outcome of PML."

Several European groups have collaborated on an algorithm for selection and management of patients. Dr. Ludwig Kappos of Switzerland noted that the classic presentation of PML is progressive dementia, motor dysfunction, and vision loss, but there are no pathognomonic signs or symptoms. The initial symptoms of PML can include: weakness, speech abnormalities, cognitive abnormalities, headache, gait abnormalities. MRI has 100% sensitivity for PML but lacks specificity, so it may need to be repeated to rule out PML. PCR of the CSF is both a sensitive and highly specific diagnostic tool, but even that may need to be repeated to rule out PML.

Differentiating MS Relapse and PML

Feature	MS	PML
Onset	Acute	Subacute
Presentation	Hours to days	Weeks
Evolution	Normally stabilizes in days/weeks	Progressive
Resolution	Resolves spontaneously or with treatment	---
Clinical presentation	Diplopia Paresthesia Paraparesis Optic neuritis	Cortical signs and symptoms Behavioral changes
MRI features	Symmetrical lesions Defined borders	Asymmetrical cortical abnormalities Ill-defined borders Hyperintense T-2 lesions Hypointense T-1 lesions

Experts hope that the reduction in relapses with Tysabri will help reduce the instances where physicians have to deal with the issue of whether or not a relapse is PML or MS-related. An expert predicted, "In most cases, it will be unequivocal that it is a relapse or no relapse."

If patients present with new or worsening neurological signs or symptoms, the algorithm recommends a clinical assessment. If there is a suspicion of PML, Tysabri should be suspended and an MRI obtained (before initiation of any steroids).

- If the MRI rules out PML, Tysabri can be resumed.
- If the MRI cannot exclude PML, a CSF assessment should be made.
  - If JCV is not found, but the clinical suspicion of PML is high, then repeat the CSF to increase the sensitivity of the assay.
  - If JCV is detected, Tysabri should be ***permanently*** discontinued, and the patient treated for PML.
  - If JCV is not detected and there is a low clinical suspicion of PML, Tysabri can be resumed.

If there is a suspicion of PML, is steroid use safe? Dr. Kappos said, "We can assume that treating with steroids may increase the risk of immune-incompetence in the case of JCV infection…but there are many clinical relapse situations where you, as a neurologist, would be quite certain there is no suspicion of PML…In these cases, the use of steroids is still justified. If the symptoms are atypical or there is uncertainty, then you have to refrain from this treatment."

If the MRI does not exclude PML, can patients just be watched for a while before a CSF test is done? Dr. Kappos did not recommend that. He said, "In our center we would do CSF right away and not wait."

What will neurologists do if patients relapse on Tysabri? There is a strong feeling among doctors that they will be able to distinguish between a "normal" MS relapse and PML. If the relapse is optic neuritis, for example, they will consider that as MS-related. If there is hemi-paralysis, that would raise questions about PML, and then the patient would get another MRI. If the MRI is inconclusive, many doctors said they would then do a spinal tap to check for JC virus. A U.K. doctor said, "Neurologists think they can pick out the abnormal signs and find PML."

If the doctor believes the relapse is or could be PML, Tysabri will be stopped, and if PML is later ruled out, Tysabri would be restarted right away. There would be no significant "drug holiday." Neurologists believe they can rule PML in or out pretty quickly. Comments included:

- *U.K.:* "We still expect 20% of patients to have a relapse, so a relapse doesn't mean the drug failed…If there is a (safety) concern, I'll stop Tysabri until there is no longer a concern. That might be a month or a year or forever… But PML is not perceived with the same concern as BSE (bovine spongiform encephalopathy). Patients don't recognize a risk of 1 in 1,000 as dangerous."
- *Germany #1:* "Just because a patient relapses, doesn't mean I will stop Tysabri. A relapse is usually quite a neurological deficit, and the patient gets better with or without treatment. But if there is a personality change or hemi-paralysis, then I would stop Tysabri, do another MRI, and then test for JCV. But if the patient isn't positive for PML, I would restart the Tysabri."
- *Germany #2:* "How slow or fast the symptoms evolve and what the symptoms are will help me decide if it is PML. But I won't necessarily do an MRI before starting Tysabri…If the relapse is something visual, I'll know it isn't PML. If I'm not sure if it is PML, I'll do an MRI."
- *U.K.:* "If a patient relapsed, and the relapse was typical of MS, I would keep dosing. But some of my colleagues say they will stop Tysabri immediately at any relapse."

Biogen is initiating the TYGRIS registry, a five-year, global observation study of 5,000 patients (3,000 in North America and 2,000 in Europe). It is powered to detect rare events that

occur with an incidence of 0.06%. The company also will do a pregnancy registry of 300 cases.

Treatment cessation

A speaker presented data on what happens when Tysabri is discontinued: Patients slowly return to baseline levels over about three months. There has been a concern that patients could or would rebound when Tysabri was stopped, but researchers reported that this was not seen in patients from Study C-1808, a 1,615-patient, open-label extension of the Phase III trials, which was stopped early when Tysabri was withdrawn from the market in February 2005. Those patients continued to be evaluated every three months, and MRIs were obtained on 341 of them. Researchers reported:

- Disease activity slowly returns upon cessation of Tysabri ***without rebound***.
- The relapse rate after cessation never exceeded the on-study placebo relapse rate.
- Gd+ lesion activity post-cessation did not exceed pre-study activity.
- The post-treatment effects were not dependent on the duration of exposure.
- Disease activity begins to return within 2-3 months of cessation of therapy.
- The post-treatment relapse rate increases month-by-month for the first 7 months, but is mostly below the on-study placebo relapse rate, and at 8 months trends down.

While Biogen-sponsored studies found no rebound when Tysabri is discontinued, a Spanish researcher reported that her patients did appear to rebound when Tysabri was stopped. The annualized relapse rate in her 7 patients was 1.0 pre-Tysabri, 0.5 on study, and 1.7 12 months post-study. Her patients have since gone back on Tysabri in an extension study and are "very happy." She said two other groups had stopped by her poster to say they had the same experience with Tysabri rebound in their centers.

Asked whether this data suggest that a periodic "holiday" from Tysabri would be possible or useful, a speaker said, "My conclusion from this data is that three years of treatment appear safe. After cessation of therapy, there is a carryover effect for 2-3 months, but eventually, the CD4:CD8 ratios revert to normal…and I think beyond three years we don't really know…If you stop for three months, you don't get a lot of reactivation, so it could be safe…(A 'holiday') is a thought, but it needs more study. I'm not sure you would get that carryover effect with three months of use…Even in the placebo patients (switched to Tysabri), the average duration of therapy was six months…So three months may not be long enough to get the therapeutic effect you are looking for."

SCHERING AG'S Betaseron/Betaferon (interferon-β-1b)

This is the only A-B-C-R drug to be approved for use in SPMS as well as RRMS. At ECTRIMS, Schering focused primarily on the issues of early diagnosis and treatment, not new therapies. Schering's effort appeared aimed at expanding the number of patients getting a disease modifying drug (DMD).

A poster by European researchers compared injection site pain and reactions with Betaseron and Rebif 44 µg in a prospective, non-randomized study of 454 RRMS patients, and the results were somewhat surprising: *The frequency and severity of pain was significantly greater with Rebif,* but this could not be explained by pH, the use of pain medication, or needle size (since a larger needle was used for Betaseron). A researcher suggested the difference could be due to formulation, osmolarity, or the buffers used, but the study didn't point specifically to any of these explanations. Injection site reactions were also significantly lower with Betaseron.

Comparison of Rebif and Betaseron

Measurement	Rebif 44 µg	Betaseron 250 µg	p-value
Patients pain free over 15 injections			
Immediately	4.8%	16.7%	<.0021
30 minutes post-injection	16.2%	40.2%	<.0001
60 minutes post-injection	31.4%	55%	---
Patients without injection site reaction			
Visit 1	35.2%	46.9%	0.0184
Visit 2	33.8%	51.8%	<.001

Another poster was presented by Canadian researchers on a randomized, multicenter, open-label, 38-week Phase II study of the combination of Betaseron 250 µg EOD and tacrolimus BID (low dose and high dose) in 24 patients with RRMS or SPMS who had failed immunomodulatory therapy. Only 16 patients completed the study. Researchers reported the combination did not cause any unexpected side effects or drug interactions, but tolerability was an issue which they speculated could be improved with better patient selection. The therapy appeared to stabilize the clinical course and MRI evolution, and relapse rates were improved significantly.

Long-term (16-year) data on Betaseron on 328 patients (88.2% of the original cohort) from the pivotal Phase III trial were presented, and there was a surprising finding: ***A decrease in all-cause death with Betaseron vs. placebo.*** A Schering official said, "We tried to find reasons, but there wasn't a reliable answer…But when you talk to epidemiologists and experts, based on the experience in other indications, particularly cardiology, it doesn't make sense to try to figure out what is disease-related and what isn't…The only thing that counts for patients is all-cause mortality. I've heard there is similar data with Avonex in some early trials, but they never made anything out of that, but it was still a trend in the same direction. My feeling is it could well be a real effect…We don't know everything interferons do…I think this is a very

reassuring signal that nothing goes wrong long-term, and there is a chance that there is a beneficial effect that we haven't understood…Maybe some of the registries can verify this."

16-Year Results with Betaseron

Measurement	Placebo	Betaseron 50 µg	Betaseron 250 µg
Alive	72%	79%	85%
Not found	11%	14%	10%
Dead	16%	7%	5%

The BEYOND trial of double-dose Betaseron (500 µg) is ongoing, but results are not expected until the end of 2007 or early 2008. A Schering speaker said, "We are trying double dose to check if we can improve efficacy. The safety profile seems pretty good up to now, but we are waiting for efficacy results from that trial." A Schering official said, "The underlying assumption is that double dose will improve efficacy beyond what we see with the current dose. If we can improve on that, my feeling is that we are in the range of Tysabri or could match it."

Canadian researchers reported on their experience with five RRMS patients who relapsed on DMD therapy and were given double-dose Betaseron, which was obtained on a compassionate use basis from the company. They found boosting the dose (to 500 µg) re-established efficacy and lowered neutralizing antibodies. They concluded, "There was no apparent correlation between disease stability and the reduction or disappearance of NAbs, raising the question of how much NAbs were contributing to disease activity. The re-emergence of disease activity is probably a better indicator of disease progression and a suboptimal response to treatment than the development of neutralizing antibodies."

SERONO'S Rebif and Rebif New Formulation (interferon-β-1a)

Rebif

A nurse practitioner for Serono cited some steps her company has taken to improve treatment adherence with Rebif, including:

- New auto injector.
- Thinner needle (29 gauge).
- Titration pack.
- Improving formulations.
- Nurse support programs.

Rebif New Formulation (RNF)

A 48-week interim analysis was presented from a 96-week, Phase IIIb, multicenter (48 centers in 12 countries), single-arm, open-label study evaluating the safety and immunogenicity of the new liquid formulation of Rebif 44 µg TIW subcutaneously in 260 patients with RRMS. The new formulation (RNF) has no human serum albumin and no fetal bovine serum. The primary endpoint is proportion of neutralizing antibodies at 96 weeks.

The study showed much fewer injection site reactions with RNF but more flu-like symptoms. The principal investigator said this was primarily due to doctors in Russia and Argentina not pre-treating patients prophylactically with anti-inflammatories, but he admitted that even if those two countries are excluded from the data, there is a somewhat increased incidence of flu-like symptoms with RNF. Serono failed to mention this issue in two media briefings, but it did come up at the formal presentaton.

The majority of patients who became NAb positive did so between six and 12 months (that is, most were negative at six months but positive at 12 months). Only one patient converted from NAb+ to NAb-. Dr. Gavin Giovannoni of University College in London said, "We really need 18-month and 24-month data to give final figures on NAbs…It is too early to comment on the end NAb positivity rate based on this, but a large number of these titers were low, so a large number may revert (from NAb+ to NAb-) before the end of the study."

Dr. Giovannoni said he has "no doubts" that neutralizing antibodies stop Rebif from working, but Dr. Freedman disagreed, saying an association – but not a causal relationship – has been shown between NAbs and a decrease in efficacy. Dr. Giovannoni responded, "The new Rebif formulation is designed to address the problem of neutralizing antibodies if that is an issue. There is no doubt the new Rebif formulation is less immunogenic than the current formulation."

48-Week Interim Analysis of Phase IIIb Study of Rebif New Formulation

Measurement	RNF n=260	Rebif in EVIDENCE trial n=339
Baseline		
Mean age	34.0	39.0
Number of relapses	1	2
Key results		
Injection site reactions	29.6%	83.8%
Neutralizing antibody positive	13.9%	24.4%
Persistent NAbs	2.5%	14.3%
Flu-like symptoms	70.8%	48.1 %
Other safety results		
Any adverse event	95.0%	98.8%
Serious adverse events	3.8%	5.6%
Cytopenia	9.6%	11.8%
Depression	5.8%	19.8%
Hepatic events	13.1%	16.8%
Relapse-free	66.8%	---
Annualized relapse rate	0.37 vs. 1.03 pre-baseline	---
NAb+ patients with titers <200 nU/mL up to Week 48	50%	---

A U.K. survey found that "a large majority of patients want to be more involved in decisions about treatment: 87% of patients <age 40 said this, 62% of patients age 40-59, and 51% of those >age 60. Dr. Giovannoni said, "There is a move from a compliance (treatment) model to a concordance model, with the prescriber and the patient discussing and negotiating treatment…This (concordance model) is now becoming the standard in the U.K…It is expected that the new Rebif formulation will result in an improved risk:benefit profile."

What is the place for RNF in clinical practice vs. current therapies?

Dr. Giovannoni said, "It will replace the existing Rebif, which will be phased out over time. And patients will have fewer side effects with it (new Rebif). I find that local skin reactions are an issue over time, so people already on Rebif will be switched, and for new patients who are choosing a therapy, because the skin reactions are less (with the new formulation), they will be more likely to start treatment…And I think efficacy will be better (with the new formulation)… Neutralizing antibodies impact the overall efficacy of the drug…so I personally believe the efficacy will be better with the new formulation…There is no logic to continuing with the old formulation (after the new formulation is available)." A company official added, "We have plans for new trials with the new formulation, but…we will be replacing the current form of Rebif with the new formulation when it is approved." The official said the new formulation will come in both 22 µg and 44 µg doses.

Regulatory status of RNF. Serono officials said RNF has been submitted both to the FDA and EMEA, and an FDA decision is expected by the end of 1Q07.

TEVA PHARMACEUTICALS' Copaxone (glatiramer, copolymer-1)

Study 9006 of standard dose Copaxone (20 mg) vs. double dose Copaxone (40 mg) failed to meet its primary endpoint of a 60% reduction in the mean number of Gd+ T-1 lesions at Months 7-8-9. Gd+ lesions were reduced, but not sufficiently to meet the goal, though an investigator said, "It is likely that with more patients, significance would have been reached (on the primary endpoint)." Teva is not giving up on high dose Copaxone, and a Phase III trial of 40 mg is just starting.

Double Dose Copaxone Study 9006

Measurement	Copaxone 20 mg	Copaxone 40 mg	p-value
Baseline			
Prior relapses	1.5	1.5	---
Mean number of lesions at baseline	3.4	3.4	---
Results			
Early discontinuation	14%	14%	---
Primary endpoint: Mean Gd+ T-1 lesions at Months 7-8-9	3.62	2.26	Nss, 0.0898 (38% risk reduction)
Median number of Gd+ lesions at Months 7-8-9	2.0	0	---
T-1 Gd+ lesions at Month 3	62% reduction	---	0.0051
T-1 Gd+ lesions at Months 8-9	65% reduction	75% reduction	---
Relapse rate (mean) at Month 9	0.52	0.30	Nss, 0.121 (41% reduction)
Relapse-free patients at Month 9	52.0%	76.0%	0.0183
Time to first confirmed relapse	80 days	213 days	0.0367
Responder analysis			
Relapse free (no Gd+ lesions in the last trimester or the mean number of Gd+ T-1 lesions was reduced ≤50% vs. baseline)	38.5%	69.0%	0.0078
NNT for responders	7.0	3.1	---
Safety			
Injection site reactions	86%	85% (little more painful)	---
Immediate post-injection reactions	22.7% (mild)	32.6% (moderate)	---
Serious adverse events	1 patient	1 patient	---

Study 9006 was a 81-patient, 9-month, double-blind, multicenter (U.S.), randomized, parallel group, Phase II study in RRMS. Both doses were administered daily by subcutaneous injection. Researchers reported 40 mg Copaxone was safe, with slightly more headache, hypoesthesia, diarrhea, arthralgia, dizziness, and palpitations than with 20 mg.

NEW THERAPIES: ORAL AGENTS

There appeared to be a consensus that the introduction of an effective oral agent would increase the percent of MS patients getting treatment in Europe by about 10%, from ~28% to ~38% of MS patients in Europe, but definitely would not double it – at least for a long time. Even an industry source with an oral agent in development agreed, projecting only a 10%-15% market expansion with orals. Another industry source said, "Will patients doing well on an injectable switch to an oral. Some will and some won't, so the uptick will be slow."

At the conclusion of ECTRIMS, President Hans-Peter Hartung of Germany commented, "I think we all sense the excitement and the added momentum resulting from the many-fold explorations of novel therapies which we all hope will help to enlarge our therapeutic armamentarium…I think there was

Oral Drugs in Development to Treat MS

Company	Drug	Type	Status
Already approved for other indications			
Acorda Therapeutics	Fampridine-SR	selective potassium channel blocker	Phase III
GlaxoSmithKline	Avandia (rosiglitzone)	thiazolidinedione	Phase II
Lilly/Takeda	Actos (pioglitazone)	thiazolidinedione	Phase II
Pfizer/Eisai	Aricept (donepizil)	cholinesterease inhibitor	Phase II
New agents			
Active Biotech/Teva	Laquinimod	immunomodulator	Starting Phase III
Antisense Therapeutics	ATL-1102	Antisense (VLA-4)	Phase IIa trial restarted
Biogen Idec	BG-00012	fumarate ester compound	Phase II
Biogen Idec/UCB-Celltech	CDP-323	VLA-4 antagonist	Phase II
French Ministry of Health	3,4-diaminopyridine	selective potassium channel blocker	Phase II
GlaxoSmithKline/Tanabe Seiyaku	T-0047 (683699)	VLA-4 antagonist	Phase II
Novartis	Fingolimod (FTY-720)	spingosine-1 phosphate-1 receptor agonist	Phase III
Sanofi-Aventis	Teriflunomide	protein tyrosine kinase inhibitor	Phase III
Schering AG	ZK-811752	microglia modulator, CCR-1	Preclinical
Schering-Plough	TBC-4746	VLA-4	Preclinical
Serono	Cladribine	immunosuppressant (purine nucleoside analogue)	Phase III (FDA fast track status)

growing awareness at the meeting of new treatments and about information on possible options coming up in the next 1-3 years. Fumaric acid (Biogen's BG-00012) and fingolimod (Novartis's FTY-720) have been explained to people who had not been exposed to them up until now, and they are eager to hear more about whether the clinical effects are sustained in further clinical studies." A Spanish doctor added, "Perhaps the most interesting...were the new products that are very promising and probably will change the therapeutic panorama in the coming year."

Each of the interferon companies – Biogen, Schering AG, and Serono – has an oral agent in development, and there are a variety of newcomers that hope to bring an oral treatment to market. Of the newcomers, the ones getting the most attention are probably Novartis's fingolimod and Sanofi-Aventis's teriflunomide.

ACORDA THERAPEUTICS' oral fampridine-SR

Two days before ECTRIMS, Acorda announced positive results from its double-blind, placebo-controlled, multicenter Phase III trial of oral fampridine-SR, a potassium channel blocker. That 14-week trial was conducted in the U.S. and Canada in 301 patients with relapsing remitting MS or progressive relapsing MS. Patients were permitted to remain on a stable regimen of their current medications, including interferons.

14-Week Phase III Results of Fampridine-SR

Measurement	Fampridine-SR n=229	Placebo n=72	p-value
Primary endpoint: Timed 25-foot walk	N/A	N/A	0.046
Secondary endpoint: Leg strength	N/A	N/A	<.001
Average increase in walking speed	25.2%	4.7%	<.001
MSWS-12	N/A	N/A	<.0001

The trial was conducted under a Special Protocol Assessment (SPA) with the FDA, and the company said that the SPA provides that if all three requirements of the SPA are met, the trial can be used as ***one*** of the trials required to show efficacy:

1. Significantly more consistent walking responders vs. placebo. A responder was defined as a walking speed consistency greater during at least 3 of 4 on-drug visits than their fastest speed on any of the 5 off-drug visits.
2. Statistically significant improvement in walking speed on the last on-drug visit vs. placebo.
3. Responders reported a significantly greater improvement than non-responders on the MSWS-12 scale, a self-rated assessment of walking disability.

Generally, when a company meets the requirement of an SPA, its drug gets approved.

A competitor predicted that fampridine would be an add-on therapy because it is not disease modifying. He said, "Some patients will respond. Those who do will probably get an increase in ambulation."

ACTIVE BIOTECH/TEVA'S laquinimod

This is starting Phase III, but a competitor said it isn't expected to reach market until 2011 and it "has not shown that much efficacy."

BIOGEN IDEC

Biogen has BG-00012 in development and shortly after ECTRIMS announced it will co-develop another oral therapy, UCB-Celltech's CDP-323.

BG-00012, an oral fumarate derivative

This second generation fumaric acid is a small molecule. The first generation fumarate has been approved, particularly in Germany since 1994. It is an anti-inflammatory but may also have a neuroprotective effect. The Phase III trial of BG-00012 is expected to start enrolling the first patients in 1Q07.

A 223-patient Phase II trial found a 69% reduction in new Gd+ lesions at the highest dose (240 mg), which was described as statistically significant (p<.001) and "roughly the same order of magnitude seen with interferons." In a blinded extension, placebo patients were switched at the end of six months to BG-00012. There was also a non-significant trend toward a reduction in the annualized relapse rate, though the trial was not powered to show an effect on relapses. Dr. Kappos, the principal investigator, said, "This (trial) creates hope that this (the annualized relapse rate) may increase over time…The interesting aspect is that this is orally available, and there is the prospect of an increasing effect over time, but that must be explored in further studies. And perhaps there is an indication of a neuroprotective effect."

The most common side effects with BG-00012 were GI side effects, headache, and flushing – which was more than placebo throughout the entire 12 months, but decreased in severity in the second six months. GI side effects also became less frequent from Months 7-12, though they, too, remained more than placebo. There was no signal of increased infections. ALT 3xULN occurred in 13% of treated patients, but was reversible, and there was no concomitant bilirubin increase ≥2xULN.

Fumarate has been used for many years, particularly in Germany, to treat psoriasis. BG-00012 is a second generation fumaric acid. The active agent is dimethyl fumarate. BG-00012 is an enteric-coated microtablet designed to improve GI tolerability, and there is now a suggestion it may have dual action in MS. Dr. Kappos said, "Fumaric acid esters (FAEs) may have both anti-inflammatory and neuroprotective effects. *In vitro* experiments have shown FAEs can influence the presence of cytokines and adhesion molecules thought to be involved in the inflammatory cascade. In addition, preliminary data have also implicated DMF in the regulation of a pathway for detoxification that is central for protection of cells from metabolic and inflammatory stress."

Asked about liver toxicity and ALT elevations with BG-00012, a Biogen official said, "We did notice a few ALT elevations, but no patient had hyperbilirubinemia, so we think it is manageable and reversible after stopping the drug."

24-Week Phase II BG-00012 Results

Measurement	Placebo n=65	BG-00012 120 mg QD n=64	BG-00012 120 mg TID n=64	BG-00012 240 mg TID n=63
Baseline mean EDSS	2.67	2.52	2.51	2.87
Baseline Gd+ lesions	1.6	1.4	2.5	1.3
Completers	59	60	59	57
All discontinuations	9%	9%	13%	16%
Discontinuations due to adverse events/intolerance	2%	8%	11%	13%
Primary endpoint: Reduction in new Gd+ lesions at Week 24	N/A	N/A	N/A	44% reduction
New/newly enlarging T-2 lesions	N/A	N/A	N/A	48% reduction
New T-1 lesions	N/A	N/A	N/A	53% reduction (p=0.014)
Annualized relapse rate	0.29	0.26	0.46	0.17
Reduction in relapses	52%	18%	26%	58%
Adverse events during Months 0-6				
Nervous system side effects	8%	6%	9%	8%
Infection	0	0	2%	0
Flushing: Months 0-6	9%	53%	48%	40%
Flushing: Months 7-12	N/A	9%	11%	12%
Nausea	8%	2%	14%	16%
Abdominal pain	3%	8%	6%	14%

CDP-323

Shortly after ECTRIMS, Biogen Idec announced that it will collaborate with UCB on development of this oral alpha4-integrin inhibitor. At ECTRIMS, a poster reported on PK and PD from three Phase I trials of this VLA-4 inhibitor. CDP-323 was well tolerated in human volunteers at oral doses up to 1000 mg/week. The study found "typical" adverse events and no increase in blood pressure, ALT, or heart rate. The most common side effects were headache and rash. A Phase II trial is expected to start in January or February 2007, though the doses for that study have not yet been chosen. An investigator called it "sort of an oral Tysabri." The advantage to this drug may be that you can stop it and wash it out of the body in a couple of days, so patients could have a "holiday."

NOVARTIS'S fingolimod (FTY-720)

Novartis officials said they are fully committed to fingolimod development. An official explained the company uses a grading system to choose which program to support, with points awarded for things like first-in-class, unmet need, cost of trial, size of market, etc., and he said

fingolimod is now a "high priority," evidenced by the plan to test it in >3,000 patients and by the company starting to build awareness of the drug through press briefings, satellite symposiums, etc.

Asked how fingolimod compares to Serono's oral cladribine, an expert said, "Cladribine is a cytostatic agent with the potential of unspecific immunosuppression. FTY-720 has shown a better efficacy to side effect relationship. The cladribine studies are not so convincing yet." Fingolimod is a continuous QD agent, while cladribine is three pills once a day for 2-4 weeks only.

Novartis officials would not concede that cladribine will be the first oral, but they are not worried if they aren't first. They also pointed out that oral cladribine:

- Really only has one study so far.
- Had mixed results when injected in a Phase II trial.
- The one-trial strategy may not work (for example, the benefit could fall short).
- There may be a dosing issue since no dose-finding study was done. Serono could find it picked the wrong doses for the Phase III.

Notes about fingolimod:

- The half-life is 9-10 days.
- A follow-on with greater specificity is unlikely. A Novartis official said, "We do not expect a more specific (version) would be better. We also note that the efficacy of selective agents is not as good as with dual receptor activation."

PK/PD data

New PK/PD data on FTY-720 was presented at ECTRIMS. This was a pooled analysis of Phase I and Phase II patients treated at the 0.5 mg, 1.0 mg, and 1.5 mg doses (150 healthy volunteers at all three doses, and 134 RRMS patients at 1.25 mg). The study found:

➢ **Lymphocyte counts.** Are decreased dose-dependently, but they stabilize by Day 7. However, levels return to normal in 4-8 weeks after drug discontinuation in healthy volunteers. In MS patients there was a low (2.2%) incidence of serious or severe infections, but there was no correlation between low lymphocyte count and the incidence of severe or serious infections.

➢ **Heart rate and rhythm.**

- In both healthy volunteers and MS patients, there was a dose-dependent decrease in heart rate that begins within 2 hours of the first dose, reaching a maximal effect at 4-5 hours post-dose, then attenuating with continued dosing and finally normalizing by three months. No symptomatic bradycardia was reported.
- In MS patients, a dose-dependent 9 ms increase in the mean PR interval was seen. This returned to baseline by Day 7 on drug.
- Two MS patients (of 31) developed low level (first-degree) AV block.

24-month extension study – early benefit sustained at 2 years

The 24-month results were presented at ECTRIMS from the D-2201 Phase II extension study of two doses (1.25 and 5.0 mg QD) of fingolimod. Of the 281 original patients, 250 patients entered the extension study, and 189 completed an additional 18 months on the drug. After 15 months, the protocol was amended so that everyone in the extension was switched to the lower, 1.25 mg, dose.

24-Month Fingolimod Phase II Extension Study

Measurement	Placebo switched to fingolimod 1.25 mg n=40	Placebo switched to fingolimod 5 mg n=43	Fingolimod 1.25 mg n=94	Fingolimod 5 mg n=94
Relapse free at Month 24	54%	60%	75%	77%
EDSS progression	19%	26%	17%	25%
Annualized relapse rate				
Months 0-6	0.70	0.69	0.36	0.32
Months 0-24	0.38	0.28	0.20	0.22
Discontinuations				
Months 0-6	6 patients		5 patients	11 patients
Months 7-24	25%	19%	27%	25%
Due to adverse events in Months 7-24	5.0%	11.6%	12.6%	10.0%
Due to unsatisfactory therapeutic effect	7.5%	2.3%	0	2.5%
Adverse events in Months 7-24				
Any	87.5%	90.7%	88.5%	95.0%
Any severe adverse event	12.5%	14.0%	10.3%	13.8%
Any serious adverse event	5.0%	11.6%	8.0%	15.0%
Any infection	37.5%	44.2%	50.6%	57.5%
Any severe infection	0	0	2.3%	2.5%
Any serious infection	2.5%	4.7%	0	0
Nasopharyngitis	12.5%	18.6%	19.5%	26.3%
Headache	17.5%	18.6%	14.9%	11.3%
Influenza	17.5%	9.3%	9.2%	16.3%
Leukopenia	2.5%	7.0%	11.5%	13.8%
ALT increase	12.5%	14.0%	4.7%	5.0%
Hypertension	5.0%	4.7%	10.3%	5.0%
URTI	0	9.3%	4.6%	11.3%
Depression	0	11.6%	5.7%	3.8%

At 6-months, the drug looked efficacious, and the results held up over the next 18 months for both fingolimod patients and placebo patients switched to fingolimod. There were no new safety effects.

Researchers reported:

- **Disability.** There was no change in mean EDSS with fingolimod over 24 months in the Phase II trial, and Dr. Kappos said, "This may indicate a treatment effect, but it is still too early to say. We need the Phase III data to say that."
- **Annual relapse rates.** 0.20-0.22. And 75%-77% of patients were free of relapses at 2 years vs. 55%-59% of the former placebo patients (which is roughly comparable to where FTY-720 patients were after their first year of therapy).
- **Active MRI lesions.** After 2-3 months, a difference began to be seen by MRI between fingolimod and placebo in terms of the number of Gd+ T-1 lesions. That difference reached significance by 3 months, and the effect was maintained over 24 months. >80% of patients were free of active MRI lesions at 2 years, and patients who switched from placebo to FTY-720 showed a "clear reduction" in Gd+ lesions, which researchers saw as corroboration of the results of the core study.

Issues to watch with fingolimod

- **Liver.** There are some liver elevations with fingolimod, but an investigator said, "They appear to stabilize, so I think this is not really a concern. We see the same thing with interferon-1a." Another speaker said ALT 3xULN occurs in 12%-14% of patients but was clinically asymptomatic.
- **Adverse events.** GI (diarrhea and nausea), respiratory disorders (mostly dyspnea) which mainly occurred at the higher 5 mg dose (that is not going forward in the Phase III trials), and non-serious infections (nasopharyngitis and flu).
- **Heart rate.** There was a transient, dose-dependent decline in heart rate in the first hours after dosing, which attenuated with continued dosing. This was explained as the result of receptors for this drug in the heart.
- **FEV_1.** There is a mild dose-dependent FEV_1 decline upon treatment initiation (mainly at 5 mg) but no changes in pulmonary function so far.
- **PRES (posterior reversible encephalopathy syndrome).** One case occurred in the first six months of the Phase II trial. This was a 52-year-old woman who developed PRES after 10 weeks on the 5 mg dose. She had headache, acute cortical blindness, ophthalmoplegia, dysarthria, and ataxia. On MRI she had diffuse occipital and brainstem T-2 hyperintensities. The patient only partially recovered, having residual right homonymous hemianopsia and mild ataxia. There have been no additional cases.
- **Teratogenicity.** This was observed in some animal species but not all. In the trials, women are required to use contraception.
- **Macular edema.** There were cases of macular edema when FTY-720 was tested in transplant patients, but there haven't been any confirmed cases in MS patients. An investigator said, "In the transplant patients, it was given with cyclosporine…In MS, there was an extensive program to look repeatedly at all patients who were treated with FTY-720, and there has been no single confirmed case in the patients in the extension study. So, we seem to be reassured." He said OCT (optical coherence tomography) was done on "many" MS patients on FTY-720 without any sign of a problem. However, the FDA is requiring careful monitoring for this.
- **Lymphocytes.** There is no negative impact on the lymph nodes, no swelling. A Novartis official explained, "Only 2% of total lymphocytes are in the blood. Fingolimod reduces blood lymphocytes by 50%-60% and puts them into the lymph node system, but we don't see an increase in (node) size." At the doses being used in the Phase III trial, the company expects lymphocyte counts to decrease to 30%-40% of baseline.
- **Drug-drug interaction.** FTY-720 is not metabolized through CYP450; in fact, it is metabolized by enzyme activity, so the company does not anticipate any major drug-drug interactions, but that still needs to be evaluated further.

Ongoing studies

Three randomized, double-blind trials of two doses of fingolimod (0.5 mg and 1.25 mg) are ongoing:

- **FREEDOMS.** This is the ~1200-patient, 2-year (plus extension), ongoing ex-U.S. Phase III trial, comparing fingolimod to placebo in RRMS. There will be no interim data analyses. The primary endpoint is reduction in relapses. Enrollment is expected to be complete by the end of 2006 or early 2007, with data available at the end of 2008 and a 2009 EMEA submission. According to **www.clinicaltrials.gov** the only country that has started enrolling in this trial is Italy.

- **FREEDOMS-2.** This is a ~950-patient, 2-year (plus extension), U.S.-only Phase III trial. It compares fingolimod to placebo in RRMS. There will be no interim data analyses. The primary endpoint is reduction in relapses. The first patients have been enrolled, but Novartis reportedly was not successful in getting the FDA to drop some of the more onerous monitoring requirements. A Novartis official said, "In our initial discussions with the FDA, they wanted more monitoring. Essentially it is the same monitoring as in the ex-U.S. trial, but more often." An investigator said, "It is a new compound, so the requirements make sense." Full details on the protocol will follow, but the U.S. trial requires:

- A 24-hour Holter-monitor for the first day of therapy only in a subset of patients (a few hundred patients).
- An ophthalmologic exam at ***every*** visit.
- Periodic FEV_1 testing, but not at every visit, to show there is no change.
- Lab values at every visit.
- EKGs at unspecified intervals.

➢ **TRANSFORMS.** This is a 1,200-patient, global, double-dummy, 1-year (plus extension) comparison of fingolimod to Avonex QW in RRMS. Fingolimod patients will get sham injections. Asked why Avonex was chosen as the comparator, an investigator said, "The difference between the interferons are not so important, and we wanted to provide patients with the option with the lowest number of injections." There will be an interim data analysis.

SANOFI-AVENTIS'S oral teriflunomide

This is a derivative of Sanofi-Aventis's Arava (leflunomide), which is approved in rheumatoid arthritis. The results were presented from an interim analysis of an open-label 144-week extension of a Phase II randomized, double-blind, placebo-controlled, two-dose trial. Researchers reported that teriflunomide was well-tolerated with few dropouts, but placebo patients switched to teriflunomide showed an ***increase*** rather than a decrease in the number of MRI lesions at the higher dose. A Phase III trial of teriflunomide is ongoing, with results expected at the end of 2009. The company also is planning another Phase III trial in CIS patients.

Asked what advantages teriflunomide might have over oral cladribine, a Sanofi-Aventis official said, "Teriflunomide is a pure immunomodulator, it is a metabolite of a product already registered, and tolerance is good." But he said the efficacy of teriflunomide is not completely demonstrated yet.

SERONO'S oral cladribine

A week before ECTRIMS, Serono announced that the FDA granted fast track status to oral cladribine – (purine nucleoside analogue that interferes with the behavior and proliferation of certain white blood cells, particularly lymphocytes). Serono believes this will be the first oral agent to get approved, with at least a year's lead time on Novartis's fingolimod (FTY-720).

Recruitment is just finishing for CLARITY, a two-year, double-blind, multicenter, 1,300 patient Phase III trial. The trial is testing two doses against placebo, both 3 pills once-a-day. A Serono official said they expect to be able to get approval with only one Phase III trial. No data will be available until late 2008, and the company hopes to file this drug by the end of 2008. An official said, "Our data requirements with the FDA are different (one trial instead of two) because of the market history of cladribine. We were told one large Phase III will be sufficient if the efficacy is compelling."

There are no planned interim analyses in CLARITY. An official said, "We've seen some downside to trying to do that (interim analysis) with a new molecular entity."

A study by U.S. researchers retrospectively evaluated a series of six patients with aggressive RRMS and active MRIs who were treated with cladribine due to a rapid increase in the number and severity of relapses in the previous 6-12 months leading to a progressive accumulation of disability. Cladribine was given at 0.07 mg/kg/day monthly in 2-4 courses, and it was administered again at one year in 4 patients due to severe relapses.

Cladribine Compassionate Use Study

Measurement	Pre-cladribine	At 6 months	At 12 months
EDSS	5.5 - 7.0	1.5 - 5.5	1.5 - 5.0
Mean relapse rate	2.67	---	0.71

144-Week Teriflunomide Phase II Extension Study

Measurement	Placebo patients switched to 7 mg teriflunomide	Placebo patients switched to 14 mg teriflunomide	7 mg teriflunomide	14 mg teriflunomide
Baseline annualized relapse rate	0.64	0.50	0.56	0.40
Relapse rate at 144 weeks	0.36	0.58	0.48	0.21
Median change from baseline in relapse rate	-0.28	+0.08	-0.08	-0.19
EDSS mean change from baseline	2.88 (Nss)	2.37 (Nss)	3.15 (Nss)	2.61 (p=0.002)

OTHER MS DRUGS IN DEVELOPMENT

BIOGEN IDEC

➢ **Rituxan (rituximab).** This is being developed with Genentech (U.S.) and Roche (OUS). He said, "We are excited about it in MS." The company announced in August 2006 that a North American Phase II trial in 104 patients with RRMS met the primary endpoint of a reduction in the total number of Gd+ T-1 lesions by MRI vs. placebo, but no additional details were made available. In that trial, Rituxan was administered in two infusions (Day 1 and Day 15).

A two-year Phase II/III study in primary progressive MS (PPMS) has completed enrollment and data will be presented at a meeting in early 2007, but the company would not say what meeting (perhaps the American Academy of Neurology in April 2007). Currently, there is no FDA-approved treatment for PPMS.

➢ **Zenapax (daclizumab).** Zenapax is FDA-approved and sold by Roche for renal transplant. In MS, development is a collaboration between Biogen Idec and PDL BioPharma.

Biogen senior vice president for neurology R&D, Dr. Alfred Sandrock said the NIH pilot study was "exciting" and showed a 78% reduction in new contrast-enhancing lesions (CELs) on MRI after 7 months. Currently, daclizumab is in the Phase II CHOICE trial, an add-on study in RRMS. The primary endpoint is the number of new Gd+ lesions by MRI. A Phase II monotherapy trial will start soon.

Utah researchers reported on the seven patients who have completed 27.5 months of therapy with this anti-IL-2 humanized monoclonal antibody in an NIH-designed Phase I/II trial. They found:

- A significant reduction from baseline in total CELs, new CEL, and relapses was observed by three months, and the effects were maintained throughout the study.

Other Drugs in Development to Treat MS

Company	Drug	Type	Status
Interferons			
Atada AG	interferon beta	interferon	N/A
BioPartners	interferon beta	interferon	Phase III
GeneMedix	interferon beta	interferon	N/A
Nautilus Biotech	interferon beta	interferon	N/A
Inhaled agents			
Biogen Idec	Inhaled Avonex	interferon	Discovery
Serono/Syntonix	Inhaled Rebif	interferon beta-Fc	N/A
Antibodies and biologics			
Abbott	ABT-874	anti-IL-12 monoclonal antibody	Phase II
Biogen Idec	IDEC-131	monoclonal antibody	N/A
Biogen Idec	Rituxan (rituximab)	monoclonal antibody	Phase II in RRMS Phase II/III in PPMS
Genzyme/Schering AG	Campath (alemtuzumab)	humanized anti-CD-52 monoclonal antibody	Phase II
Johnson & Johnson	CNTO-1275	anti-IL-12 and anti IL-23 monoclonal antibody	N/A
Neurocrine Biosciences	NBI-5788	peptide-based immunomodulator	Phase II
PDL BioPharma/Biogen Idec	Zenapax (daclizumab)	anti-IL-2 (anti-CD-25)	Phase II
Schering AG	Mesopram	PDE-4 inhibitor	Dropped because of tolerability (vomiting)
Vaccines and tolerizing therapies			
BioMS Medical/Teva	MBP-8298	tolerizing (Dosed twice a year)	Phase III
Immune Response Corp.	NeuroVax	vaccine	Phase II
Opexa Therapeutics	Tovaxin	autologous T-cell vaccine	Phase IIb to start by end of 2006
Pipex Therapeutics	Solovax	T-cell vaccine	N/A
Other agents			
Biogen Idec	Nogo	Nogo receptor blocker	Preclinical to start soon
Biogen Idec	LINGO-1	a component of the Nogo-66 receptor/p75 signaling	Discovery
Biogen Idec	Galiximab	monoclonal antibody, anti-CD-80	N/A
Biogen Idec	Lumiliximab	monoclonal antibody, anti-CD-23	N/A
Neurocrine Biosciences	NBI-5788	altered peptide ligand	Discontinued (Phase II trial missed primary endpoint)
Teva Pharmaceuticals	TV-5010	synthetic copolymer	Phase II

- EDSS improved by three months and became statistically improved over time.
- Timed ambulation improved significantly by 4.5-7.5 months.
- Monotherapy may be sufficient for some patients, but others will require combination therapy.
- Patients start relapsing as soon as the therapy is stopped.

2-Year Phase II Results with MBP-8298

Measurement	All patients		HLA DR2 and/or DR4 patients	
	MBP-8298	Placebo	MBP-8298	Placebo
Patients with SPMS	11	11	7	7
Patients with PPMS	5	5	3	3
Disease duration	13 years	14 years	15 years	12 years
Median EDSS score at baseline	6.5	6.3	6.5	6.5
Results				
Patients who progressed	31% (p=0.29)	56%	0 (p=0.01)	60%
Median time to confirmed disease progression (EDSS)	---	---	78 months	18 months

➢ **Nogo inhibitor.** This is a protein on the growth cone of regenerating axon sprouts that interacts with all known inhibitors of axonal regeneration expressed by oligodendrocytes. Blocking interaction of the Nogo receptor with its ligands could improve the regeneration of nerve fibers damaged by MS. Biogen is collaborating with Yale on this. Dr. Sandrock said the collaborators "never saw anything like it. Remyelination was almost complete (in animals) in 3-4 days." Preliminary animal studies have been done, but it is still in the discovery stage. Preclinical studies (toxicology studies) are to start soon.

Dr. Sandrock said, "We've shown *in vitro* and *in vivo* that if you block NogoR, you can improve nerve fiber regeneration. And we've shown that…we can improve remyelination…We found that CNS myelin inhibits neuronal outgrowth…Myelin discourages axonal regeneration. But with myelin + a NogoR inhibitor, we see beautiful outgrowth of axons, indicating we can improve axonal regeneration by blocking NogoR. Nogo treatment improves hind limb movement in animals at Weeks 2-4."

➢ **LINGO-1.** This protein on the cell membrane of neurons and oligodendrocytes is a negative regulator of myelination. Dr. Sandrock said, "Blocking LINGO-1 could enhance remyelination in MS lesions…We found LINGO is only expressed in the CNS, not in any other tissue. Two cell types express it: neurons and oligodendrocytes. I can think of no other protein expressed only in the CNS and by these two cell types." He said that in LINGO-1 knockout mice, there is evidence of early myelination in the spinal cord, but not having LINGO or blocking LINGO improves myelination, "We took adult rats and injected anti-LINGO and found it promotes remyelination after a lysolecithin-induced demyelination."

Could you combine the Nogo inhibitor and LINGO-1? Dr. Sandrock said, "Yes, we have actually thought about that, and we are starting some animal studies of the combination."

BIOMS MEDICAL/TEVA'S MBP-8298. There was a poster on a prospective, double-blind, placebo-controlled, 24-month, open-label study that found MBP-8298 significantly delayed disease progression in 32 patients with either SPMS or PPMS with no relapses in the prior two years. MBP-8298 was administered IV at 500 mg at six-month intervals.

- CNS anti-MBP autoantibodies appeared after 36 months of treatment in one patient with HLA DR3,3 who registered the first progression at six months.
- There were no serious adverse events related to the drug.
- The most common drug-related adverse events were injection site reactions and occasional facial flushing.
- Neither HLA DR haplotype nor suppression of anti-MBP autoantibodies was an absolute predictor of clinical benefit in individual cases.

This synthetic peptide is currently in a large, confirmatory Phase III trial in PPMS, and a compassionate use program is ongoing.

BIOSIDUS'S Blastoferon. The company presented a poster on its biosimilar interferon-β-1a, which is approved and sold in South America, vs. Rebif. The *ex vivo* genome expression profile study showed the genomic pharmacodynamic action of the two drugs was similar.

OPEXA THERAPEUTICS' tovaxin T-cell vaccine. This is in Phase II.

PEPTIMMUNE'S PI-2301. Peptimmune is developing this new peptide copolymer, which has a 1-amino acid substitution. Currently, it is in animal studies, and the company has filed an IND for a Phase I study. An official said the FDA has some questions about the IND, and the company expects to respond in the next five weeks and hopes to be allowed to begin the Phase I in 1Q07.

In a poster at ECTRIMS, Peptimmune researchers reported that a study in an animal model of MS found PI-2301 more efficacious than Copaxone. They also concluded that PI-2301 could be administered daily or weekly and may be useful where Copaxone is not.

SCHERING AG/GENZYME'S Campath (alemtuzumab). There appears to be a growing sense that Campath is as effective, or even more effective, as Tysabri, but there is no excitement about this, and no marketing effort behind Campath as there is with Tysabri, oral cladribine, and FTY-720. A Schering source said that the comment I got from a senior official last year is still true: Schering is very risk averse. The company is choosing to go slowly with Campath and see what happens with the re-launch of Tysabri. His question was: How risk averse will Bayer be? That could be the wild card in development of Campath for MS.

Two U.K. doctors without industry ties said they are using Campath off-label now, and they said they will prefer Campath to Tysabri even if Tysabri gets NICE approval because Campath is so much cheaper – and, they insisted, more effective. They reported on their experience with Campath in 32 patients with aggressive RRMS with accumulating disability.

- Annualized relapse rates fell from 2.55 to 0.24 over 12 months and to 0.18 overall ($p<.001$).
- EDSS remained stable in 17 patients and improved in 6.

A Schering official said the company is committed to Campath, but Campath has not been promoted yet because there just isn't enough data to do that yet. He explained why there appears to be little excitement in the neurology community about Campath, "The knowledge we have on Campath is based on a pilot study and on an interim analysis from an ongoing study, so there are limited data…There have been no public presentations on the results, and there is no other information available, allowed to be distributed or even known to speakers who do presentations. So, there is nothing to work with PR-wise. And the DSMB wouldn't like us to discuss the ongoing study."

There are likely to be three-year data on Campath next year at ECTRIMS. Shortly after that (before the end of 2007), a Phase III trial is planned to start, and the company is currently in the planning stages for that trial. An official said, "Based on the current data, we have reasons to be cautious but very optimistic at the same time, because the Year 2 interim data showed a level of efficacy which is unprecedented."

Campath will require a risk management plan, but the key risk – idiopathic thrombocytopenic purpura (ITP) – can be monitored and reversed. An official said, "Most if not all the patients who got ITP are off treatment now. One patient even resolved spontaneously. It is possible the cause is more benign than the natural cause of idiopathic ITP. The key difference for me is that, with Campath, patients need to be compliant with monthly blood counts, but they can do those anywhere; they don't have to see the neurologist or go to an infusion center. And the blood tests keep patients somewhat alert…I think the risk management plan is key and very import to implement adequately. I am relatively optimistic (about Campath)."

Doctors are interested in this but not especially excited, though interest may pick up now that it is "on a more even footing with Tysabri."

SERONO'S Inhaled Rebif. A Serono official said this is a long-term – an 8-year – program. There will be no data in the near future.

MISCELLANEOUS

GENOMICS. Schering AG is sponsoring the BEST PGx pharmacogenomic and pharmacogenetic study to identify predictors of treatment response to Betaseron. The trial is fully enrolled with 147 patients, and data are expected at ECTRIMS next year. The results are expected to demonstrate how well gene expression microarrays are as predictors of response to Betaseron in RRMS, including treatment efficacy and risk of adverse events.

Plasmapheresis. This is being tested, particularly for patients with pathology dominated by B-cells.

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