Trends-in-Medicine

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SUMMARY

Half the neurologists questioned plan to use Tysabri for their MS patients when it comes back on the market, but usage may ramp slower than expected, with doctors estimating that on average only 15% of their MS patients will be on Tysabri in six months. ♦ Neurologists are very anxious for an oral therapy, and Sanofi-Aventis' teriflunomide and Novartis's fingolimod (FTY-720) both look promising, but the FDA is imposing such tough monitoring on any U.S. Phase III trial that the future of fingolimod is in question. ♦ A double-dose of Teva's Copaxone did not prove better than the usual 20 mg/day dose. ♦ No new data were presented from the MIST-I trial of PFO closure with NMT's StarFlex, and neurologists were critical of the company for withholding data – and the principal investigator of the trial has been censured by the U.K. medical licensing board for improper conduct in another clinical trial. ♦ Pseudobulbar syndrome is not a common disorder, but there is nothing very effective to treat it, and doctors are willing to try a new drug, like Avanir's Neurodex, if it gets FDA approval and has data to show it works.

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Multiple sclerosis appeared to dominate the meeting, but there was also news and comments on migraine headaches, Parkinson's Disease, and pseudobulbar syndrome.

MULTIPLE SCLEROSIS (MS)

MS is the most common chronic debilitating disease in young adults. Worldwide 1.0-2.5 million people are thought to have the disorder. Of the ~400,000 Americans with MS, only about 165,000 are taking one of the four drugs commonly used to treat MS.

Biogen Idec's Tysabri (natalizumab), which was on the market briefly then withdrawn in 2005 after three patients developed progressive multifocal leukoencephalopathy (PML), is expected to be available in late summer. Several other promising drugs – including some oral agents – were also put on hold during the safety review of Tysabri, and doctors hope they will be permitted to resume their trials soon.

MS Market

Company	Brand	Generic name	Worldwide market share *
Biogen Idec	Avonex	intramuscular interferon-β1a	32%
Ares Serono	Rebif	subcutaneous interferon-β1a	25%
Teva Pharmaceuticals	Copaxone	glatiramer acetate, copolymer-1	23%
Schering AG/Berlex	Betaseron/ Betaferon	interferon-β1b	20%

*Source: Novartis

BIOGEN IDEC'S Tysabri (natalizumab) – wide use expected when it returns to market, but ramp may be slower than expected

Seventeen U.S. neurologists were asked about their plans for Tysabri when it is returned to the market later this year. Half are in private practice, and the other half in an academic or military setting. On average, they each treat 70 MS patients a year.

➢ **Half plan to use Tysabri as soon as it is available.** Eight of these doctors plan to use Tysabri once it comes back on the market, and on average these doctors each treat 58 MS patients per year. Five doctors do not plan to prescribe Tysabri, three are not sure yet what they will do, and one had no comment. More

academic and military doctors plan to use Tysabri than private practice doctors, which is not surprising. However, usage plans do not separate by the size of the MS practice; some high volume doctors are holding back, and so are some low volume doctors. Comments by doctors who either don't plan to prescribe Tysabri or are undecided included:

- *Colorado #1:* "We were using a fair amount of it, but we won't use it as enthusiastically as in the past."
- *Colorado #2:* "Colorado doesn't have a lot of patients who want that kind of stuff. They are more into complementary medicine."
- *Arizona:* "My use will depend on the (FDA) stipulations and caveats on use."
- California *#1:* "(My usage) depends on what additional information is available when it is released."
- *Iowa:* "It's not clear that Tysabri is more efficacious than other agents."
- *California #2:* "I won't use it. It's still controversial, and I need more information before I start using it."
- *Michigan (academic):* "I'll wait until there is a test for the (PML) virus."

➢ **No waiting list.** Not one source has started or plans to start a waiting list of patients for Tysabri, indicating there may not be a bolus of patients when the drug is approved.

➢ **No major medicolegal concerns.** Doctors generally are not worried about a medical malpractice risk in prescribing Tysabri. They indicated the patient consent form should be sufficient to protect from litigation. A West Coast neurologist is considering prescribing Tysabri but he cautioned, "It's (litigation is) a consideration, we have to be very careful how it is presented." A Florida doctor added that there could be a concern if Tysabri is used first-line.

➢ **Neurologists cautious in what they say to patients about Tysabri, and few are proactively calling patients.** Asked what they are telling patients about Tysabri's return, doctors said they are trying to manage expectations. Most are advising patients that it will be several months before Tysabri is available: two tell patients to expect it in 2 months or less, three say summer 2006, three say within 6 months, three say within a year, and one says in 2 years.

- *Colorado (private practice):* "I talk to almost every patient about it and explain what happened. I will talk about it more if it is approved."
- *Missouri:* "I tell patients that I will be neither the first nor the last to prescribe it."
- *California:* "I tell patients that it depends on the information and recommends (from the FDA) when it is released. I tell them I will exercise 'great pause' in using it, and that I was not and am still not an enthusiastic proponent of its use."
- *Arizona:* "I tell them it may be worth the risk."
- *Colorado #2:* "I tell them I hope there are advances, that Tysabri is not enough advanced to use it because of the PML risk."
- *Iowa:* "I don't talk to patients about Tysabri."
- *Michigan:* "I tell patients the clinical trials show promise, but there is a problem with it."
- *Alaska:* "I tell them that there is definitely a significant risk with it, but it's all about the risk:benefit ratio."

➢ **Few patient queries.** Only about a third of patients are calling their doctors about Tysabri, but that may be because patients are following the progress of the drug in the news. A California doctor said, "Patients aren't calling me, but they are well informed about it." Another West Coast doctor said, "Patients already are aware of it, so they aren't calling me about it." A New Hampshire neurologist said, "Patients are asking when it will be out and they are actively demanding it." A Midwest doctor said patients are calling with questions about Tysabri.

➢ **Usage may ramp slower than expected.** On average, sources estimated that 15% of their MS patients (range <1%-50%) will be on Tysabri six months after it is back on the market. Surprisingly, the five largest MS practices estimated that only 7% of their MS patients, on average, will be on Tysabri within six months of availability.

➢ **First Tysabri candidates will be prior Tysabri and refractory patients.** The patients most likely to get Tysabri, at least initially, are those who had previously taken it and/or who are progressing on another therapy. If the FDA doesn't label Tysabri for second- or third-line use (which it is not expected to do), about a third of these sources would consider using Tysabri for some first-line patients. Among the comments on who will get Tysabri were:

- *Colorado:* "Patients with whom I have good communication and who would tell me about side effects may get it, and patients who are well educated about the benefit:risk ratio…If I understand better why it happened – and if there are no more PML cases documented on Tysabri monotherapy, I might use it first-line, but it would be a year or more down the road. And I'm slightly less likely to use it first-line if the label says second- or third-line."
- *California #1:* "I will use it for patients who failed all the other drugs or are not doing well on them – not newly diagnosed patients."
- *California #2:* "I might use it first-line, but not often and not if the label says second- or third-line."
- *New Hampshire:* "I'll use it for really refractory patients, not newly diagnosed patients."
- *New York:* "I'll give it to my sickest patients."

- *Maryland:* "I'll only use it for patients with very progressive disease. If the label said second- or third-line, I might use it first-line in a very severe case."

Ten Canadian and European neurologists were also questioned about Tysabri, and all predicted that Tysabri would be allowed to be sold in their country, but a U.K. neurologist predicted that NICE may not approve reimbursement for it. On average, they estimated that <5% of their MS patients will be on Tysabri six months after it is available. They plan to use it primarily for patients who fail other drugs or have aggressive disease, not newly diagnosed patients. A Canadian doctor plans to use Tysabri first-line even if the label says second- or third-line, but most other sources said they would not use it first-line.

European and Canadian doctors generally believe it will have a warning and be contraindicated for both first-line and combination use. They also expect that a risk management program will be required. An Austrian neurologist said, "I expect the risk management program will require reporting and maybe offer some advice or a proposal on what to do before treatment." A German doctor said, "I expect there will be monitoring every month in the office at first and then every three months." A U.K. doctor suggested, "Maybe regular MRI scans or monitoring for (PML) virus will be required." A Swiss doctor said, "I think the program will require reporting anything (adverse) about patients, and I can imagine a registry." A Canadian neurologist said, "I can't see how Health Canada would approve it."

As in the U.S., there are no Tysabri waiting lists among these Canadian and European doctors. They also are not worried about medicolegal issues if they prescribe Tysabri. Only one of these doctors is proactively calling patients to talk to them about Tysabri. A German doctor said, "I tell them about the issue and maybe explain that the problem may be because of combination use." A U.K. doctor said, "I tell patients there is a 1 in 1,000 risk of PML."

However, some patients in Canada and Europe are calling their doctors to ask about Tysabri. A Canadian doctor said, "Patients like it." A U.K. doctor said, "Some patients ask about Tysabri, but I offer them other things." Another U.K. doctor said, "Usually, they are pressing me to get a drug rather than me pressing for it."

Several papers were presented with new data on Tysabri, including:

- **Mediates the migration of lymphocytes** from the peripheral blood into the CSF in MS patients.
- **Quality of life.** Another analysis of the AFFIRM and SENTINEL trials found Tysabri improved scores on both physical and mental components of the SF-36 and well-being on the VAS, and there was a trend toward improvement in fatigue and pain subscales with Tysabri monotherapy. However, an expert noted that a 2-point change in SF-36 "doesn't have any clinical significance."
- **Antibodies.** In the AFFIRM and SENTINEL trials:
  - Persistent antibody positivity was low (6%).
  - Patients with antibodies had markedly reduced Tysabri concentration in the serum.
  - Patients with persistent antibodies had a loss of clinical benefit, higher adverse events, and a higher rate of infusion reactions upon re-dosing. A speaker said, "If a patient gets an infusion-related event, you should start thinking of the possibility of antibodies."
  - Most antibodies occurred within 12 weeks, with another jump in antibodies at 24 weeks.
  - An antibody assay will be available upon re-approval of Tysabri, and he recommended discontinuing Tysabri in patients who have hypersensitivity reactions and in patients with persistently positive antibodies. He advised considering antibody testing in patients treated ≥6 months who have infusion-related symptoms or continued disease activity.

Quality of Life Data with Tysabri

Measurement at 2 years	Placebo	Tysabri	p-value
AFFIRM monotherapy trial			
SF-36 physical component	-1.3	+0.7	0.003
SF-36 mental component	-0.5	+2.0	N/A
MSQLI	Nss but favored Tysabri on fatigue, mental health, and modified social support		
VAS	-6.2	+0.2	---
SENTINEL add-on trial			
SF-36 physical component	-0.93	+1.03	>.001
SF-36 mental component	-0.96	+0.18	0.198
MSQLI	Trended better in modified social support	Significantly better in fatigue and pain, trended better in mental health, sexual satisfaction	---
VAS	-6.5	-2.7	---

Tysabri Antibody Data

Antibody status	Incidence in Tysabri monotherapy	Incidence in Tysabri add-on therapy	Relapse rate with monotherapy	Effect on disability over 2 years
Placebo	---	---	0.7	~30%
Negative	91%	88%	2.0	~17%
Transiently positive	3%	5%	1.7	~18%
Persistently positive	6%	6%	4.7	~33%

- **Reduced the progression of visual disability.** An analysis of patients in the AFFIRM (monotherapy) and SENTINEL (add-on therapy) trials found that Tysabri was associated with a 35% reduction in the risk of sustained visual deterioration, as measured by low-contrast visual acuity.
- **Infections.** Data presented at the meeting indicated that infections do not increase in MS patients with prolonged (2-3 year) use, with the exception of one case of gastro-enteritis and 2 cases of PML.
- **No rebound.** There was no evidence of rebound when Tysabri was discontinued.

IMMUNE RESPONSE CORPORATION'S NeuroVax, a TCR peptide vaccine – moving into Phase III trials later this year

Development of T-cell receptor peptide vaccines has been slow because of the immunogenicity of the early vaccines. A speaker explained, "Up until the last few years, the vaccines were relatively weak and ~50% of MS subjects responded." NeuroVax reportedly is safe and "strongly immunogenic" in 100% of MS patients. A 25-patient, open-label, safety/ immunogenicity study found NeuroVax is safe and is ready for larger clinical trials. A Phase II trial in 300 MS patients is expected to begin in late 2006, using MRI and clinical outcomes.

GENZYME/SCHERING AG'S Campath (alemtuzumab) – waiting for FDA approval to resume dosing in Phase II trial

Both Genzyme and Schering AG officials confirmed that the two companies are seeking FDA permission to resume dosing in the ongoing Phase II trial and to start a Phase III trial in the U.S. later this year. The Phase II trial was put on clinical hold after three cases of idiopathic thrombocytopenia purpura (ITP) occurred in the 334 patients in the trial. However, nearly all the patients in the study had already received the specified second cycle, so it was only the optional third cycle that was prevented. The patients are still being followed, but no new patients are being given the drug. The three-year data from this trial will be available in late 2007, but another interim analysis is planned at the end of 2006, and the question is whether the results of that analysis will be released.

ITP isn't the only safety concern with Campath. An increase in thyroid autoimmunity (e.g., Graves Disease) was also seen with the drug. However, sources are confident that a risk management program can be developed that would not be onerous. A source said, "A simple CBC can diagnose ITP, and I could envision a RiskMap with monthly CBC testing or every-three-month monitoring, and CBC is an inexpensive test…ITP is a potentially life-threatening disorder, but it is easy to find with an inexpensive test, and easy to treat, usually with prednisone, an inexpensive drug."

Bayer is buying Schering AG, but investigators believe that Bayer will continue this program. A source said, "Bayer wants to develop both an oncology franchise and Campath."

Last fall, a Schering official suggested that Schering might not participate in further development of Campath in MS, but the company has decided to continue. A risk management plan has been submitted to the FDA, and the companies are waiting for the FDA's response – but that is not expected quickly. A source explained, "The FDA is busy with Tysabri right now and all the other trials are taking a back seat." Another MS expert said, "Campath looks extremely promising from an efficacy standpoint, but it has safety issues." A West Coast neurologist described Campath as "intriguing."

MSBIO'S MBP-8298 – good data but doctors not yet convinced

A 20-patient Phase II trial compared placebo to 500 mg MBP-8298 (a myelin basic protein peptide) given IV once every six months. The results indicate the agent is effective in patients with immune response genes HLA-DR4 and HLA-DR2. In the first two years, sustained disability (SAD) was decreased by 60% with MBP-8298, and over five years, there was a 'profound' decrease in SAD. The question that has been raised about this trial is whether the entry criteria of EDSS 3.5-6.5 is representative of secondary progressive MS (SPMS).

Doctors asked about MBP-8298 were skeptical. One said, "The data indicate a 'reasonable' effect, prolonging disability progression by 60 months, but it was a small number of patients, and there are limited immunology data on those patients. It suppresses the immune response against myelin specific antibodies, but that hasn't been shown to be a valid surrogate yet, and we haven't see the effect on T-cell function…In addition, MBP-8298 is not the only myelin protein…So, there are theoretical reasons it could work; there's a chance it could work."

A two-year, double-blind, placebo-controlled, multicenter, parallel group, pivotal trial in SPMS is underway, with ~200 of 553 planned patients already enrolled. The primary endpoint is time to disease progression (confirmed worsening of disability) by EDSS in patients with immune response genes HLA-DR4 and HLA-DR2. Reportedly, MRIs are being conducted in at least a cohort of these patients.

NOVARTIS'S fingolimod (FTY-720) – promising efficacy and possible first oral, but FDA safety requirements make U.S. future uncertain

Although FTY-720 (an S1P receptor modulator) has been discontinued as a transplant drug, it is alive and well in MS. There was a strong buzz about this agent among MS opinion leaders who believe it is effective and are excited that an oral agent may finally become available. A researcher said, "The change in EDSS progression wasn't enough in Phase II, but

that's what counts at the end of the day. I'm not so concerned with safety." An MS expert said, "I'm very excited about the preliminary data. I'm impressed by the immunology rationale …So far, safety is not a problem, even though there probably is more concern in transplant patients."

In a 281-patient, proof-of-concept Phase II trial, the two doses tested were 5 mg and 1.25 mg, and the data indicated that the two doses have equal efficacy on both MRI and clinical endpoints, but the lower dose had a better side effect profile. An investigator suggested this was due to a "ceiling effect," so a lower dose (0.5 mg) is being tested in Phase III. Benefits were observed at two months and increased over time.

The key side effects with this drug have been:

- **Decreased heart rate** (5-10 beats per minute). The advice, a researcher said, would be not to give it to patients with a very low starting heart rate. FTY-720 is acting like a muscarinic stimulator, a researcher explained. However, over time, the receptor adjusts through internalization or desensitization and the effect fades. The researcher said, "The people with a low heart rate to start are the ones to watch."
- **Increased blood pressure** (~5 mmHg).
- **Liver elevation.** At 5 mg, ALT3xULN was reported in ~7% of patients, but there was no information on how many patients had ALT5xULN or higher or whether the ALT returns to normal with drug discontinuation.
- **Macular edema and pulmonary edema.** Novartis researchers believe these side effects are both due to interaction with cyclosporine, and that was cited as the reason for discontinuing development of FTY-720 for transplant. These side effects have only been seen in transplant, not in MS, patients. In MS, a patient's macular edema actually gets ***better*** with FTY-720 vs. placebo, but it worsens significantly vs. placebo when given in combination with cyclosporine.
- **A slight increase in FEV_1.** A researcher speculated that this is due to smooth muscle cells expressing the receptors. An investigator said, "We know there is an effect on smooth muscle cells, which leads to a slight contraction of the alveoli, but it is not a cumulative effect over time. Beta blockers had a similar effect. It is not something dangerous."

A >1,000-patient Phase III trial started enrolling in Europe earlier this year, testing two doses – 1.25 mg and a new, lower dose of 0.5 mg. Patients have to see seven different doctors/departments in the hospital in order to participate in the trial: a first-dose physician who sees the patient on the first visit and checks heart rate, cardiology for an EKG, pulmonology for an FEV_1 test, ophthalmology for an eye exam, two neurologists (one for treatment and one for evaluation), and MRIs. And patients need to be seen every 3 months, which an investigator called "a burden for patients."

6-Month Results from Phase II FTY-720 Study

Measurement	Placebo n=92	FTY-720 1.25 mg n=93	FTY-720 5 mg n=92
Demographics			
Disease duration	8.4 years	8.6 years	9.5 years
Relapsing-remitting MS	90.2%	89.2%	87.0%
Baseline T1 Gd+ lesions	2.8	3.4	2.82
Relapses in last 2 years (mean)	1.8	1.9	1.9
EDSS mean	2.58	2.65	2.53
Completed 9 months on FTY-720	93.5%	94.6%	88%
Lymphocyte count in months 1-6			
≤0.4	83%	77%	87%
>0.4-0.6	85%	87%	83%
>0.6-1.0	90%	94%	N/A
Median volume of T1 Gd+ lesions			
≤0.4	114	89	132
>0.4-0.6	47	0	157
>0.6-1.0	134	146	60
Other efficacy findings			
Annualized relapse rate	0.77	0.35 (Down 55%, p=0.009)	0.36 (Down 53%, p=0.014)
EDSS	---	No change	
Number of Gd+ lesions (mean)	14.8	8.4 (Down 43%, p<0.001)	5.7 (Down 61.5%, p=0.006)
Lesion-free patients by MRI	~45%	~80%	~76%
Relapse-free patients	~65%	86% (p=0.007)	86% (p=0.012)
Patients with confirmed relapses	30.4%	14%	14%
Safety			
Any adverse event	81.7%	84.0%	95.7%
Any serious adverse event	5.4%	6.4%	9.6%
Drug-related adverse event	29.0%	39.4%	60.6%
Any infection	39.8%	51.1%	60.6%
Any severe infection	1.1%	0	0
Nasopharyngitis	15.1%	17.0%	27.7%
Discontinuations due to adverse events	4.3%	5.3%	8.5%
Diarrhea	2.2%	9.6%	11.7%
Nausea	2.3%	8.5%	10.6%
Headache	14.0%	23.4%	19.1%
Dyspnea	1.1%	4.3%	12.8%
Liver (ALT) abnormalities	2.2%	6.4%	7.4%
Leukopenia	0	2.1%	5.3%

Novartis reportedly is ready to start a Phase III trial in the U.S. – if safety requirements for the trial can be resolved with the FDA. The FDA is demanding either that Novartis conduct additional safety studies before starting the pivotal Phase III or perform what the company considers onerous safety studies for the Phase III U.S. trial, reportedly everything required in Europe plus a three-year duration and a placebo control.

Novartis is doing animal studies in a mouse model of the polyoma virus to try to show that FTY-720 is different from Tysabri with the hope that they can convince the FDA to lighten the study requirements. An FTY-720 researcher said the company believes that the PML virus in the brain of Tysabri patients comes from the bone marrow to the CNS, and they are trying to prove that it is not the direct effect on T-cells but induction of more polyoma virus into the CNS that is Tysabri's problem – and that this bone-to-CNS migration does not occur with FTY-720.

If the FDA remains firm on the safety studies, Novartis might ***drop*** development of this drug altogether in the U.S. A senior researcher said the company is "on the fence" right now on the future of FTY-720. The company has invested a lot of money in this drug over the last 8 years, but it reportedly is reaching the point where it is not sure it wants to invest as much as the Phase III U.S. trial would cost. He said, "The company is resisting spending more money…The company has an internal problem with investing more money in FTY-720."

TEVA PHARMACEUTICALS' Copaxone (glatiramer acetate) – failed trial but a strong trend

The results of a 9-month, 90-patient, multi-center, double-blind, placebo-controlled trial comparing high dose (40 mg/day) Copaxone with low dose (20 mg/day) Copaxone in patients age 18-50 with relapsing-remitting MS. The trial failed to meet the primary endpoint. The moderators and an AAN official were unhappy with the way the company presented this as a positive trial, including a press release calling it positive. They indicated they will also be discussing what to do about this "misconduct."

Several other drugs are in development, but there were no data on them at this meeting, and several doctors expressed general pessimism about all of the investigational agents. An Arizona doctor said, "None are great." Another Arizona doctor said, "None are promising. There are too many things that never make it." A Missouri doctor said, "They all scare me." A U.K. doctor said, "None are very exciting. Neuroinflammatory agents may not be addressing the disease. Real promise may be quite a long way off."

Other MS agents – Tysabri appears to have made the development path tougher

- **ARES SERONO'S Mylinax (cladribine).** There was no news on this oral agent, but an MS expert warned against ruling it out.
- **BIOGEN IDEC'S BG-12 (oral fumarate).** There may be data on this at ECTRIMS in Madrid in September 2006. An MS expert commented that it looks "somewhat" promising.
- **BIOGEN IDEC'S Rituxan (rituximab).** Several doctors mentioned this as promising. A New York doctor said, "Rituximab works in a lot of things. It clearly does something." A California doctor described Rituxan as "more interesting than Tysabri." Another expert said, "The mechanism of action will be interesting to sort out."
- **CELLTECH'S CDP-323.** Doctors were hopeful that studies will resume once the FDA gives final approval to the return of Tysabri.

High vs. Low Dose Copaxone

Measurement	Low dose Copaxone 20 mg SC QD	High dose Copaxone 40 mg SC QD	p-value
Primary endpoint: Total number of Gd+ enhancing lesions on T1 weighted MRI at Months 7-8-9	2.96	1.84	0.0898 RRR 38%
Total number of Gd+ enhancing lesions on T1 weighted MRI at Month 9	Down 75% from baseline	Down 65%	<0.0001
Total number of Gd+ enhancing lesions on T1 weighted MRI at Month 3	Down 52%	N/A	0.0051
New T1 Gd+ enhancing lesions	1.13	0.82	0.31 RRR 27%
New T2 Gd+ enhancing lesions	1.04	0.73	0.26 RRR 30%
Proportion relapse-free	52.0%	76.0%	0.0183
Annual relapse rate	0.57	0.34	0.12 RRR 41%
Time to first confirmed relapse	80 days	213 days	0.037
Responders #1: Free of relapse and no additional lesions in the last timeframe, and the mean was reduced by ≥50%	38.5%	59.0%	0.0078
Responders #2: Relapse-free, no EDSS regression, no Gd+ enhanced lesions in last treatments, and no new or enlarged T2 lesions	13.5%	32.5%	0.0499
Discontinuations early	14%	14%	Nss
Early discontinuations for adverse events	1 patient	4 patients	---
Deaths	0	0	---
Injection site reaction	86%	85%	---
Immediate post-injection reactions	22.7% (generally mild)	32.6% (mild-to-moderate)	---

- **GLAXOSMITHKLINE'S GSK-83699.** Doctors were hopeful that studies will resume once the FDA gives final approval to the return of Tysabri.
- **ROCHE'S Zenapax (daclizumab).** There was no news on this, but an MS expert said, "It is promising; it's just not new."
- **SANOFI-AVENTIS' teriflunomide.** This oral agent reportedly is a less liver-toxic version of Sanofi-Aventis' rheumatoid arthritis drug Arava (leflunomide), and several sources suggested it is further along in development than Novartis's fingolimod and could be a "sleeper." However, an investigator with Novartis's FTY-720 said, "The data on teriflunomide are not as convincing as FTY-720." Another expert said, "Teriflunomide has a head-start on FTY-720, and the efficacy is comparable to the interferons."
- **Alpha-fetoprotein.** Questions about this agent raised eyebrows and were quickly dismissed. One source commented, "It won't go anywhere."

MIGRAINE HEADACHE

Patent foramen ovale (PFO) closure – no new data but increasingly controversial

Researchers presented the results of the randomized, sham-controlled MIST-I trial of NMT Medical's StarFlex to treat migraine with aura. It was a shortened version of the presentation given at the American College of Cardiology (ACC). At ACC, researchers promised additional data at AAN, but there was nothing new in the AAN presentation, which did not appear to go over well with neurologists. The data presentation was criticized by several AAN opinion leaders and it got slammed by a prominent headache expert. In addition, it was revealed that the principal investigator in MIST-I was censured by the British medical licensing board on March 24, 2006, for improper conduct in another clinical trial and will be on probation for the next five years.

MIST-I Results

Measurement	StarFlex n=74	Sham n=73
Primary endpoint: Complete cessation of migraine	5% 3 patients (Nss)	4% 3 patients
Secondary endpoint: ≥50% reduction in migraine headache days	42% (p=0.038)	23%
Headache burden (frequency x duration)		
Baseline	136.1	116.8
Follow-up	86.06	96.32
Reduction from baseline	37%	17%
Deaths	0	0
Serious adverse events	Tamponade Epicardial effusion Retroperitoneal bleed Atrial fibrillation Chest pain	Incision site bleed Anemia Nose bleed Brainstem stroke

MIST-I enrolled migraine-with-aura patients who had failed ≥two classes of medications in the U.K. from January to July 2005. The study found that of all the patients entering the study, 60.2% had a shunt, 16.7% had a small shunt, and 37.7% had a large shunt.

The principal investigator, Dr. Andrew Dowson of the U.K., said the lessons from MIST-I that could be applied to other PFO/migraine trials are:

- Collect data for a longer time to see if the early benefit is maintained and to see if there is more – rather than less – benefit with time.
- The cessation endpoint was not realistic.

There were several interesting points that can be made about the presentation and data:

- **No proof-of-concept.** Dr. Dowson called the trial "analogous to a Phase II proof-of-concept study," and he claimed that the trial proved proof-of-concept "that closing PFO did affect the amount of headache patients were having." However, since the trial failed the primary endpoint, the FDA apparently does not believe this trial was proof-of-concept. In fact, at another medical conference a few days earlier, an FDA official, discussing PFO closure, noted that the FDA does not consider MIST-I to have shown proof-of-concept.

- **Missed primary endpoint.** Dr. Dowson included a slide in his presentation that showed the primary endpoint. This would not be noteworthy except that at the first MIST-I presentation at ACC, the presenters (who included Dr. Dowson) were criticized by the moderator for not having a slide with the primary endpoint in their presentation. The primary endpoint of cessation of migraines was 5% (3 patients) in the StarFlex group and 4% (3 patients) in the sham group. Dr. Dowson admitted, "It was not significant and clearly missed the primary endpoint."

- **Secondary endpoint positive.** The positive showing on the secondary endpoint of ≥50% reduction in migraine headache days (42% with StarFlex, 23% with sham, p=0.038) was mentioned but not emphasized as strongly as at ACC.

- **Data withheld.** Further analyses of the data and additional secondary endpoint data are being withheld by NMT and the investigators. Dr. Dowson said the company first wanted to modify the MIST-II trial design based on these results and then get FDA approval of the revised trial design before disclosing any additional data from the trial. This did not go over well with the AAN audience. Dr. Dowson not only declined to answer an audience question about what those endpoints showed but also would not even disclose how many secondary endpoints were used in the trial. He said only, "We are not sharing that data now. If you want more data, talk to the sponsor (NMT Medical)." The questioner responded, "To understand that data, it should have been presented fully…I think the Academy (of Neurology) should request that data."

Criticisms of the MIST-I trial data

Key opinion leaders at AAN were clearly upset with the MIST-I presentation, and there were indications there would be a protest to AAN officials. In addition, Prof. Peter Goadsby of the Institute of Neurology in London, a renowned headache expert and strong PFO closure critic, discussed the MIST-I presentation during a review session on headache. He cited several problems with the trial and the investigator's conclusions:

- **Definition of patients with aura.** He said, "It is not clear what migraine with aura means…It is not clear to me how much active aura there was in the patients studied."
- **Refractoriness of patients.** He said, "I take issue with calling these patients refractory…Two failed preventives are a walk in the park for most migraineurs. That is not a refractory patient."
- **Risks.** He emphasized, "PFO closure if ***not*** risk free."
- **Endpoints.** The principal investigator's refusal and/or inability to reveal how many secondary endpoints were in the trial or what they were raised questions. Dr. Goadsby said he found the information on a website: 6 secondary efficacy endpoints, 2 secondary safety endpoints, 8 secondary failure endpoints, and 3 tertiary endpoints. He questioned why Dr. Dowson wouldn't provide this information.
- **Negative trial.** The primary endpoint was clearly negative. Prof. Goadsby said, "Can you cure (migraine) with (PFO) closure? The answer to that was pretty much, 'No.' No matter how big a study you do, the answer will still be no." He pointed to an older trial of riboflavin that had a higher rate of ≥50% headache reduction than PFO closure.

Riboflavin vs. PFO Closure

Treatment	≥50% headache reduction
Riboflavin	59%
Placebo	15%
PFO closure	42%
Placebo	23%

- **Role of PFO closure.** He declared, "I think there is no role for PFO closure in migraine outside of clinical trials. ***Is it ethical to continue these studies without further information from the first (MIST-I) study?***...I have never referred patients (for PFO closure of migraine), and I have no intention of doing that." He is suggesting that not only must the MIST-II trial be redesigned, but that all PFO closure trials should be put on hold until we know what happened to the other so-far-unidentified endpoints in the MIST-I trial.
- **Large PFOs**, which were found in 37.7% of patients screened for the trial. He said, "There is some important question here on why these people have a large PFO. Does this have to do with a causative or genetic association? This wouldn't be the first condition known where a congenital cardiac abnormality is associated with another effect but not related."

MIST-I principal investigator sanctioned

The MIST-I principal investigator, Dr. Andrew John Dowson, was recently put on probation by his medical board for misconduct as the principal investigator in a different clinical trial, but this was not disclosed at AAN. On March 24, 2006, the Fitness to Practise Panel took four disciplinary actions against Dr. Dowson.
(www.gmc-uk.org/concerns/decisions/index.asp)

The Fitness to Practise Panel findings did not relate to the MIST-I trial but to another migraine headache study, an Allergan-sponsored trial of Botox (botulinum toxin-a) as a prophylactic for migraine headaches that was conducted from October 2001 to March 2004. The findings are quite serious. Dr. Dowson was ***not*** found to be dishonest, but his behavior was ruled "unacceptable," "unprofessional," and "not in the best interests" of his patients. The panel determined that his "fitness to practise is impaired because of (his) misconduct."

In the Allergan study:

- **All patients had to personally visit Dr. Dowson's office** at regular intervals and have their vital signs (heart rate, blood pressure, and body temperature) monitored and recorded. The board found:
  - 12 cases in which Dr. Dowson or his study nurse interviewed the patients by telephone rather than in person.
  - 7 instances where case reports were falsified. Vital signs data were entered based on a previous visit, not on new readings, making it an inaccurate record of the patient's vital signs on the relevant date.
- **All potentially childbearing female patients had to undergo a pregnancy test**, which had to be negative, prior to the administration of any study medication. The board found that:
  - Some pregnancy tests that had been done were unavailable for review because the study nurse had been on maternity leave.
  - One patient had not undergone the required pregnancy test.
- **The Board found Dr. Dowson back-dated an Allergan file note** acknowledging non-compliance with the trial protocol.

The Panel imposed four requirements on Dr. Dowson:

1. **Continued, regular appraisals**, starting on September 23, 2006, and yearly thereafter for five years.
2. He and his nursing staff had to take a **course in Good Clinical Practice**.
3. To **notify** all employers, all research contractors, and all prospective employers or research contractors – paid and unpaid – of this disciplinary action.
4. **To inform the General Medical Council in writing** before undertaking any position of employment or research contracts.

Other headache highlights

- **Barriers to migraine prevention.** A population based study of 162,576 patients found:
  - 56.2% were aware they had migraine.
  - 49% used prescription drugs.
  - 12.4% used preventive medications.
  - 25.7% should have had a preventive and didn't.
  - 13.1% should consider a preventive.

- **Progression of migraine.** A population study of 145,335 people found some migraine features – throbbing, photophobia, phonophobia, effect of movement, etc. – decreased with age. The study also found that other features, especially aura and frequency, deceased with age. The conclusion was that migraine remits with age, but there is a group of patients who have worsening migraine with age.

- **Diurnal fluctuation.** A study showed a diurnal fluctuation in migraine, with a peak at ~2 pm. This raised questions about whether this is due to a social rhythm or a biological clock.

- **Treatment of chronic tension-type headache.** An open-label study of Johnson & Johnson's Topamax (topiramate) found it useful in these patients.

- **Greater occipital nerve injection.** A study of an injection of 1 ml of a 50/50 mix of 2% lidocaine and 0.5% bupivacaine found that 60% of headache patients improved at five minutes.

- **Occipital nerve stimulation.** A small study found complete relief in two patients, 50%-95% improvement in 8 patients, and <50% better or no improvement in 6 patients. A clinical trial is ongoing. A speaker called it an interesting area for treatment of intractable headache.

- **Weight and headaches.** A study that looked at a database of 30,440 subjects found that obesity is a risk factor for migraines.

Correlation of Weight and Headaches

Measurement	% headache attacks per month
Morbidly obese	20.7%
Obese	13.6%
Overweight	5.8%
Normal weight	4.4%
Underweight	6.0%

PARKINSON'S DISEASE (PD)

CEPHALON'S CEP-1347 – fails to favorably modify the progression of PD

The PRECEPT study of CEP-1347 was stopped in May 2005 for futility after an average of 21.4 months of follow-up, when a planned interim analysis determined that the chance of demonstrating a statistically significant benefit at any dose (10 mg BID, 25 mg BID, or 50 mg BID) was close to zero. The trial found CEP-1347 was ineffective as a disease-modifying agent in early PD.

However, neurologists at AAN were interested in hearing more details about this 806-patient, randomized, double-blind, placebo-controlled, parallel group trial. Asked what lessons this trial has for future trials, the speaker said the major lessons are that:

- Better models are needed. The current model for PD, though it has some positive predictive value in dopaminergic agents, is not useful for non-dopaminergic agents.
- Interim futility analyses are worthwhile. In retrospect, he said he wished they had done the interim analysis earlier in this trial.

Results of PRECEPT Trial of CEP-1347

Measurement	CEP-1347 10 mg BID n=205	CEP-1347 25 mg BID n=212	CEP-1347 50 mg BID n=198	Placebo n=191
Number of patients reaching primary endpoint	133	126	127	108
Time to disability requiring dopa-minergic therapy	HR 1.30	HR 0.98	HR 1.33	---
% change in striatal β-CIT	-9.6	N/A	-9.5	-5.3

PSEUDOBULBAR SYNDROME

Twenty neurologists were asked about pseudobulbar syndrome or "emotional incontinence," including pathological crying and laughing affects. They estimated that it affects, on average:

- <2% of all of patients seen in a typical neurology practice.
- 8% of their MS patients.
- 19% of their brain trauma patients.
- 7% of their stroke patients.
- 8% of their dementia patients.
- 25% of ALS patients.
- 1% of Parkinsonism patients.

If the definition of pseudobulbar syndrome were expanded to include patients with irritability, argumentativeness, and/or agitation, the numbers would be larger, but most sources were hesitant to expand the definition that broadly.

Researchers at the University of Florida looked at 860 consecutive patients in their Movement Disorders Center and found a 5.3% overall incidence of pseudobulbar disorder.

Incidence of Pseudobulbar Syndrome in Movement Disorders

Movement Disorder	Incidence
Overall	5.3%
Idiopathic Parkinson's Disease	4.5%
Progressive supranuclear palsy (PSP)	22.2%
Psychogenic movement disorders	22.7%
Tourette's Syndrome	16.6%
Diffuse Lewy body disease	11.1%

Many patients with pseudobulbar disorder are not treated, but doctors sometimes use a tricyclic antidepressant (TCA) or an SSRI to treat it. A California doctor said, "I have patients with pseudobulbar syndrome, but I haven't treated any of them, I would treat them if I had an approved drug because pseudobulbar syndrome can be very embarrassing. Patients would like to have it treated, especially those still working." A Texas doctor said, "I don't treat pseudobulbar syndrome because there are no drugs to treat it." A New Jersey doctor said, "There is a need for a drug. The condition is disturbing to families. Treatment is more for the family than for the patient; patients generally are not bothered by it." A West Coast doctor said, "I use a TCA if it is serious and affecting the patient's lifestyle, but most of the time it is not serious. Only ~20% of cases are serious." A Pennsylvania neurologist said, "I try not to treat them because they don't respond very well, and every time you turn around the medications that might help have new warnings about the risk of sudden death."

Very few doctors questioned were aware of Avanir's Neurodex (dextromethorphan hydrobromide plus quinidine sulfate), which is in development to treat pseudobulbar syndrome – or involuntary emotional expression disorder (IEED). Although IEED is not widely recognized, and some sources are not convinced IEED should even be recognized as a separate disorder. An Australian neurologist said, "I don't necessarily recognize IEED as a distinct entity." A U.S. doctor said, "The company is trying to redefine things to create a market for its drug."

Most neurologists said they would try a new medication for this disorder if it were FDA approved and had data to support its efficacy, and several neurologists said the number of patients eligible for treatment may go up once an effective drug is available. However, most doctors were skeptical of the impact Neurodex would have. Among their comments were:

- *Texas:* "If there were a new drug, it would be very helpful, but I wonder if it will be good enough to justify the cost."
- *Georgia:* "The endpoints (in the Neurodex study) are mushy. I'm skeptical about it (Neurodex)."
- *Florida:* "If it works, I would try it but cost will be an issue."
- *Pennsylvania #1:* "I'm skeptical…I would try it in very rare patients where I can't convince the families to ignore it. If you can educate families to deal with the outbursts, you don't need to treat the patient…And cost is an issue."
- *Pennsylvania #2:* "I would try it for all my (pseudobulbar) patients. That is a bad thing to have."
- "About 5% of my MS patients have pseudobulbar syndrome, but I don't treat them because nothing is effective. Even if there were something effective, only about 20% of these would need a medication because the disorder is not all that bad."
- *Ohio:* "Only about 5% of MS patients have pseudobulbar syndrome, but if you expand the definition to include irritability and emotional lability, then 10%-20% of MS patients have it. These are distressing symptoms, so a large percentage of these patients would use an effective drug, perhaps 20%-25% of them…Many patients don't feel well on an SSRI. Behavioral, psychological, and neuropsychological symptoms are a big problem with MS."
- *Investigator:* "Neurodex works very well…From 5%-10% of ALS patients would take it because pseudobulbar syndrome bothers them…It works wonderfully, but people have to want to get treated."

Doctors pointed out several issues that may affect the uptake of Neurodex if and when it is approved by the FDA:

➢ **Appropriate doctors.** A California doctor suggested that it might be more appropriate to market Neurodex to rehabilitation doctors than neurologists.

➢ **Market size.** A West Coast doctor said, "It would be an orphan drug; the 'n' (number of appropriate patients) is small." A Texas doctor agreed, saying, "Only about 1% of MS patients might take it."

➢ **Price.** A Georgia doctor spoke for many other doctors when he said, "Price is a big factor. Nursing homes may not want to pay for it."

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