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by Lynne Peterson

SUMMARY

Results were positive from the BENEFIT trial of a high dose of Schering AG/Berlex's Betaseron/Betaferon in early MS, but doctors said this may not change their prescribing practices. ♦ Novartis's oral fingolimod (FTY-720) looks promising as an oral therapy for MS. ♦ Schering AG/ Genzyme's Campath has safety issues, but it is very effective, and doctors believe it will find a role. ♦ Protein Design Lab's daclizumab and Serono's Myelinax (oral cladribine) are both worth watching. ♦ The spectacular efficacy of Biogen Idec/Elan's Tysabri held up at two years in the SENTINEL trial. Tysabri was a hot topic at the meeting, with most doctors predicting it will return to the market. European doctors were taking a much more conservative approach to possible future use than U.S. doctors. There is no predictive test, just a diagnostic test, for PML or JC virus.

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MULTIPLE SCLEROSIS UPDATE

A joint meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) in Thessaloniki, Greece, from September 28 - October 1, 2005, offered a good glimpse at new drugs in development for multiple sclerosis (MS) as well as new developments with approved agents.

Currently, about 62% of relapsing remitting MS (RRMS) patients in the U.S. are on immunomodulatory therapy. National Multiple Sclerosis Foundation guidelines advise doctors and patients to consider one of the four immunomodulators – Biogen Idec's Avonex [intramuscular (IM) interferon-β1a], Schering AG/Berlex's Betaseron/Betaferon (interferon-β1b), Ares Serono's Rebif (subcutaneous interferon-β1a), or Teva Pharmaceuticals' Copaxone (glatiramer acetate, copolymer-1) – in definite MS ***as soon as possible***.

Doctors were fairly optimistic about Novartis's fingolimod (FTY-720), but several sources noted that studies are getting harder to do in MS and there are a lot of drugs in development with a limited number of patients. A U.K. doctor said he has more requests for trial patients than he can accommodate, so he plans to limit his participation to trials of drugs that are already approved in another condition – because there are safety data on those drugs – or to monoclonal antibodies with monthly (or less) infusions. That may be good news for:

- **SCHERING AG/GENZYME'S Campath (alemtuxumab),** which is approved to treat B-cell chronic lymphocytic leukemia (CLL).
- **SERONO'S Myelinax (cladribine),** which is approved for treatment of hairy cell leukemia and chronic lymphocytic leukemia that does not respond to other chemotherapy agents. A U.S. doctor said, "Oral cladribine and FTY-720 have the least baggage…I believe there are more side effects with Campath than we've heard about."
- **PROTEIN DESIGN LAB/ROCHE'S Zenapax (daclizumab),** which is approved for prophylaxis of acute organ rejection in patients receiving renal transplants, as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

MS trial design

Experts believe that future MS trials will require a new design. Placebo-controlled trials are getting harder – if not impossible – to perform. Non-inferiority studies require too many patients to be feasible. What's the answer? FDA officials and leaders in the field met in December 2004 on MS trial design, and a paper is due to be published soon that will outline the recommendations that came out of that

meeting. The paper is expected to suggest that a Phase III dose-response type of trial with a range of doses, where the lowest dose has a minimal effect and there is a dose effect, is sufficient without a placebo arm or a comparator arm. A participant in that meeting said the FDA will buy the recommendations, but other sources doubted the FDA would accept this type of trial design.

Early therapy

Experts continue to urge doctors to treat patients earlier and more aggressively, and physicians have heard the message, but not all are convinced. The BENEFIT trial *(see page 6)* may help reinforce this message, but it did not appear to convince many doctors at ECTRIMS to treat any more patients earlier – or to switch to Betaseron, which was the drug studied in that trial.

In Germany, a doctor said the average patient is not treated for 1.7 years after the first event. A U.S. doctor said treatment begins earlier in the U.S., but not as early as it should, "In the U.S., guys in practice are fearful…And that's where most patients are (in community practices)…A lot of folks in practice are a little nervous looking at a patient with an optic nerve lesion and otherwise well…The big challenge has been to teach them that 50%-80% of people at first attack have lesions….People focus on when patients present, not when it begins…We try to underscore what we call early therapy isn't necessarily early therapy…No one would say you only had one heart attack, let's wait for another one…MS is not different from heart disease…At least in our clinic, if you have one event that is a classic event for MS and we ruled out conditions that can mimic MS, and the patient has an MRI signature that looks like MS…then the paradigm shift is to use MS as a working diagnosis…So with one event, the working diagnosis is MS, and we treat those patients." Another U.S. doctor said, "We know we can affect the disease even more in the early phase of the illness – CHAMPS and ETOMS both showed there is a better treatment effect early on."

The question is whether affecting the disease in the early phase actually changes long-term outcomes.

Diagnosing MS

The median time from onset of MS to the secondary progressive stage is 19 years, with an average of 2.5% of MS patients progressing per year. The median time from MS onset to the second neurological episode is 1.9 years, and this declines with time. A speaker said, "If you are thinking of non-reversible disability, it takes a long time from onset to reach different levels…It is not a very sensitive measure in the short-term…Short-term confirmed or sustained worsening of disability is mainly ***not*** irreversible and is relapse-driven.

MS Diagnostic Approaches

Clinically Definite MS (CDMS)		McDonald	
Relapsing remitting (RRMS)	58%	Exacerbating remitting onset	85%
Secondary progressive (SPMS)	27%		
Primary progressive (PPMS)	9%	Progressive onset	15%
Progressive-relapsing	6%		

Combination therapy

Rationale for combination therapy:

- Single therapies alone seem to fail to contain disease activity.
- Some therapies have a theoretical potential but have not proven beneficial, but maybe in combination with first-line disease modifying therapies (DMTs) there will be a benefit, though that remains to be proven outside of what are really small trials.
- Combination therapies with different mechanisms of action may be synergistic.

Arguments against combination therapy:

- Drugs with different mechanisms may compete with each other so that the combined effect is less than either agent alone (antagonistic instead of synergistic).
- New or unexpected toxicities could be encountered, which is really a concern since PML (progressive multi-focal leukoencephalopathy) was seen with Biogen Idec/ Elan's Tysabri (natalizumab).
- There is a lack of solid data for either the efficacy or safety of combination therapy.

The CombiRx trial, funded by NIH, is underway, comparing Avonex and Copaxone in RRMS. A speaker said, "The safety results of this will be of great interest as well as the efficacy data."

Time from Onset of MS to Non-Reversible Disability

EDSS status	Definition	Median time to onset of non-reversible disability in all MS patients	Median age	Median time to onset of non-reversible disability in RRMS patients
EDSS 4	Limited walking ability but able to walk without aid or resting for more than 500 meters	8.4 years	42	11.5 years
EDSS 6	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting	20.1 years	53	23 years
EDSS 7	Unable to walk more than ~5 meters even with aid, essentially restricted to wheelchair	29.9 years	63	33 years

Steroids

Steroids are widely used in MS, but with little data on how, when, dose, regimen, route, etc. A trial of methotrexate plus Avonex is underway, with the primary endpoint MRI.

Currently Approved Therapies

Biogen Idec's Avonex (IM interferon-β1a)

Biogen is sponsoring two adherence trials:

➢ **Global Adherence Project (GAP).** Biogen launched this trial at ECTRIMS. It is a non-U.S., multi-national, observational study to evaluate patient adherence to long-term treatments in a real-world setting. GAP is designed to determine adherence to MS drugs (Avonex, Betaseron, Copaxone, or Rebif) and to identify factors that contribute to non-adherence. Patients are being evaluated by their neurologists, through a validated MS quality of life scale, and with a self-reported questionnaire that collects data on disease status, treatment, and factors that may have affected adherence to treatment during the course of therapy. Only patients treated by neurologists are being enrolled. This trial, which is being led by Dr. Bernd Kieseier at Heinrich-Heine Universitat in Dusseldorf, Germany, is due to complete in October 2005, with results at the American Academy of Neurology meeting in April 2006.

➢ **U.S. study.** A similar study is underway in the U.S., led by Dr. Elliot Frohman of the University of Texas Southwestern Medical Center in Dallas. This study is looking at patients who have been on therapy for a minimum of six months. Interim results from >700 patients studied indicated that 38% of patients were non-compliant at some point during a four-week period. A speaker said that compliance at his clinic improved 33% to ~90% by spending more time talking to patients, examining their injection sites, etc.

Biogen Idec/Elan's Tysabri (natalizumab)

New data

Two-year results of the SENTINEL trial of Tysabri + Avonex in RRMS were presented, and the remarkable efficacy results reported at one year held up at two years. Relapses were reduced by 55%, sustained disability progression was reduced by 24%, quality of life improved (less pain, less fatigue), and vision (contrast sensitivity) improved. But there was no statistically significant impact on EDSS score. There also were no new non-PML safety issues raised.

2-Year Results of SENTINEL Trial

Measurement	Placebo + Avonex (30 µg QW) n=582	Tysabri (300 mg E4W) + Avonex (30 µg QW) n=589	p-value	Relative risk reduction with combination
Demographics				
Age	39.1	38.8	---	---
Mean number of relapses in prior year	1.94	1.44	---	---
Discontinuations	6%	5%	---	---
Withdrawals	16%	12%	---	---
Completed two years	84%	88%	---	---
Primary endpoint #2: Sustained disability progression at 2 years	29%	23%	.0238	24%
Sustained disability progression by EDSS status				
EDSS ≥4.0	8% (n=428)	6% (n=459)	.187	29%
EDSS ≥6.0	5% (n=579)	3% (n=588)	.162	35%
Other results				
Annualized relapse rate	.74	.34	<.001	55%
Risk of ≥relapses over 2 years	64.4%	40.1%	<.001	50%
Annualized rate of relapses requiring steroid therapy	.58	.23	<.05	60%
MSFC mean	- 0.01	+ 0.05	<.001	---
Quality of life by SF-36: physical	- 0.93	+ 1.03	<.003	---
Quality of life by SF-36: mental	- 0.96	+ 0.18	Nss	---
Change in visual function (contrast sensitivity)	- ~0.3	+ ~1.2	.039	---
MRI analysis				
Mean number of gd+ lesions	0.9	0.1	<.001	89%
New or enlarging T2 hyperintense lesions	5.4	0.9	<.001	83%
New hypointense counts	4.1	2.3	<.001	44%
Adverse events				
Hypersensitivity reaction	<1%	1.9%	---	---
Deaths	0	2 patients	---	---
Infusion reactions	20%	24%	---	---
Infections	81%	83%	---	---

PML testing

After two cases of PML were reported in MS patients taking Tysabri – and, later, a Crohn's patient on Tysabri alone (with no interferon) – an independent adjudication committee (IAC) was established to review all Tysabri patients. There were five members of the IAC:

- **3 voting members:** Eugene Major, PhD, Dr. David Clifford of Washington University, and Dr. Tarek Yousry of Queen's Square.
- **2 non-voting members:** 1 from Biogen Idec and 1 from Elan.

Dr. Major said his CLIA-certified lab has developed a sensitive, quantitative, validated assay for the JC virus and its close cousin, the BK virus, in cerebrospinal fluid (CSF). He commented, "Our assay has a detection limit of 5-10 copies per 500 µl of sample…That level of sensitivity gives us a very good measurement of the levels of JC or BK virus DNA. So when we find a positive sample, we are sure of a biological relevance."

The IAC testing found no additional cases of PML in Tysabri patients, but there also was no increased incidence of the JC virus in the cerebrospinal fluid (CSF) of MS patients. Dr. Major said, "In none of the samples did we find JC virus present…We never found JC virus present in non-PML patients. In this study, we did not find any JC virus present in any of the study participants."

Dr. Major explained that JCV is ubiquitously distributed worldwide in the population, at a rate of 2%-3%, "The majority of individuals have the JC virus (in their plasma), so 2%-3% of healthy individuals are always positive at any time point. That is probably true of the BK virus as well."

CSF is different – JC virus is only present when the person has PML. An analysis of CSF from 329 Tysabri patients and samples from 401 MS patients collected by the Karolinska Institute in Sweden found no JC virus in those patients. By comparison, a 2.3% incidence of JC virus, in line with the expected rate in the general population, was found in plasma samples from 214 patients.

He concluded:

- JC virus DNA is not found in the CSF of non-PML patients, including MS.
- The levels of sensitivity of Q-PCR assay are related to template extraction methods.
- Detection of JC virus DNA needs to be examined in the cell compartment in blood (i.e., PBMCs as well as serum/plasma).

Dr. Major insisted that testing CSF for JC virus can confirm a case of PML, but it cannot be used as a screening test. He also found no risk factors that could predict who would develop PML. "PCR testing of CSF can be diagnostic but not prognostic," he said, adding, "We've never found JC virus in the CSF of a non-PML patient…We would like (a screening tool), but we are not there yet. But we do have a detection test. The diagnostic test for PML is by PCR in CSF, not in serum…You can have PML without JC virus in the blood – if there is a background of immunosuppression."

Dr. Major also warned that it is wrong to think that MS patients can be monitored for PML and simply treated if they get the virus. He said, "There is no reason to think any of these individuals (Tysabri patients) initiated PML or that they cleared the virus."

Asked how he would advise regulators if asked – and he said he has not yet been asked – about the best way to manage the risk of PML, he said, "Every few months test the serum, and if the (JCV) number is high, then test the CSF…But you might miss a spike with serial monitoring (of serum)…Immuno-suppressed individuals are at (additional) risk." He estimated the risk of PML is <1% in transplant patients, about 5% in HIV patients, and, so far, 0.1% (1:1,000) with Tysabri.

Asked how awareness of the risk of PML with Tysabri could help doctors avoid the next case if they can't predict who will develop the disease, a Biogen speaker said, "We should try to see if there are predictors, but possibly we won't find them…I think it is very important to be aware of the risk…I think it is impractical to do repeat MRI…I think clinical vigilance is most important to watch out for it, for clinical signs and symptoms." An American doctor added, "We would want to avoid the drug (Tysabri) in patients with immunosuppression …which might be an independent risk factor beyond the risk of Tysabri…So, you might want to avoid the use of concom-itant immunosuppressant drugs…Beyond that, there is no predictor that we know."

Outlook for future use

European neurologists have a very different view from American neurologists of how Tysabri should be used if and when it ever returns to the market. European doctors are taking a very cautious approach to Tysabri, predicting it would be used for <5% of patients, on average. In contrast, American doctors estimated that they would use it for 25%-33% of their MS patients. Yet, there was no consensus among doctors who said they would use Tysabri as to who should get it; some said they would give it only to interferon (IFN) naïve patients, and others said they would only give it to patients who were continuing to progress on an IFN/Copaxone.

Among the European comments were:

- *Germany #1:* He estimated that after 12 months on the market he would expect to be using Tysabri for <5% of his patients, "There are a low number of patients who desperately need something. We really need to learn the mechanism (of PML); I don't believe it is combination therapy with Avonex."

- *Sweden #1 (Biogen speaker):* "For the first two or three years, I'd use it in newly diagnosed patients who are rapid deteriorators, which is about one-third of the naïve population. I think we could do a study in that group…I think the next thing we will do is a re-dosing (re-challenge) study of the patients who were in trials…It is important to get this back on the market, but it may be restricted like Novantrone (Serono, mitoxantrone) at first to see how it works…Patients all want it back." He estimated that 25%-30% of his patients would be on Tysabri within a year of a re-launch if use were not restricted, and he said use as salvage therapy would depend on how the re-dosing study goes."
- *Australia:* "I would use Tysabri, and not just for salvage patients. Patients can make the risk:benefit decision, and I'm not worried about PML."
- *Germany #2:* "I wouldn't have a problem giving Tysabri to those patients (who don't respond to other drugs)… There is a certain place for Tysabri…but we have to learn how to manage those patients…So many patients ask for it, saying, 'I don't care about the risk, just give it to me.'"
- *Switzerland:* "Tysabri would be a niche product – if it gets approved in Europe – for salvage therapy. I think it will need more data to get European approval. And I would ***not*** use it first line."
- *Netherlands #1:* "The American Academy of Neurology should set guidelines for Tysabri use. I doubt I would use it except perhaps as salvage therapy."
- *Netherlands #2:* "I'd only use Tysabri in exceptional cases – in very severe patients where nothing else was working."
- *Canada:* "The problem with Tysabri is how to use it with rebound when you stop it. To suppress the rebound, do you keep patients on it or switch to an IFN…There are no data on sequential therapy with an IFN. There are no data that sequential therapy is safe, so you can't give Tysabri to IFN-failures…Tysabri will ***never*** get approved in Canada. I would never use it."
- *U.K.:* "You could count on one hand the number of patients I would give Tysabri to – only patients with a malignant course. I'd probably try Novantrone first."
- *Sweden #2:* "I would use Tysabri only in naïve patients. There is no excess JC virus in MS patients, so you can't predict PML risk before treatment."
- *Canadian nurse practitioner:* "We need to know the predictive factors (for PML) before using Tysabri. And we need more data."

U.S. neurologists appear much more willing to use Tysabri, and they repeatedly commented that patients want the drug and will be willing to undertake the risk, which they described as small.

Among the comments by Americans were:

- *Schering speaker:* "An NIH assessment of viral load is important because if 50% of MS patients have the virus, and two patients were diagnosed with PML, that makes it unsafe. But if only those two patients had the virus in their blood, and it predicted the onset (of PML) by months, that would make it safer…But even if the incidence of PML is only 1:600 over 2-3 years, we don't know what happens in 5-6 years…Right now, Tysabri is a substantially better product, but the caveat is it is therapy in very early MS, and if you give Avonex early, it doesn't look that much worse than Tysabri…It looks as if all the disease-modifying therapies (DMTs) are more effective early, but Tysabri was studied…I think Tysabri was better, but is it better enough to warrant the risk? I wouldn't use it first line, but I would use it second line."
- *Biogen speaker:* "Patients need to be made aware of the risk so they can make an informed decision, but I would use it in patients with frequent flare or who show activity on MRI. But not all patients would take the risk if it is 1:500 or 1:1,000. Some patients couldn't live with that risk."
- "Of all the therapies, Tysabri is the most effective on the planet…We've had few cases of a very serious and often fatal infection that we think in some way is associated with this drug…I think Tysabri will have a place…If I had someone who was not doing well enough on existing therapy or early in the disease with active inflammation …yes, I would be willing to (use Tysabri), but I would like to know how to follow the patient – with blood tests, with MRI – and to be sure this person would not be adequately treated with something else…It will be a select group…I don't know if it will be 50% of patients or 20%, but in my hands it would be more than Novantrone."
- "Tysabri is the biggest news in immunotherapy in the last 10 years…Quality of life was improved, and that was not shown clearly in other trials. The MRI effects are dramatic, impressive, robust, and consistent."
- *Texas:* "Biogen wants to resume trials in November with no washout for interferons or Copaxone, a six-month washout for Novantrone, and a three-month washout for steroids."
- *Ohio:* "I would use Tysabri, but not first line. I'm not 100% convinced it can be combined with an interferon, so I would use it as monotherapy but not in naïve patients, and I would wash out the interferon before starting Tysabri. In a year, I might have 10%-25% of my RRMS patients on it…Patients are asking about it."
- *Nurse practitioner:* "U.S. doctors are more bullish on Tysabri because they will make money on the infusions, but I'd guess that 50% of the IRBs would not approve the use of Tysabri or even a new study of Tysabri. This is an ethical issue…There may be other opportunistic infections that we haven't heard about...The Tysabri studies were very, very short."

U.S. sources agreed there has to be some form of risk management program, but Biogen Idec officials were not saying much about what the company is proposing. One official said, "We are testing the water to see what the FDA will accept." At the very least, a black box would be required, sources agreed. And some sources suggested that the company is proposing a loose plan, perhaps just a registry, with the recognition that it may have to modify that – perhaps several times – as it attempts to get approval for the least restrictive program possible.

SCHERING AG/BERLEX'S Betaseron (interferon-β1b)

The two-year results of the five-year BENEFIT trial were presented. As expected, the results showed that early, high dose Betaseron was more effective than placebo in preventing conversion to clinically definite MS (CDMS).

Doctors insisted that BENEFIT's most important contribution is that it reinforces the early-is-better approach. Every source questioned called BENEFIT an important trial, but only one doctor said the trial would in any way change their prescribing practices. This was a physician from New Jersey who said he will now look more favorably on Betaseron and may increase his use of it. All the other doctors said they will not do anything differently post-BENEFIT. A Netherlands neurologist said, "BENEFIT is another confirmation that early treatment is important – but not all doctors are convinced of that. High dose is better. Now, there are several studies that show that quite convincingly." A Canadian doctor said, "I hope BENEFIT will change what our government pays for…This trial says we should use high dose IFN." A U.S. doctor said, "The benefits of high dose Betaseron are counter-balanced by neutralizing antibodies." An Israeli doctor added, "Two years is too short a time (trial length) to change practice."

BENEFIT is a five-year, 468-patient, placebo-controlled, Phase IV trial of high dose Betaseron (titration to 250 µg every other day) vs. placebo in patients presenting with a ***first*** MS event. The trial was attempting to convince doctors that aggressive, high dose, high frequency Betaseron therapy should be started at the first clinical MS event rather than waiting for a recurrent event. After an initial two years of therapy, patients were allowed to go into a three-year, open-label extension, which will be completed in 2008.

2-Year Results of BENEFIT Trial

Measurement	Placebo n=176	Betaseron n=292	p-value
Adherence to therapy	90%	85%	---
Patients staying past 2 years into the extension trial	96%	94%	---
Reasons for discontinuation			
Withdrawal of consent	4.0%	3.8%	---
Adverse events	0	2.1%	---
Lost to follow-up	1.1%	1.0%	---
Other	0.6%	0.3%	---
Results at 6 months			
Time to MS by McDonald criteria	51%	28%	---
Results at 2 years			
Primary endpoint #1: Time to CDMS	45%	28%	<.0001 (50% risk reduction)
Primary endpoint #2: Time to MS by McDonald criteria	85%	69%	<.00001 (46% risk reduction)
MSFC overall change from baseline (median Z-score)	~0.075	~0.17	---
Patient characteristic	**Treatment effect**	**Patient characteristic**	**Treatment effect**
Multifocal	37%	Monofocal	55%
≥9 T2 lesions	43%	<9 T2 lesions	60%
≥1 gd+ lesion	38%	No gd+ lesions	57%

Researchers reported:

- Reduced the risk for progression to MS by McDonald criteria by 46%.
- Betaseron demonstrated robust and compelling effects on progression to CDMS in patients with a first clinical event suggestive of MS.
- Reduced the risk of progression to CDMS by 50%. A speaker said, "You can interpret this as pushing the onset of CDMS out a year."
- Prolonged the time to CDMS by one year (363 days) compared with placebo. A speaker said another way of

Results of Early MS Treatment Trials

Measurement	BENEFIT n=468	CHAMPS n=383	ETOMS n=309
Design	Betaseron 250 µg every other day vs. placebo	Avonex 30 µg QW vs. placebo	Rebif 22 µg QW vs. placebo
Mode of administration	Every-other-day subcutaneous	IM weekly	Subcutaneous weekly
Dropouts	7%	15%	10%
Monofocal patients included	Yes (53%)	No	Yes
Multifocal patients included	Yes	No	Yes
Prospective follow-up	Yes (95%)	No	No
Steroid treatment	71%	100%	N/A
Patients converting to CDMS within 2 years (drug vs. placebo)	28% vs. 50% (p<.0001)	35% vs. 50% (p=.002)	34% vs. 45% (p=.047)

looking at this is that this Betaseron regimen doubles the possibility of not developing MS over two years, from 15% to 31%.

The trial, which had a relatively low dropout rate (6.6%), also reported Betaseron was associated with:

- A stable score in patient-reported outcome measures.
- Flu-like symptoms and injection site reactions that diminished in the second year of treatment.
- Maintenance of quality of life.
- A treatment effect that is even more pronounced in patients with less disseminated/active disease at onset. A speaker said, "The thinking has been that maybe in milder cases we can get by with a low-dose interferon, but this is the group that benefited even more (with high dose Betaseron)."
- Antibody formation in 20%-25% of patients, which was described as "rather similar" to other Betaseron studies. Researchers also reported no impact from the antibodies during the two-year observation period.

Although BENEFIT was a positive trial, many doctors saw it as simply confirming the value of early treatment – with any of the interferons. They pointed out that the differential treatment benefit of Betaseron over Biogen Idec's Avonex (intramuscular IFN-β1a) or Serono's Rebif (subcutaneous IFN-β1a) in early patients was not really clear from the BENEFIT results. Rather, they saw BENEFIT as confirming the results of two earlier trials – CHAMPS with Biogen Idec's Avonex and ETOMS with Serono's Rebif – both of which also found that early treatment is important. While the patient populations in these trials were not identical, making comparisons difficult, it is clear that all three drugs do better than placebo when given early.

He explained that in Europe, treatment began, on average, after 3.4 relapses in 2003, down from 4.1 in 2000. In the U.S., treatment begins sooner, after an average of 1.8 relapses in 2003, down from 2.8 in 2000.

A Schering speaker attempted to differentiate BENEFIT from the other trials, insisted, "There has been a tendency for physicians to use drugs after a mean number of relapses…We learned the first clinical event must be taken seriously. Most patients will have another event, often within six months, but certainly within two years…The treatment effect of every-other-day Betaseron appears to be greater than that of once weekly Rebif…And there is a greater treatment effect (in BENEFIT) with every-other-day Betaseron than once weekly Avonex…This (Betaseron) is a reasonable drug to try."

Comparison of Monofocal Patients in BENEFIT and CHAMPS

Measurement	BENEFIT monofocal patients n=246	CHAMPS monofocal patients n=383
CDMS risk reduction	55% (44% Betaseron vs. 24% placebo)	44% (38% Avonex vs. 20% placebo)

The BEYOND trial comparing double dose (500 μg) Betaseron and placebo is ongoing, with results expected in 2007.

ARES SERONO'S Rebif (subcutaneous interferon-β1a)

There was nothing particularly exciting or newsworthy on this agent at ECTRIMS.

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

There were no new data on Copaxone at ECTRIMS. Instead, Teva emphasized the long-term data available on this agent. And long-term data are key issues with doctors. There were repeated calls at the meeting for longer-term studies, though doctors also realize that this is not necessarily feasible. A speaker said, "We really do need biomarkers – imaging or non-imaging – to allow us to better assess current disease status. We also need to improve our statistical methodology to allow us to use smaller cohorts. I think it will be a while before pharmacogenomics are available, but there will be a payoff in who is responding and what the optimal therapy is for an individual. We also need more Phase IV post-marketing studies."

DRUGS ON THE HORIZON

The current therapies will continue to have a role, sources agreed, but there are several promising drugs in development. Some may prove helpful as neuroprotectants or for remyelination or repair. A speaker commented, "Neuroprotection in MS may be a different story from neuroprotection in stroke (which has proven very difficult)." A multicenter, double-blind, placebo-controlled neuroprotection trial in SPMS is planned "soon" for minocycline, a tetracycline antibiotic approved for the treatment of bacterial infections.

A speaker offered this perspective: "There is no free lunch, immunologically speaking, and an oral therapy is likely coming but won't be here for several years. Drug safety is of increasing concern to neurologists, patients, and regulators; and this will affect the design of all current and new clinical trials in MS."

ABBOTT'S AB-874, an anti-IL-12 monoclonal antibody

The Phase II dose-finding study that is underway in RRMS and SPMS is a 24-week trial with two doses vs. placebo. Following the 24-week treatment period, a 24-week extension study will begin, with all patients on the drug.

GENENTECH'S Rituxan (rituximab)

Preliminary data from a RRMS trial have already been announced, and a trial is underway in PPMS. This agent also looks promising for neuromyelitis optica.

MEDAC'S treosulfan

This alkylating agent is approved to treat ovarian cancer, and researchers reported on a small (21 patients), Phase I trial in SPMS patients with exacerbations. The schedule reported at ECTRIMS was an induction phase with four infusions in one week, followed by a maintenance phase of 36 weeks. Researchers found that the drug halted progression, reduced the relapse rate, and reduced gd+ lesions. A double-blind, placebo-controlled Phase II trial is now planned.

Most patients remained stable or halted progression, with the median EDSS value stable. The annual mean number of relapses was 1.5/year prior to entry in the study and none after therapy. By MRI, gd+ lesions dropped "impressively" in the first six months, and the mean volume of T2 lesions remained stable. Adverse events included the usual chemotherapy side effects: 27% nausea, 18% vomiting, 36% urinary tract infections, 27% neutropenia, 18% respiratory tract infections, etc. There were only two dropouts: one for persistent leukopenia in a patient with a history of this disorder, and one because the patient lost interest in the study.

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

The 12-month results of the Phase II trial of FTY-720 were presented, and the six-month extension data appear to hold in terms of efficacy, with both doses – 1.25 mg and 5.0 mg – equally efficacious. The safety data also continue to indicate that the higher dose is more toxic, which explains Novartis's decision to drop that dose and use the 1.25 mg dose plus a lower 0.5 mg dose in the pivotal Phase III trial.

In the first six months of this Phase II trial, patients were randomized to three arms: 1.25 mg, 5.0 mg, or placebo. For the second six months, there were just two arms – 1.25 mg and 5.0 mg, with placebo patients randomized to one of these doses. In the first six months, FTY-720 reduced the relapse rate by 50% and MRI activity dropped up to 80%. No change (or trend) in EDSS was seen.

The results at 12 months:

- Placebo-switched patients showed a clear reduction in relapse rate and in the number of gd+ lesions.
- No difference in efficacy was seen between the doses, but adverse events were more common with 5 mg. A speaker said, "The 5 mg dose seems to have more serious adverse events, infections, and drug-related adverse events."
- The study is continuing with all patients switched to the 1.25 mg dose.
- Relapse reduction in the second six months did not appear to be just drug-related.

The Phase II FTY-720 trial used two doses – 1.25 mg and 5 mg. The efficacy was virtually the same at six months, but there was a trend to dose-dependent adverse events in the trial, with a slight increase in upper respiratory tract infections with the 5 mg dose. Thus, for the pivotal Phase III trial, which Novartis hopes to begin by the end of 2005 or early 2006, the 1.25 mg dose plus a lower dose – 0.5 mg – will be tested against placebo. A researcher commented, "We are very excited about the 0.5 mg dose because we think it will work." Enrollment might be expected to be quick for a Phase III trial of an oral agent, but a researcher warned that the placebo arm may discourage participation. He said the FDA wanted a placebo arm, not an interferon comparison. The FDA is requiring a two-year safety trial, Novartis officials and researchers said. The principal investigator for the Phase II trial said, "The FDA has gotten tougher on safety since Tysabri. They want more safety data now."

There were three posters presented at ECTRIMS on animal (rat) studies of FTY-720. All the researchers were very upbeat about this agent. They insisted there have been no safety

6-Month Results of Phase II Trial of FTY-720 *(previously reported)*

Measurement	Placebo n=92	FTY-720 1.25 mg n=93	FTY-720 5.0 mg n=92
Demographics			
Mean age	36	37	38
RRMS	90%	89%	N/A
Previous corticosteroids	78.3%	74.2%	83.7%
Prior use of Avonex or Rebif	21.7%	20.4%	20.7%
Prior Betaseron use	7.6%	4.3%	6.5%
Prior Copaxone use	5.4%	5.4%	7.6%
Prior Novantrone use	2.2%	2.2%	1.1%
Results			
Primary endpoint: Mean number of gd+ lesions	14.8	8.4 (Down 43%)	5.7 (Down 62%)
Patients free of gd+ lesions	~47%	~80%	~80%
Annual relapse rate	0.77	0.35 (Down 55%) p=.009	0.36 (Down 53%) p=.014
Patients with confirmed relapses	30.4%	14%	14%
At least one adverse event	81.7%	84.0%	95.7%
Serious adverse events	5.4%	6.4%	9.6%
Any serious adverse event	5.4%	4.3%	8.5%
Any drug-related adverse event	29%	39%	61%
Any infection	39.8%	51.1%	60.6%
Any severe infection	1.1%	0	0
Discontinuations due to adverse events	4.3%	5.3%	8.5%

signals in the MS studies, though the transplant studies in combination with cyclosporine did show some infection issues. One researcher said, "There were no red flags in the Phase II data." Another said, "The safety profile is very good. This is the best drug (for this disease) that I've ever seen. It is more effective than Tysabri." A third researcher said, "FTY-720 was in transplant trials for three years with other immunosupressants, and there were some adverse events, particularly enhanced infections, so we lowered the dose for MS, and we are giving it as monotherapy. FTY-720 works in ***all*** animal models of MS. It has at least the same efficacy as Tysabri at six months…We were lucky we tried it first in MS and not lupus, psoriasis, or rheumatoid arthritis. It behaves very differently in MS from those diseases…There is a 100-times higher concentration of drug in the brain than in the periphery, which may explain why it works in MS."

Though Novartis researchers were insisting that this is a very safe drug, it is not entirely clean. These side effects may be manageable and may not prevent approval, but they warrant watching.

- **Dose.** There were 11 adverse events in Months 6-12, and eight of these occurred in patients who either switched to 5 mg or were in the continuous 5 mg arm. A speaker concluded, "The 5 mg is a higher risk factor than 1.25 mg."
- **Heart rate.** Patients who initially go on therapy experience a transient decrease in heart rate, down about 20%, which normalizes after 4-5 hours. At Month 6, placebo patients who were put on drug experienced the same phenomenon – a transient decrease in heart rate after the first dose. About 1% of patients had to discontinue the drug because of bradycardia – all at the 5 mg dose. In all other patients, the heart rate was normalized without pharmacologic intervention.
- **Blood pressure.** On average, the drug was associated with a mean increase of ~5 mmHg of blood pressure on treatment initiation at both doses. There was no additional increase in blood pressure beyond six months in the patients on continuous therapy.
- **FEV_1.** FTY-720 was associated with a mild reduction in FEV_1. The change was statistically significant for the 5 mg dose, but not the 1.25 mg dose.
- **ALT elevation.** Asymptomatic ALT elevations >3xULN occurred in 5%-8% of patients switching from placebo to FTY-720. In the second six months, 3%-4% of patients on continuous FTY-720 therapy had ALT >3xULN.
- **Dyspnea.** No dyspnea events occurred in the second six months of therapy.
- **Macular edema.** This side effect occurred in transplant patients treated with FTY-720, but there were no cases in the MS trial.
- **Encephalopathy.** There was one case of this in a transplant patient, but no cases so far in MS.
- **Leukopenia.** There was some leukopenia reported in this trial, but researchers said there were no clinical effects.

PROTEIN DESIGN LAB/BIOGEN IDEC'S Zenapax (daclizumab)

A University of Utah researcher reported on off-label use of daclizumab, using about the same dose as in oncology, and he said he found the drug helpful. There was one case of

Results of Extension Phase of the Phase II Trial of FTY-720 *(Results at Month 12)*

Measurement	Placebo followed by FTY-720 1.25 mg n=40	Placebo followed by FTY-720 5.0 mg n=43	FTY-720 1.25 mg continuous n=87	FTY-720 5.0 mg continuous n=80
Completed extension	90%	86%	92%	91%
Mean annualized relapse rate	0.7 at 6 months placebo 0.21 at Month 12 on FTY-720 (down 70%)	0.69 at 6 months placebo 0.1 at Month 12 on FTY-720 (Down 66%)	---	---
Mean number of gd+ lesions	3.1 at 6 months placebo 0.4 at Month 12 on FTY-720 (Down 87%)	1.6 at 6 months placebo 0.3 at Month 12 on FTY-720 (Down 81%)	---	---
Patients free of gd+ lesions at Month 12	83%	73%	83%	89%
Safety				
Any adverse event	77.5%	81.4%	72.4%	85.0%
Any severe adverse event	2.5%	9.3%	2.5%	5.3%
Any serious adverse event	2.5%	7.0%	2.1%	5.4%
Any infection	35.0%	32.6%	33.3%	51.3%
Any severe infection	0	0	0	2.1%
Any serious infection	0	2.3%	0	0
Adverse events in Months 6-12	Bradycardia, arrhythmia, palpitations, abnormal heart frequency	Abdominal pain, nausea, bronchospasm, herpes zoster, otis externa	Hepatitis (ALT >5xULN), MS relapse	Neutropenia, pregnancy, left arterial mass, asthma, salpingitis

Epstein-Barr virus, based on PCR, and the drug was discontinued in that patient, and then restarted successfully.

A 250-275-patient Phase II trial of daclizumab added to IFN therapy has started to enroll in North America and Europe. This trial, testing two doses of daclizumab given by subcutaneous injection BIW with dose escalation, involves 5.5 months of treatment with 12 months of observation. An investigator said, "It is easy to administer by IV over 15 minutes, and the subcutaneous injection profile is good – just rash and a little fever so far. I see this agent used in patients who progress or relapse on an interferon. It is easier than using Novantrone…And I would use daclizumab over Tysabri."

ROCHE'S Roferon (interferon-α2a)

Investigators are investigating this oral cancer agent in MS without the support of Roche. University of Texas at Houston researchers said they are seeking an NIH grant for a Phase IIb investigator-led trial of Roferon 300 mg vs. 3,000 mg vs. placebo. A researcher said, "Trials of oral Rebif and oral Avonex (both INF-β drugs) didn't show efficacy, but maybe IFN-α is different…Inflammation is just not an area of interest for Roche."

Roferon also is being tested in a Phase II trial in newly diagnosed diabetes, with results expected in 1Q06 and the data are expected to be presented at either the American Diabetes Association meeting in June 2006 or the Immunology of Diabetes Society (IDS) 2006 meeting.

SANOFI-AVENTIS'S teriflunomide

This is a cousin of Sanofi-Aventis's Arava (leflunomide), which is approved to treat rheumatoid arthritis. Adverse events in a Phase II trial (of 7 mg and 14 mg doses) have included neutropenia and liver abnormalities (changes in LFTs). The trial showed a favorable trend toward reducing relapses by one-third, but the reduction was not statistically significant, but the higher dose did show a statistically significant lower increase in EDSS progression.

SCHERING AG/GENZYME'S Campath (alemtuxumab)

Investigation of this agent is on hold and dosing in all studies were stopped while the company and FDA determine what safety controls need to be added to this or a planned Phase III trial after three of 334 patients in a Phase II trial developed idiopathic thrombocytopenia purpura (ITP), and one of these died. All three patients were in Year 2 or Year 3 of the trial. The patients are still being followed, but no new patients are being given the drug. A Genzyme official said, "All patients got two cycles of drug. The protocol called for only some patients to get a third cycle, and all we did was eliminate the third cycle, though dozens of patients got a third cycle. I doubt suspending the dosing will impact the three-year efficacy data…In the trial, we were monitoring CBC every three months. Now, we will increase that to monthly monitoring or perhaps more often." Another source said, "I don't believe the FDA will require a placebo arm for the Phase III trial."

In mid-September, Schering and Genzyme announced interim results from this single-blind, open-label (but masked evaluator), three-year, Phase II trial in Europe and the U.S. – CAM-MS-223 – comparing once-a-year infusion of two unspecified doses of Campath to Rebif 44 μg TIW as first-line therapy in naïve MS patients. The first patient in this trial was enrolled in December 2002, and the trial was closed to enrollment in April 2004, with 334 patients enrolled. The primary efficacy endpoint was reduction in relapse rate at two years. The interim analysis found a 75% reduction in relapses at one year (p=.00267) with Campath. There was also a 60% reduction in the risk of progression of clinically significant disability. A Genzyme official said, "This compares to a 68% reduction in relapse at one year with Tysabri, and about a 40% reduction in the risk of disability with Tysabri." Two cases of Graves disease in Campath patients have been observed so far in this trial.

In an earlier, pilot study in 52 patients, Campath reduced the relapse rate by 30%, but 30% of patients developed Graves disease. So, there are serious safety concerns about this agent, but experts emphasized that the efficacy is substantial and may outweigh the risks – in certain patients.

Interim results from another Campath trial in MS that was stopped at the same time were presented at ECTRIMS. This was a two-year, three-site, single-blind, investigator-initiated Phase II trial comparing once-a-year infusion of high dose Campath (24 mg/day for 5 days the first year and then 24 mg/day for 3 days the next year) to Rebif 44 μg TIW in patients who had failed IFN therapy. The primary efficacy endpoint was percent of relapse-free patients at two years. At one year, 86% of patients were relapse-free with Campath, and 46.7% of patients had a reduction in EDSS score. One patient experienced Grade 3/4 neutropenia and pneumonia, and infusion reactions occurred in 64.4% of patients, though most of these were described as mild. There were no cases of Graves disease.

A Schering official indicated the company has no plans to continue development of Campath, a humanized monoclonal anti-CD52 antibody (already approved to treat B-CLL) in a broad MS market. He said Schering is very concerned with safety and thinks restricting Campath to salvage therapy would be appropriate, at least at this point. However, a Genzyme official indicated his company still expects to see Campath developed for a broader MS market – patients on an IFN or Copaxone who continue to have relapses. A U.S. investigator said, "The FDA has already accepted the definition of 'worsening MS' with Novantrone, so it would be practical for Schering to go for that label first." Another U.S. source said, "Campath couldn't be used like Novantrone

because it wasn't studied for that…With Novantrone, we have clear parameters for monitoring, and many of us use much less than the label." A third U.S. doctor said, "ITP is treatable if caught early." A German neurologist said, "It (Campath) is promising but the side effects are too common. It is highly effective, but the risk is high."

To date, this monoclonal antibody has been given as an infusion once daily for 5 consecutive days, producing immunosuppression that lasts ≥6 months (and up to 1 year). A speaker said, "There is a clear indication it has a profound effect on relapse reduction and inflammatory cytokines…but it hasn't shown any effect on disability progression…There has been a recent shift to using it in the early RRMS population…I think there will be a Phase III down the road, assuming patients are followed carefully and there is a way to safely monitor them…The data are remarkable at one year…This is a very powerful drug with significant side effects. Does this story sound familiar?"

SERONO'S Myelinax (oral cladribine)

A couple of early studies of an IV formulation suggested a beneficial impact of this agent on disease slowing, but that benefit was not seen in other studies. An oral formulation – that patients would take for perhaps five days four times a year – was developed and now a two-year, international, 1,200-patient Phase III trial is underway.

A Serono poster on the oral bioavailability of cladribine reported:

- Bioavailability at the lower end of the range previously reported.
- Inter-individual variability was low, and intra-individual variability was <20% for AUC.
- An oral dose of 10 mg gives an exposure equivalent to ~4 mg parenterally, allowing the number of doses administered during a 5-day course of treatment to be adjusted for the patient's body weight to correspond to that previously tested parenterally (0.07 mg/kg/day).

Adverse events in small studies have included purpura, thrombocytopenia, anemia, and pneumonia. In a small Phase II IV study there was no effect for the first six months, but then from Months 7-18, there was a 32% reduction in relapses with cladribine vs. an increase in relapses with placebo. Cladribine also has been tried in SPMS with what was described as "unconvincing results." A speaker said, "The message is clear. This drug causes a 68%-92% reduction in the percent of subjects with T1 enhancing lesions. There is a very impressive ability to suppress gd+ enhancement."

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

A study of a related agent – Pharmacia's Linomide (roquinimex) – was stopped early due to pleuritis, pericarditis, and MI, but researchers insist laquinimod does not have the same problems and that the safety profile is actually good. The results of a short, 229-patient Phase II trial of 0.1 mg and 0.3 mg oral laquinimod vs. placebo were reported earlier this year. That trial showed a 44% reduction in the number of new action lesions at the 0.3 mg dose, and a 52% reduction in new lesions in the subgroup with at least one new active lesion. However, there was no difference in clinical measures.

A poster reported on a 48-week open-label safety study which found high dose laquinimod (0.9 mg/day) was associated with a high incidence of potentially treatment-related adverse events, in some cases requiring a drug holiday or dose reduction. Adverse events included headache, infections (particularly nasopharyngitis), increases in CRP and ALAT, arthalgia, and others. The majority of patients remained relapse-free during the treatment period. Researchers concluded that this study supports investigation of a dose higher than 0.3 mg.

Another poster reported that laquinimod in 10 mM and 0.1 mM concentrations effectively reduced LPS-induced TNF-α secretion and NO production in a mouse cell culture. Researchers concluded that it is an active immunomodulator with potential therapeutic value in treating inflammatory processes and autoimmune diseases, but they also noted that additional studies are needed into the mechanism of action of this agent and into whether or not there are species-dependent differences in the way the drug influences the production of inflammatory mediators in glial cells.

A Phase II trial is currently enrolling, and a Phase III trial is planned. A speaker suggested it may be possible to increase the dose.

MISCELLANEOUS

GLYCOMIND'S Glycochip

This blood test is being developed to test patients who present with a first neurological event to determine who will convert to CDMS over the next few years. The test uses a low-medium density microarray to scan for anti-Ga4Ga antibodies. Dr. Mark Freedman of Canada reported that retrospective tests at his hospital and in Belgium on frozen samples from 88 patients presenting for a work-up of CIS (suspected MS) found that high levels of anti-Ga4Ga IgM antibodies identified a subset of patients at the time of first acute neurological event (36%) that went on to become RRMS with >91% specificity.

Optical Coherence Tomography (OCT)

Interest is growing for the use of OCT analysis of retinal nerve fiber layer thickness as a structural biomarker in MS trials of neuroprotective agents and other disease-modifying therapies. ♦