Trends-in-Medicine

March 2006

by Lynne Peterson

SUMMARY

An FDA advisory committee voted ***unanimously*** that Tysabri is effective and should be returned to the market as ***monotherapy*** but only for ***adults*** *with* ***relapsing*** MS who are not taking any immunosuppressant or immunomodulator. ♦ They did not recommend that Tysabri be restricted by disease severity or prior treatment experience, and they were split on whether patients should be allowed to have Tysabri first-line, so that decision will be made by the FDA. ♦ The panel accepted the company's proposed ***mandatory risk management program*** – a registry of all Tysabri patients – with the additional requirements that patient checklists be reported to the company monthly and distribution be halted to patients, doctors, and infusion centers that are non-compliant. ♦ However, the panel agreed there is still a risk of PML – and cases of PML are likely when patients start taking the drug again.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Panel Recommends Tysabri Return to the Market for Multiple Sclerosis

Gaithersburg, MD
March 7-8, 2006

The FDA's Peripheral and Central Nervous System Advisory Committee unanimously recommended that Biogen Idec/Elan's Tysabri (natalizumab) be allowed to come back on the market, and the FDA indicated it is going to take that advice, but the panel and the FDA both want restrictions on how the drug is used and a mandatory program to minimize the risk of progressive multifocal leukoencephalopathy (PML), a rare, severe, and often lethal brain disease that has been associated with Tysabri.

Tysabri is an alpha-4 integrin-specific humanized monoclonal antibody that has to be infused at a hospital, infusion center, or doctor's office. It was first approved in the U.S. in November 2004 for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations. Its marketing was suspended on February 28, 2005, after PML was reported in a Tysabri clinical trial. Of the ~3,000 patients treated with Tysabri in clinical trials, three patients developed PML, and two of these died. In September 2005, Biogen submitted a supplement to the original biologics licensing application (BLA), seeking to reintroduce Tysabri.

Only one other drug has ever been taken off the U.S. market and returned – GlaxoSmithKline's Lotronex (alosetron). An FDA official said there are similarities between Lotronex and Tysabri. Other drugs that have been pulled from the market had "perfectly good substitutes," the official said.

The panel chair, Dr. Karl Kieburtz, a neurologist specializing in movement disorders at the University of Rochester, summarized the panel's decision: "We voted essentially to recommend that Tysabri be re-entered to the market. We put some quite specific recommendations around that, in particular that it be limited to individuals with relapsing MS and that it be monotherapy. We didn't limit use by either minimal or maximal degree of disability for those individuals. Doctors who prescribe Tysabri and patients who receive it should have scheduled, periodic assessments – some of those being in advance of every infusion to try to reduce the risk of the greatest identified safety concern, PML – and regular, in-person evaluations by a physician. A few other minor safety issues were identified – e.g., details on the checklist and evaluations have to be negotiated between the Agency and the sponsor."

Yet, the panel unanimously told the FDA they didn't want combination trials started until there is more experience with monotherapy. Dr. Kieburtz tried to put Tysabri in perspective: "Bear in mind that this is a population (MS patients) with an average age of 30...With two year follow-up (in clinical trials of Tysabri), only

half of placebo patients had a relapse, and only 25% had progression of disability. This is a young and, on average, fairly healthy population who have MS. The risk we are talking about is with PML, which was fatal in two of the three cases. The possiblity of benefit is great, but still a minority of individuals had the problem. So, the risk is of a lethal complication in a group of people, the majority of whom will not experience the thing we are trying to prevent. So, the comprehensive risk management plan…may seem like a lot (of oversight), but I think it is appropriate."

The panel:

- ***Unanimously*** agreed Tysabri should be returned to the marketplace for at least some patients.
- ***Unanimously*** determined that Tysabri is effective in reducing the frequency of relapses over two years, reduces the accumulation of physical disability, and has shown a sustained clinical benefit.
- ***Unanimously*** voted that Tysabri has no safety issues beyond PML that would preclude approval. Hypersensitivity reactions, opportunistic infections, and antibody formation are concerns but are manageable.
- ***Unanimously*** decided that the PML risk is not entirely eliminated by monotherapy.
- ***Unanimously*** voted that the committee had enough information to discuss the return of Tysabri to the market.
- ***Voted against*** imposing either an upper limit (11 No, 1 Yes) or lower limit (10 No, 1 Yes, 1 Abstention) of EDSS disability for patients to get Tysabri.
- ***Unanimously*** that only patients with relapsing MS should get Tysabri, even in clinical trials, and that ***no*** children should receive it.
- ***Unanimously*** voted that Tysabri should be given ***only*** as monotherapy and not allowed in combination with chronic steroid therapy, one of the interferons – Biogen Idec's Avonex, Schering AG/Berlex's Betaseron, and Ares Serono's Rebif – or Teva Pharmaceuticals' Copaxone (glatiramer acetate).
- ***Was split*** (7 Yes to 5 No) over whether Tysabri should be allowed to be used as a first-line agent. A Biogen official commented, "I didn't hear anything that says this is second-line therapy." Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Director of Drug Evaluation 1 (which is in charge of oncology, neurology, and cardiac drugs), said, "It is worth saying this was not recommended only for patients who fail other therapies. Obviously, given the concern (with PML), people will think twice about using it, but the recommendation is that it not be limited to patients who failed interferons or other things or who have a particular severity of disease…Some people with early disease might try it, and the committee recommendation was not to restrict that." Dr. Russell Katz, Director of the Division of Neurology Products, added, "We asked the committee specifically if Tysabri should be reserved for second-line or if it could be first-line, and they were split down the middle on that, so we have to think about who it will be indicated for – if they will have to fail other treatments first. So, ***that is an unanswered question at the moment.***"
- **Generally agreed** the risk management program (RiskMAP) proposed by the company is acceptable, with the details to be worked out between the FDA and the company, but should definitely include:
  - A mandatory registry of all Tysabri patients. An FDA official said, "This is very, very different from most post-marketing studies where we don't usually know how many patients are treated or how many cases occur…This registry is dramatically different from what usually happens when a drug is introduced into the market…We will know every single patient, every single doctor, and every single (PML) case."
  - Consent/information sheets signed by both the physician and the patient.
  - Checklists to ensure patients at highest risk of PML do not get Tysabri. The panel recommended these be reported in real-time monthly via a web-based system to the drug distribution center.
  - Monthly real-time reporting to the distribution center or the company of monthly checklists, and the panel generally agreed with that approach. Thus, it appears likely that the FDA will require that Biogen have physicians and infusion centers electronically (web) submit the monthly checklist for each patient in real-time or near-real-time. Then, centers and doctors who do not send in expected forms are to be queried by Biogen and dis-enrolled if they remain out of compliance.
  - Suspension of authorization to participate in the program to patients, physicians, or infusion centers that did not promptly and properly submit the completed monthly checklists that will be required.
  - Regular physician evaluations of the patient – probably at baseline, three months, six months, and every six months thereafter.

Initially, the company proposed a voluntary risk management program, and the FDA's Office of Drug Safety concluded that program did "not adequately address the risk of PML." A couple of weeks before the advisory committee meeting, Biogen changed their proposal to a mandatory program. The details of the RiskMAP were in evolution even during the meeting.

Dr. Gerald Dal Pan of the FDA's Office of Drug Safety said his office is now satisfied with the new Tysabri RiskMAP. He said, "The company's initial proposal we reviewed did not call for a mandatory registry or mandatory enrollment. Essentially all aspects were voluntary, and it was our view that it is

important to have complete ascertainment of all cases of PML…We had correspondence with the company, and the company agreed to a mandatory registry…We raised a lot of concerns but a lot of those were about details...The most important thing to me was the mandatory nature of the registry."

The FDA appeared to go into the panel meeting wanting a ***very*** restrictive distribution system, but patients and panel members seemed to convince Agency officials that less restrictive access and more patient/physician choice was a better approach. Dr. Temple said, "We clearly felt the potential value of the drug in a very bad disease was great… We were impressed by the idea that patients and physicians ought to decide on taking risk and seeking benefit, and it was important to allow that discretion. There is a belief, at least without a direct comparison, that Tysabri has particularly strong benefits."

Dr. Temple said the FDA will need to get the meeting transcript and read it before making its final decisions, but he thought that could be done quickly. He said, "What we need to do is take into account all the recommendations, which means reading the transcript to see the nuances, and reaching our own conclusions about what various critical components the RiskMAP will have to have…There are a number of details to work out, and we will try to do that very rapidly so the drug can be made available as quickly as possible." Thus, the devil is likely to be in the details of this program, but it appears that the FDA and Biogen are not too far apart, so a program is likely to be able to be worked out fairly expeditiously.

Dr. Temple called the proposed Tysabri RiskMAP, with the committee's proposed changes, "probably as stringent as any" risk management program. He said, "It is on the more stringent side." He emphasized that there is a real risk with Tysabri, "The main thing in deciding to use the drug is not deciding if you have MS, but to understand the 1:1,000 risk you might get a devastating disease…It may not kill you all the time, but it is very bad…and they (patients) need to understand that and decide if they are willing to take the risk in return for the potential benefit…That will be a tough decision…Our major objective will be to explain to people as clearly as possible the nature of the risk and its severity. The patient has to have the presumption that if he/she gets this (PML), it will be very terrible."

FDA officials and panel members emphasized that there will be cases of PML when Tysabri is reintroduced to the market; the risk management program will not eliminate all cases, if any. Dr. Temple said, "We expect cases. We don't think it occurred just because of combination therapy (with another immunomodulator or immunosuppressant). For all we know, it (PML) will be the same with monotherapy. That is our assumption, even though we don't want anyone to do anything but monotherapy." Dr. Katz said, "We fully expect additional cases of PML, many likely to be fatal…We don't know the rate…but the crude rate appears to be 1:1,000. And we don't know about factors that may affect the risk – whether concomitant use of immunosuppressants increases the risk or whether the risk increases with increasing duration of treatment…There will be additional cases of PML, perhaps many cases, and likely considerable mortality associated with the drug…This is something families and prescribers need to consider…There are still risks with the proposed risk management plan." The panel chair added, "It is likely there will be cases of PML, and it is likely there will be deaths from it. That has to be the background, but there are death and disability with other interventions on the market, and in the face of the disability of the disease, is it a decision patients and physicians can make together? Our unanimous decision was, Yes, with certain restrictions."

The PML cases will not cause Tysabri to be withdrawn again from the market unless the rate by which they occur increases, an FDA official said. He explained, "It is the rate, not the number of cases. If the rate goes up, we may have different views and probably would have to go back to the Advisory Committee." The panel chair also suggested that patients who say they are willing to accept the risk today may be less tolerant of risk when PML cases start occurring, "People with side effects (from a drug) are quite upset at the time, but they are tolerant about side effects in the future. Disability is quite a hardship, but people are more tolerant about it for the future. It is a question of the reality of current problems vs. the possibility of future problems."

After the panel concluded its votes, Dr. Burt Edelman, Biogen's Executive Vice President for Development, said his company was very happy with the final outcome. He predicted the final details of the risk management plan will be worked out by the FDA's March 29, 2006 PDUFA (action) date, and he estimated that Tysabri could be launched in weeks, not months, post-approval.

- Asked about the size of the market now for Tysabri, he said, "More than 50,000 patients (in the U.S.) have fallen out of treatment, and the same number have active disease on therapy."
- He had no comment on the expected price for Tysabri.
- He described PML as a risk but an acceptable risk, "The risks are real but probably manageable and acceptable. No one said our strategy would eliminate the risk of PML. Unfortunately, we have to accept these risks as part of immunomodulatory therapy…With the restrictions on use of the drug to patients on monotherapy and no immuno-suppressants, the incidence of PML may be even lower than 1:1,000."
- Asked how many people Biogen will have to hire to handle the risk management program, he said, "We'll put together a significant back office operation to support the RiskMAP…And we'll beef up our sales force, but not significantly. We will also get an infusion team from Elan to help at infusion centers."

The National MS Society also was pleased with the outcome of the advisory committee meeting. Dr. John Richert said, "We are particularly pleased that the committee has recommended that Tysabri be brought back on the market – and that they found a means to determine a reasonable balance between efficacy and safety issues…We funded some of the early research on the antegren (Tysabri) molecule, and that seminal work led to a drug with this (high) level of efficacy…One of the concerns was there might be an onslaught of people getting Tysabri – a rush of MS patients to get on this drug without adequate consideration for the risks and benefits. I think it is safe to say that a large number of people insisted on additional information before they wanted to make a decision for themselves."

FDA Presentation

The FDA's Dr. Katz explained the FDA's decision a few weeks ago to allow Tysabri clinical trials to be re-started. He said, "We agreed with the sponsor that patients who had been in Tysabri trials could…reinitiate treatment under the IND with extensive and close monitoring, including measurement of serum JC virus prior to each monthly infusion. It is clear that agency has decided that in certain circumstances that certain patients can receive Tysabri…Limiting Tysabri to patients who already received it and are doing well is a very different circumstance from (full marketing)."

Dr. Susan McDermott of the FDA's Division of Neurology Products said the FDA believes efficacy was shown in terms of relapse rate and disability progression, but 6% of patients developed persistent anti-Tysabri antibodies, which is associated with less efficacy.

She reviewed the two PML cases in MS in detail, and made these points:

- On PML, she said one of the key questions for the FDA is how neurologists will be able to distinguish MS from early PML.
- The FDA doesn't think any PML cases were missed, "We do not think there are any lurking cases of PML that were missed."
- Monotherapy is not necessarily safer than combining Tysabri with an interferon. She said, "As an agency, we don't feel comfortable you're decreasing your risk with monotherapy…We don't have enough information to say that."
- The relationship between concomitant immunosuppression and PML is unclear.

Dr. Alice Hughes of the FDA discussed non-PML safety issues with Tysabri. She concluded that compared to placebo patients, Tysabri patients had:

- Hypersensitivity reactions.

FDA View of Tysabri Efficacy

Measurement	Tysabri	Placebo	p-value
Study 1801			
Number of patients randomized	627	315	---
Patients reaching sustained disability progression	17%	27%	.0002 (HR 0.58)
Annualized relapse rate	0.24	0.73	<.002 (HR 0.49)
Study 1802			
Number of patients randomized	589	582	---
Patients reaching sustained disability progression	22%	27%	.0238 (HR 0.76)
Annualized relapse rate	0.34	0.75	<.001 (HR 0.41)

FDA Retrospective Review of Tysabri Exposure

Doses	<12 doses	≥12 doses	≥24 doses	≥36 doses	Total
MS safety trial	718	1,151	1,053	279	1,869 patients
Crohn's Disease/ rheumatoid arthritis safety trial	721	499	285	18	1,220 patients

FDA View of Tysabri Non-PML Safety

Measurement	Tysabri	Placebo
MS Studies		
Overall infections	73.7%	73.9%
Serious infections	2.4%	2.3%
Upper respiratory tract infections	59.6%	59.8%
Urinary tract infections	21.5%	21.4%
Serious UTIs	0.6%	0.5%
Lower respiratory tract infections	13.3%	12.2%
Vaginal infections	7.5%	6.2%
Herpes infections	7.0%	6.1%
Gingival infections	1.1%	0.5%
Crohn's Disease/Rheumatoid Arthritis Studies		
Overall infections	40.4%	35.8%
Serious infections	2.5%	2.6%
Upper respiratory tract infections	27%	21%
UTIs	2.9%	2.0%
Serious UTIs	0.2%	0
Vaginal infections	2.1%	1.6%
Herpes infections	1.6%	1.0%
Perianal abscesses	1.1%	0.6%
Serious viral meningitides	0.2%	0
Serious CMV colitis	1 patient also on azathioprine	0

- A similar incidence of overall infections and upper respiratory infections but more atypical infections with Tysabri. Of particular concern are herpes infections, lower respiratory tract infections, and viral meningitides.

- 10% of patients had a positive antibody titer at least once, and antibody formation is strongly associated with more:
  - Infusion reactions and hypersensitivity reactions (occurring in 77% of antibody-positive MS patients vs. 20% of antibody-negative MS patients).
  - MS relapses (57% in antibody-positive patients vs. 35% in antibody-negative patients).
- No leukemias and no apparent increase in the risk of malignancies, though there was one B-cell lymphoma in a Crohn's patient on concomitant 6-mercaptopurine and a history of Remicade (Johnson & Johnson, infliximab).

She also concluded there is:

- A similar risk of infection whether on Tysabri monotherapy or combination therapy.
- No clear association between the increasing number of Tysabri infusions and risk of infections.

Diane Wysowski PhD of the FDA's Division of Drug Risk Evaluation, Office of Drug Safety, reviewed the Tysabri Risk Minimization Action Plan (RiskMAP) that was proposed by Biogen Idec. In the committee's briefing documents, Biogen proposed a voluntary RiskMAP, but the company has now proposed a mandatory program, in which both prescribers and patients have to enroll. The FDA said the company is also claiming that patients who do not comply with the follow-up will be denied further receipt of Tysabri and that patients will remain in the Tysabri Registry for a minimum of six months after the last dose of Tysabri. The company also recently added follow-up of patient deaths through the National Death Index and collection of death certificates from state health departments, but there is a 2-3 year lag in that data.

Biogen is proposing to query prescribing doctors every six months for:

- Patient continuation of Tysabri.
- Any PML cases.

RiskMAP Enrollment Requirements

Physician acknowledges/signs	Patient acknowledges/signs
Has read full prescribing information	Has read Medication Guide
Is aware of PML risk (disability/death)	Is aware of PML risk (disability/death)
Has discussed risk/benefits with patient	Has discussed risk/benefits with doctor
Has told patient to report new or worsening neurological symptoms	Understands need to report to MD new or worsening neurological symptoms
Is enrolling in Tysabri Registry	Is enrolling in Tysabri Registry
Is prescribing for relapsing MS	
Confirms patient has no contraindications	

This FDA official laid out several questions for the panel – mostly a re-wording of the official questions.

1. Should there be restrictions on Tysabri use by:
   a. MS severity?
   b. Failure on other MS therapies?
   c. Contraindication with concomitant and recent use of: immune modulator drugs, systemic corticosteroids, and/or immunosuppressants?
2. Should prescribers reassess and reauthorize patients to receive Tysabri and if so, how frequently?
3. Should assessment be by a doctor or a nurse? Is this an assessment a nurse should make?
4. Should the checklist have a longer list of diseases and drugs that are known to induce an immunocompromised state?
5. Should there be one-to-one patient-to-vial distribution for tight control of Tysabri distribution and tracking?
6. Would patient follow-up be aided by collection in real-time of Tysabri administration, discontinuation, and reasons for discontinuation data?

In addition, Biogen is proposing the Tysabri Observational Study, a registry of 5,000 patients worldwide, including 3,000 in the U.S. These patients will be followed for up to five years, looking for serious non-PML opportunistic infections, cancer, and the overall safety profile. The FDA official wondered if five-year follow-up is sufficient.

Panel questions for FDA officials

During a brief question and answer period with the FDA presenters, several interesting comments were made, including:

- *FDA:* "The Biogen RiskMAP program would exclude off-label use of Tysabri for anything except relapsing MS."
- *Dr. Temple:* "This (RiskMAP) is not an investigation. It is not a research tool. You can't opt out of it, and it will not go to IRBs (at academic centers)…We will not learn anything from it…Doctors could sign something that says, 'I know this drug is indicated only for MS,' but they could still prescribe Tysabri for something else…A doctor also could be required to say, 'My patient has MS.' Those are things you (the advisory committee) have to think about in writing the program."
- *FDA:* "If you link the vials to patients, there will be less off-label use...Otherwise, there could be stockpiling at infusion centers or a doctor's office. Unless that excess is sent back to the company, there is a possibility Tysabri could be used off-label. That is one point for the committee to consider – tying the vial to the patient."

- *FDA:* "The (current) checklist for neurological symptoms is very non-specific – a sudden change in eyesight, balance, or thinking…I would assume that might produce a large number of potentially false positive PML cases."
- *Dr. Temple on other risk management programs:* "For clozapine (Novartis's Clozaril), patients have to bring in a white count from the week before to get the next dose…The result is agranulocytosis is discovered much earlier, and the mortality from agranulocytosis that is seen is much lower than expected – a couple percent instead of the 10% expected. The registry assures that no one with a white count problem ever gets the drug again…But that is a fairly simply question; it is just about the white count, which is a simple lab test. But we feel quite good about that gradual rollback on how often patients need that test. There are other similar programs – like bosentan (Actelion's Tracleer) for pulmonary arterial hypertension (PAH) – which is designed to prevent pregnancy."

Based on their comments today, questions the panel will raise themselves tomorrow include:

1. Whether patients will be honest about signs/symptoms of PML if it means having to stop Tysabri.
2. What level of PML incidence post-marketing is likely to lead to withdrawal of Tysabri again.
3. Whether doctors will diagnose relapsing MS too broadly if that is the only way patients can get Tysabri.

Panel members wanted to know what the discontinuation rate was with other MS therapies, and an FDA official prepared this analysis.

MS Treatment Discontinuations

Drug	Time period	Discontinuation rate
Rebif	1 year	6%
Tysabri	1 year	6%
Avonex	~1.5 years	9%
Rebif	2 years	10%-12%
Betaseron	3 years	10%-14%

BIOGEN IDEC PRESENTATION

A Biogen official estimated that for every 1,000 patients treated with Tysabri for two years compared to no treatment, there would be:

- 1,000 fewer relapses.
- 260 more patients remaining free of relapse.
- 120 more patients remaining free of progression by 1 point on the EDSS scale.
- 60 fewer hospitalizations due to MS.
- 40 fewer patients requiring aids for ambulation.

Biogen's Dr. Edelman said the company was proposing that Tysabri be indicated ***only for the treatment of patients with relapsing forms of MS to delay the progression of physician disability and to reduce the frequency of clinical exacerbations as monotherapy in patients who are not immunocompromised***. He said, "We believe the data here will show Tysabri to be highly effective…Data from Phase III have confirmed and extended the efficacy profile originally described in the one-year label – that it can reduce disability progression as well as reduce the relapse rate."

Dr. Edelman made several interesting opening comments, including:

- "Only three patients contracted PML…And there is no evidence that Tysabri promoted the JC virus or that treatment-naïve MS patients have an increased incidence of JC virus replication in their blood or CSF."
- "Most individuals diagnosed with MS suffer progressive (disease)…The burden is similar in magnitude to RA, Crohn's Disease, and severe psoriasis – and those diseases are treated with highly active immunomodulatory drugs…Patients and physicians have learned how to use those medications and manage – but not eliminate – their risks."
- "Biogen Idec and Elan are committed to a continuing effort to better understand the JC virus and PML…We are examining the utility of various testing methods in blood. Were any of these proven useful, we would include them immediately in the RiskMAP."

Dr. Edelman said the proposed RiskMAP is:

- Intended to exclude any MS patient with evidence of immune dysfunction.
- Ensure patients and physicians are informed of the risks and appropriate use of Tysabri.
- Control distribution.
- Provide comprehensive, proactive pharmacovigilance.

Dr. Alfred Sandrock, a Biogen vice president, reviewed the efficacy of Tysabri, but there were no new data. Among the interesting points he made were:

- 15%-20% of MS patients discontinue therapy annually.
- A large number of patients are on no therapy.

Dr. Michael Panzara of Biogen reviewed the safety of Tysabri. He insisted the rate of serious infections was comparable between Tysabri and placebo, both in the clinical trials and post-marketing. Other points he made included:

- "With increased Tysabri exposure, there is no increased risk of infection. The Kaplan-Meier curves are nearly super-imposable, with a hazard ratio of 1.009 (p=0.841).

Thus, with increasing Tysabri exposure, there does not appear to be an increased risk of infection."

- "There was a slight increase (1.1%) in herpes infections in Tysabri-treated patients, primarily with combination treatment…There was a similar observation in Crohn's trials."
- The rate of opportunistic infections per 1,000 person years was 2.9 in Crohn's Disease.
- The hypersensitivity rate of 0.8% is consistent with the approved labeling.
- There was no increase in malignancy.

Biogen View of Tysabri Safety in Clinical Trials

Measurement	Placebo n=1,135	Tysabri n=1,617
Total infections	73.9%	73.7%
Serious infections	2.3%	2.4%
Appendicitis	0.3%	0.4%
UTI	0.4%	0.4%
Serious viral infections	0	0.2%
Herpes infection incidence	6.0% monotherapy 6.1% combination therapy	6.4% monotherapy 8.4% combination therapy

On PML he noted:

- Features that help differentiate PML from MS include:
  - **Tempo.** PML symptoms are typically subacute and MS symptoms are more acute.
  - **Location of lesions.** MS lesions tend to be on the optic nerve or spinal cord, but these areas are almost never involved in PML.
- There are no antiviral treatments for PML. Immune reconstitution may be the most effective treatment in terms of improving outcome.
- Baseline brain MRIs are very important to facilitate PML assessment.
- The presence of viremia is not necessary to PML, and the absence of JC virus does not exclude the diagnosis of PML.
- Biogen believes clinical vigilance by a neurologist is the most important means of screening for PML. Dr. Panzara said, "We also believe the monthly interaction between healthcare providers and patients provides a unique opportunity to enhance this vigilance with the introduction of questionnaires or checklists that have a sufficiently low threshold to prompt further investigation by the physician…The three PML patients presented with signs that were recognized by the patient, physician, or family members. Previously, they would have been assumed to be MS symptoms, and now any change on Tysabri will be assumed to be PML until proven negative, prompting Tysabri to be stopped."
- There are currently no proven means of monitoring or predicting PML; there is nothing predictive or diagnostic – no blood test, no MRI scan. Spinal fluid is very specific for diagnosis, but it tends to be negative in early disease, and it is an invasive test, so it is a poor screening tool.

Dr. Carmen Bozic, Vice President of Drug Safety and Risk Management at Biogen, outlined the company's risk management plan (RiskMAP). The plan presented was different from what was in the panel's briefing documents, and panel members did not even have a final printed copy of it in their briefing book. She said the company spoke to more than 200 neurologists about how best to minimize the risk of PML, and the company believes neurologists are the best qualified specialists to manage PML. She added, "We considered shipping Tysabri one vial at a time to approved patients, but we concluded this would not enhance safety and would create a significant burden for infusion centers, especially those in hospitals and academic centers."

New, revised labeling for Tysabri, featuring a prominent boxed warning, was proposed.

- Tysabri is associated with an increased risk of PML, which causes death or severe disability.
- Warn against concurrent use with immunosuppressants or immunomodulators (e.g., interferon beta).
- The indication is ONLY for relapsing MS.
- Healthcare professionals should be alert to any sign or symptoms that may be suggestive of PML.
- Dosing should be suspended immediately at the first symptoms suggestive of PML.
- Evaluation should include brain MRIs and CSF analysis.

The proposed label also says that an MRI scan should be obtained prior to initiating therapy with Tysabri and that Tysabri has been contracted in patients who are immunocompromised.

Number Needed to Treat (NTT)

Relapse rate	Placebo	Tysabri	Treatment effect	Absolute difference	NTT
Monotherapy					
Annual relapse rate	0.78	0.26	68%	0.52	1
Proportion relapsing	0.54	0.28	48%	0.26	4
Proportion progressing	0.29	0.17	41%	0.12	9
Combination therapy with Avonex					
Annual relapse rate	0.75	0.34	55%	0.41	2
Proportion relapsing	0.68	0.46	32%	0.22	5
Proportion progressing	0.29	0.23	21%	0.06	17

The Biogen-proposed RiskMAP:

- Enrollment will be mandatory into a registry, the Tysabri Registry.
- All prescribing physicians and patients must sign a mandatory enrollment form and send that to Biogen before initiating therapy.
- Distribution will be centralized and controlled.
- Tysabri will only be allowed to be administered in registered infusion centers.
- Patients and physicians will both have to acknowledge and sign an enrollment form.
- Data will be shared with the FDA every three months.

A Tysabri observational cohort study is also being proposed. This is a subset of registry patients – 5,000 patients worldwide, with 3,000 in the U.S. It will be powered to detect rare events (those with ≥0.06% incidence).

Tysabri is being recommended for use in relapsing remitting MS patients only as monotherapy, in patients who are not immunocompromised and who are enrolled in a Tysabri registry and fully informed about the risk of PML. In addition, the company says it is recommending that Tysabri be allowed for patients who:

- Have disease activity on current therapy.
- Are intolerant of current therapy.
- Others deemed appropriate based on individual assessments.

Proposed special requirements for infusion centers include:

- Tysabri can be used only in registered infusion centers which get educational training for personnel and attest they will follow the risk management requirements.
- Dosing would be limited to patients enrolled in the Tysabri registry.
- Every patient will get a Medication Guide (Med Guide) with every dose.
- Documentation must be entered in a Tysabri infusion log.
- Infusion centers will be audited by Biogen.
- A patient checklist must be completed before each dose. A Biogen official said, "We think it will be unlikely that patients will game the checklist."

When and if any PML cases occur, Biogen promised to:

- Thoroughly collect data related to the case.
- Analyze each case.
- Report cases in an expedited manner to the FDA.

Dr. Richard Rudick, a neurologist from the Cleveland Clinic, spoke on behalf of Biogen. He made three key points:

1. **The magnitude of the unmet need.** He said, "We endlessly debate the benefits of the current drugs…They don't stop progression of the disease, and there is no debate about that. In 10 years of using MS drugs, most patients have relapses or progressions of disability despite adherence to prescribed drugs. Patients who seem stable clinically often show silent MRI lesions and too often later enter the stage of progressive disability…Current drugs also cause side effects with diminished quality of life, and many patients imply discontinue use. My clinic is filled with patients who report disease activity despite use of current drugs…Switching (drugs) is of little benefit, in my opinion. Combining an interferon or Copaxone with methotrexate, azathioprine, etc., might help, but there are no data to support this approach, and there are questions about safety. Novantrone (Ares Serono, mitoxantrone) is approved but has significant cardiac toxicity and reported cases of leukemia...Current therapies don't come close to meeting current needs. We need new therapeutic products."

2. **Tysabri is an important new therapeutic option.** He said, "Robust Tysabri results were met with excitement and enthusiasm by doctors and patients who viewed Tysabri as a major advance…A two-thirds reduction in relapse rate simply cannot be ignored. It is a striking result, in my opinion…Many patients simply don't perceive benefits from current drugs or don't tolerate them and stop therapy. These patients need options they can accept and tolerate…Tysabri really looks like a major therapeutic advance."

3. **Responsible use of Tysabri.** He said he doesn't believe Tysabri use should be tied to a requirement that the risk of PML be eliminated, "I don't believe this is a realistic requirement. But I do think Tysabri should be used in appropriate patients who are fully informed and carefully monitored by an accessible neurologist."

Dr. Rudick said he asked his patients if they would take a drug that might be twice as effective but which carries a 1:1,000 risk of a fatal brain infection: "My patients had very little difficulty answering that question…They gave me prompt answers…Some said, yes; and others said, no, they wouldn't take it. They all seemed to grasp the situation pretty easily… Whether the benefit outweighed the risk to them was based on

Additional Infection Information on Tysabri

Measurement	Placebo n=1,235	Tysabri n=1,617	Cumulative Tysabri experience n=2,283
Overall infections	73.9%	73.7%	65.6%
Herpes	6.1%	7.2%	6.1%
Serious infections	2.3%	2.4%	2.2%
Serious herpes infections	0	0	0
Opportunistic infections	0	0.12%	0.13%
PML	0	0.06%	0.09%
Malignancies	1.3%	0.7%	0.7%

their disease state, value system, family, etc…I believe the neurologist has to decide if Tysabri is an option, but I think the patient has to be a full participant in deciding whether to use the drug…If it is appropriate in a patient and the patient agrees to monitoring, I think treatment should proceed. Tysabri offers the likelihood of significant benefits because it is a therapeutic advance in a disease with a major unmet need. It should be available."

Biogen and FDA responses to panel questions

Biogen officials clarified some issues at the request of the panel. They distributed a new, more detailed checklist to be used by doctors and infusion centers, and they provided new information on infections with Tysabri as well as estimates of the number needed to treat (NTT) with Tysabri.

PUBLIC WITNESSES

The FDA always reserves time for the public to have input at Advisory Committee meetings, but an unusually large number of people took advantage of this opportunity at the Tysabri panel. More than 40 people spoke, mostly MS patients and their family members, but also a few doctors and patient advocates, and their message was clear: Let us make the choice, give us the option of Tysabri.

The FDA's Dr. Temple said, "They (the patients) are invariably moving. People who come to these (panel meetings) always have terrible disease, but today, in particular, the speakers helped summarize the very issues the committee has to grapple with tomorrow…On the one hand, we heard Tysabri should be for very advanced MS, but some of them are saying they want to avoid getting very far advanced…I thought that was extremely useful…You expect it (the patients) to be heart wringing, and we know MS is a devastating disease to many people…I thought it was interesting how they said how much risk to accept and for what benefit is something patients and their doctors should have something to say about."

Nearly everyone pleaded for the return of Tysabri. Among their comments were:

- *Crohn's patient who took Tysabri:* "I know this drug is not coming back for Crohn's...and you need to do the right thing and bring this back for the people it can help."
- "The risk of doing nothing for me is too great. The risk of doing nothing to me means continuing to take ineffective drugs."
- *Arguing against a mandatory RiskMAP program:* "In our center, day-to-day MS care is in the red. If we add an onerous risk management effort to this and the opportunity to give Tysabri, we won't be able to use the drug because it will drive our losses even higher…I thought the voluntary plan was reasonable, and I favor that."
- *Michigan Institute for Neurological Disorders:* "Virtually every one of our patients is eager to resume taking Tysabri…I'm confident those who wish to receive this will be well-informed about the risk…Any of us can get hit by a bus, but those of us with MS see the bus coming. The bus represents disability, and it is imperative we have as many choices as possible to slow the bus down. I truly believe Tysabri is a way to slow the bus down."
- *Elan shareholder:* "I will adhere to any risk management plan. Please do not make us wait any longer for Tysabri."
- *Former Betaseron user:* "I quit Betaseron without telling my doctor because it was making me sicker…I got two Tysabri infusions, and I felt so good. I didn't feel like I had MS anymore…I am fully capable and willing – with the help of my chosen professional – to consider the possible risk of 1 in 1,000 to achieve a higher quality of life…I truly believe Tysabri is the cure for my MS…I would like to give up my 24/7 job as an MS patient and get a full-time paid job."
- "I'm a classic non-responder to all the (MS) drugs… There is a 1:1,000 chance of developing MS. After winning that lottery, I'm willing to take the 1:1,000 risk of PML."
- "During five months on Tysabri alone, I felt terrific…and I had two days of each week returned to my life (because I wasn't sick from the interferons)…It was an amazing five months...I urge the committee to bring Tysabri back…I believe the risk is manageable at this time…I also urge the committee to make Tysabri available to newly diagnosed patients. I think it would be absolutely wrong to make Tysabri only a drug of last resort. The best advantage to Tysabri is that it may be able to slow disease progression."
- "Five years ago I wouldn't have taken Tysabri, but it would have given me peace of mind to know it was available if I needed it…Each day without Tysabri is a day without hope."
- "Quality (of life) is more important than quantity. I ask you to approve Tysabri for me – and for my daughter (who also has MS). I want Tysabri badly, but for my baby, I want it desperately."
- "Cognitive loss was the greatest problem for me (with MS)…I got it back with Tysabri…I understand there is a small risk with Tysabri…I would take that risk…If I had Tysabri back, I would have a life…If I don't get it back, I don't even know if I'll have a future."
- *Physician:* "The much higher efficacy of Tysabri will allow us to arrest many more of those aggressive cases that get away from us now. So the benefit:risk ratio becomes enormous. We have never had a benefit:risk ratio in a drug like this before."

- "I know I could face any obstacle as long as I had my Tysabri."
- *Abigail Alliance for Better Access to Development Drugs:* "There are still only 3 cases of PML – a one-tenth of 1% chance the lifeboat will sink…Tysabri should never have been taken off the market. That was an over-reaction by the FDA. The media, advisory committees, and politicians also played a role…Many thousands of MS patients have progressed…because of over-reaction of false and ill-considered magnifications of drug safety concerns."
- "Patients in consultation with physicians should have greater control on how they fight for their lives…Patients need to be put first."

A few speakers either opposed the return of Tysabri at this time or they had mixed opinions. The family of the MS patient who developed PML and died argued against the return of Tysabri, accusing Biogen of enrolling Anita Smith without first properly diagnosing her as having MS. Other speaker comments included:

- *Neurologist:* "Longer exposure (to Tysabri) could exponentially increase the risk of opportunistic infections ...I would argue there is no crisis in MS therapeutics, so there is no need to rush back to market a drug with serious hazards. I would urge further study of Tysabri. Only with longer-term safety data can neurologists feel comfortable using this drug in the future."
- *MS Association of America:* "Informed consumer consent is our objective…Most patients do very well on the current drugs, ***especially*** if they are started on treatment early…We struggle with whether a black box is sufficient as a warning…Patient safety must be primary…Can (informed consent) be assured in the more than 50% of patients who have cognitive dysfunction (as a result of their MS)?"
- *Physician who reviewed the medical records of Anita Smith, the MS patient with PML who died:* "Anita Smith was healthy and lived a full life…It is possible Biogen and Elan offered substantial financial rewards to doctors for enrolling patients…She has since been verified not to have MS. If Biogen and Elan had not inappropriately enrolled her in the Tysabri trial, she would be alive today. Tysabri is not the miracle drug for MS that people hope it is…I strongly feel Biogen and Elan should have to do more animal studies before it is again given to humans."
- *Husband of a Tysabri patient who developed hypersensitivity reaction:* "My wife had a serious side effect that could have been avoided if a series of simple allergy tests had been given to her before the study…We found she is allergic to polysorbate 80…There is no cure for this hypersensitivity, and no one knows the effect of this on her MS…Where was the protection, care, and treatment Biogen, Yale, and the IRB promised?...And why did Biogen get to review its own data when Tysabri was removed from the market. The FDA should mandate an independent body do the review."

Dr. John Richert of the National MS Society presented a survey of 810 MS patients that was paid for by Biogen – but analyzed independently, not by Biogen. The survey found:

- 25% had a positive impression of Tysabri, 25% had a negative impression, and ~33% had a neutral opinion; the others had no comment.
- 26 respondents had received Tysabri when it was available, and 76% of these wanted to take it again, while 12% did not, and 12% were undecided.
- ~One-third wanted to have Tysabri available, whether or not they took it, and half wished to have more information before making a decision.
- 80% had a relapse in the previous year, and 25% suffered ≥3 relapses in the last year.
- 50% switched drugs, and one-third switched twice.
- 55% said they definitely or probably would use a drug that reduced relapses or retarded disability even with a 1:1,000 risk of a fatal side effect, and one-third said they would probably use a drug with a 1:500 incidence of fatal side effect. Willingness to tolerate risk was unrelated to disability level.
- 72% had seen a neurologist at least four times in the previous two years.
- 79% said they and their physician were equally involved in drug decisions.
- 71% said that once the FDA provided a warning, patients should be free to decide what to use.
- Almost all said they would be willing to visit their neurologist more often in order to use riskier drugs.

Following the public testimony, the panel had a short discussion with FDA officials. Among the interesting issues and comments during this period included:

- **The PML patient who died may not have had MS,** and Biogen was criticized by public speakers for enrolling her in a Tysabri trial. Panel members wanted to know more about this patient, her diagnosis, and why she was included in the trial. The panel chair said, "It is inevitable that people will be misdiagnosed…We will have to figure there will be some finite level of misdiagnosis. It is human and unavoidable. We all have to talk about how to minimize that."
- **Early detection of PML is important,** even though there is no cure for PML because stopping the immunosuppressant (Tysabri) may improve survival.
- **Misdiagnosis.**

FDA Questions and the Panel Votes

QUESTION 1. Has Biogen demonstrated natalizumab's efficacy on reduced frequency of relapses through two years, and fulfilled the commitment made under the Accelerated Approval regulations to verify the sustained clinical benefit?
Unanimously YES

The panel did not feel the need to discuss this but went directly to a vote.

QUESTION 2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?
Unanimously YES

QUESTION 3. Outside of PML, are there safety-related issues associated with use of natalizumab that you consider to be important considerations in making a risk:benefit assessment, including:

A. *Non-infectious disease risks?*
YES, hypersensitivity reactions and antibody formation, but monitoring is sufficient.

B. *Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS infections)?*
YES, opportunistic infections are a concern, but monitoring is sufficient.

C. *The FDA also asked if there is anything in the data other than PML that would preclude approval?*
Unanimously NO

However, the panel did not recommend patients be tested for antibody formation – which generally occurs early, by Week 12 – before administration of Tysabri, but they suggested that patients be tested for antibodies if Tysabri efficacy waned or side effects occurred. When antibodies are identified, the panel recommended that Tysabri treatment be stopped.

Panel member comments included:

- "Development of neutralizing antibodies is important for two reasons. It is a signal of a risk for a hypersensitivity reaction and for a population with decreased benefit, so the benefit (with Tysabri) may exist in the non-antibody population…(Biogen) said it would suggest or propose clinically-based testing based on occurrence of side effects and not recommend further treatment in antibody-positive patients."
- *A Biogen official:* "In Study 1801, the incidence of neutralizing antibodies was 4% (25 patients), and there were 1.3% serious hypersensitivity reactions…There will be a commercial test available for neutralizing antibodies …Anyone suspicious of diminished antibodies or the occurrence of certain adverse events such as flushing, we recommend testing, and if the test is positive, the patient should not receive Tysabri."
- "I think they (antibodies) will be a concern over time."
- *FDA official:* "Not all hypersensitivity reactions were associated with antibodies, but all anaphylactic reactions were."

QUESTION 4. Is the PML risk entirely eliminated by monotherapy?
Unanimously NO

The chair said, "The committee believes there is treatment-associated risk of PML even when given as monotherapy. None of the observed cases happened in that situation, and it is possible that co-administration of a secondary immunosuppressive agent increases the risk, and it is possible that the risk only occurs in those individuals, but we don't know that yet."

QUESTION 5. Are there additional data (or studies) that you recommend FDA obtain prior to determining whether natalizumab may return to the marketplace? This was reworded to: Do we have insufficient information to discuss the larger questions or are you prepared to discuss them?
Unanimously YES, the committee had enough information to discuss the return of Tysabri to the market.

QUESTION 6.

A. Should Tysabri be allowed as a first-line agent?
SPLIT VOTE 7 Yes to 5 No

B. Would you impose an upper limit of EDSS disability?
11 No, 1 Yes

C. Would you impose a lower limit of EDSS disability?
10 No, 1 Yes, 1 Abstain

D. Should Tysabri be prescribed to individuals who do not have relapsing MS?
Unanimously NO

E. Should Tysabri be allowed as combination therapy with Avonex, Betaseron, Copaxone, or Rebif?
Unanimously NO

Panel comments included:

- "I suggest individuals should try other agents first. There are decades of experience with other agents. We know the safety profile of those agents, and we don't know the long-term safety of Tysabri…But I would not restrict Tysabri to a specific level of disability."
- "I'm not saying second-line. I think it should be first-line."

- "I'm conflicted about this question. What we are beginning to realize is that the earlier the treatment you get, the more you prevent disability and presumably brain atrophy…On the other hand, if you have a patient who is very mild, there is a percent who you really do not see progression. That is a minor percent, but if you have a patient with a series of attacks and increasing enhancing lesions, that is the patient you want to put on mono-therapy early in the clinical course. And we also talked about patients who are not able to tolerate the ABC (Avonex, Betaseron, Copaxone) drugs and are having attacks. This is the type of person you want on Tysabri."
- *Consumer representative:* "You will not see primary care doctors or general neurologists prescribing Novantrone… The concern that Tysabri will be used willy-nilly is fairly unlikely…Time is running in MS…You really do need to individualize treatment, and if someone is clearly going downhill quickly, waiting for that patient to fail current therapy, given the higher efficacy with Tysabri would be harmful to patients…There are a substantial number of patients we know who are not being treated…Needle phobia and the idea of self-injections has really turned a lot of people away…When I talk to patients about an IV infusion, there is an attractiveness to that…I do not agree that this should be a second-line therapy."
- "I would not set a minimal level of disability…We all see patients with no disability and terrible scans, and I think those patients should be treated aggressively."
- *Patient representative:* "There is a big needle phobia and a huge unmet need. I have peers (with relapsing MS) who have flat out said they are not on anything, and if this drug becomes available, they will get monthly infusions."
- *Dr. Temple:* "We don't always say a drug is only for people who are studied. There is a difference between telling people in whom the studies were done, 'Don't (use it) with an EDSS of 4+'…It is hard to swallow the idea that in places where we're really worried (about the patient), to stop using a drug that appears to work well…but telling people about the lack of data is important."
- "I think we are all terrified (at the idea of combination therapy). I don't think anyone would recommend that at this point."
- *Industry representative:* "I think this has to be a second-line drug…This drug is less safe on the limited data we have at this time…We didn't hear about patients who do well on other drugs…And the medicolegal implications of this as a first-line drug before trying something else propels us to say that at the moment this should not be the first drug given to an MS patient."

QUESTION 7. Considering the currently available data, please discuss whether natalizumab should be returned to the marketplace for at least some patients, taking into account the preceding discussion of specific populations.
Unanimously YES

QUESTIONS 8A-E. This was a multi-part question about what should be in the risk management plan and whether the company should be allowed to do a more in-depth observational study of 5,000 Tysabri patients.
No vote

The chair summed up the committee discussion on this question. He said, "Nothing was voted on, but the overall sensibility was that the proposed information by the sponsor in a registry was necessary. There was a little debate on whether there should be more materials provided by the six-monthly basis registry but no clear consensus. We will leave that to the Agency and sponsor to work out…On the observational study, some things are more appropriate in the context of a research study rather than mandatory as part of clinical care…And there should be some restrictions on distribution but not on a one-to-one basis…Some mandatory monthly reporting back on the use of checklists and a feedback mechanism was discussed, and the expectation was that checklists not received would be evaluated to find out why expected forms were not received…We also endorsed the idea that there should be some in-person evaluation. In clinical care that might be an evaluation at baseline, at three months, at six months, and then every six months. Again, that will be worked out between the sponsor and the FDA…We are left with the notion that any exacerbation will be treated by the sponsor as if it could be a new case of PML and will be evaluated as such."

QUESTION 8A. What do you consider to be the essential or non-essential features of an acceptable risk management plan?
The chair said the general feeling was there should be a mandatory registry. Beyond that, the committee discussed possible features of the plan but made no formal recommendations.

The key issues discussed about the RiskMAP included:

➢ **Checklist content.** The panel was not satisfied with the brief list of diseases and drugs proposed by the company, and a revised list was prepared but not disseminated to the audience. The committee basically wanted a broad, easily read list of diseases and drugs that could make a patient immunocompromised.

However, the panel did think a nurse could complete the checklist with the patient, and that a doctor only had to see the patient if questions came up on the checklist and every six months. The FDA's Dr. Katz said, "If we said any change in neurologic status would have to be checked…We need a little more (guidance) on what the checklist should say…We don't want it so sensitive that no one ever gets treatment without

seeing the doctor." The chair said, "Part of the patient Med Guide should indicate that by asking these questions (on the checklist), it doesn't reduce the risk of a patient getting PML to zero, just that we hope this process ***reduces*** the risk…It is important to convey this is an ***attempt*** to reduce the risk."

➢ **Checklist reporting.** The FDA suggested monthly real-time reporting by the infusion center/physician to the distribution center or the company of the monthly checklists, and the panel generally agreed with that approach. The FDA and the panel also appeared to agree that doctors, patients, and infusion centers that did not comply with completion and filing of the checklists should lose their access to Tysabri, and Biogen officials said they would be diligent in enforcing compliance. However, panel members were concerned that "glitches" in filing should not keep patients from receiving the next infusion. The FDA's Dr. Katz said, "An advantage of at least getting the forms back monthly is the distribution center or sponsor could call the doctor and ask why there isn't a form…It would be a signal that some follow-up is necessary." But he said the FDA does ***not*** want the forms sent to the Agency. The FDA's Dr. Temple said, "Having it web-based and going somewhere doesn't really add that much burden… We are very mindful of not making it impossible to use the drug."

➢ **Compliance reviews.** Biogen officials said the company would contact every doctor and infusion center every six months to see if there were any cases of PML or other events that should be further investigated and to confirm that the drug is being dispensed properly. The panel appeared to think this was satisfactory.

➢ **Physician exams.** The panel wanted to be sure patients saw a neurologist at baseline, at three months, at six months, and then every six months for the foreseeable future. They felt that face-to-face contact with a neurologist was important to help pick up worrisome side effects, neutralizing antibodies, or lack of efficacy. The panel chair said, "It is possible a patient wouldn't be seen for a year or two. There is no mandated reassessment (proposed). We would make it clear that a physician can only fill out the six-month evaluation based on an in-person evaluation." Another panel member said, "It would be less than standard-of-care to prescribe this drug and not follow the patient on a continuing, regular basis… Neurologists are notoriously not very good at reporting things on a voluntary basis…That is why mandating a no form/no drug experience is what I'm proposing."

➢ **De-enrollment.** Physicians, patients, and doctors who do not comply with the RiskMAP must be investigated and removed from the program, with access to Tysabri denied, the panel agreed. However, a panel member pointed out that a system for re-certification needed to be in place as well.

➢ **Inventory.** Infusion centers should be permitted to have a small amount of Tysabri inventory to allow flexibility in scheduling, panel members pointed out.

➢ **Side effects.** The panel requested that Biogen record not only real and suspected cases of PML in registry patients but also opportunistic infections and antibody formation.

The panel rejected a proposal for each vial of Tysabri to be tied to a specific patient. That would give even more assurance that only appropriate patients get the drug, but the panel felt that would be too burdensome on doctors, infusion centers, and patients. A Biogen official told the panel, "The vial-by-vial model…is very different from how infusion centers operate. Most have a small amount of inventory on site to permit scheduling of patients in a logical fashion…If a patient shows up and the vial is not there, it will cause a lot of disturbance to the patient…But if a vial is there and the patient is not authorized, that is a problem, too…Timing is important …We did a survey of infusion centers and found many hospital-based centers and others don't want to participate in a model with no inventory on site because of burdensome issues for patients." Another panel member said, "No doubt you want safety information in hand before you dispense the drug …but you don't want an incredibly bureaucratic pass-back to the drug company where they look at data and say, 'We agree it is okay to give the drug.'"

QUESTION 8B - REVISED. Do you think it is crucial for the sponsor to commit to an observational cohort study, given that we have asked that serious adverse events be incorporated into the registry?
The panel did not vote against a clinical trial, but they were not enthusiastic about it.

During the discussion, they came to understand it could provide information that the registry will not. Dr. Temple warned, "The idea that a registry will produce useful effectiveness information is something of a fantasy."

QUESTION 8C. Which other potential ongoing monitoring should be required in patients receiving Tysabri – CSF for JC virus, MRI of the brain, quantitative cognitive testing or a brief cognitive screening questionnaire, a periodic full neurologic exam, or a brief physical function test, etc.?
No mandated testing was recommended.

There were moments during the advisory committee discussion that it appeared there would be a requirement for MRI scans at least every six months, but in the end the panel decided to leave that to the discretion of the physician. There was also a proposal for a baseline CSF exam, but that, too, was rejected. However, panel members and FDA officials did appear to agree that baseline serum should be banked for each Tysabri patient.

Panel member comments included:

- *Chair:* "We previously learned that testing serum for the JC virus has low specificity and low sensitivity…I'm not sure that CSF improves upon that."

- *Industry representative:* "(CSF) is an invasive test, and I would have to know for sure I was really going to get valuable information that would really change something before I would be enthusiastic about that for what half of you think is a first-line drug…I am against LP (lumbar puncture) before giving Tysabri."
- *Consumer representative:* "I agree that a CSF analysis prior to initiating Tysabri would be critical. We don't know what we don't know. We already heard we don't know adequately what occurs in spinal fluid, we will not ever find out (without CSF tests)."
- "Using Tysabri is an invasive procedure…and we want to be as sure as possible that we have a definitive diagnosis …There are a lot of MRIs that don't turn out to be MS…I agree doing CSF to try to make certain (it is MS) would be advisable. And it would give us more information for later comparison."
- *Biogen consulting neurologist Dr. David Clifford of Washington University School of Medicine:* "LPs belong in a research setting unless there is a clear indication. In this case, I would remind you we…did a large number of LPs in patients and found no JC with the most sensitive assay we could use…So, making it a practice to make sure we have a negative substantiated is an extraordinary and unrealistic idea."
- "Enough has been done with CSF not to make this a mandate."
- "CSF seems an excessively high bar for access to treatment."
- *FDA's Dr. Temple:* "I'm generally in favor of banking."

QUESTION 8D. Is an immunosuppression checklist appropriate and if so, what are the essential elements of this checklist?
Yes but the details were left up to the FDA to work out with the company.

Panel comments included:

- *Panel member:* "My read of the PML cases is that they presented in a somewhat different way than HIV-associated PML…Cognitive dysfunction was an early symptom in these folks…So could we concentrate more on that?"
- *Biogen consulting neurologist Dr. Clifford:* "I counsel against that because it is not right to determine the pattern of disease (in PML) on the basis of three cases…The most sensitive signal in my mind is to ask for symptoms because this is not a clinically silent disease for long…It is important clinicians have an interactive process with the sponsor and be allowed to use a degree of clinical judgment…I do think the cases seen with Tysabri have been very recognizable in the sense of tempo and the areas of involvement. They went from a silent lesion to definite clinical symptoms to severe disability by three months and death by 4-5 months."
- *Chair:* "New, focal, enduring symptoms are a reasonable framework…(But) under-reporting or misreporting is likely to occur to a certain degree."
- *A panel member was concerned patients might not tell the truth about symptoms if it meant they wouldn't get Tysabri that month:* "Why would I (a patient) tell you if I want to play the odds against the low likelihood of a fatal disorder if it means not get my medication?"

QUESTION 8E. At the routine neurological visits (at 0, 3 months, 6 months, and every six months thereafter) with a neurologist, are there tests beyond the local clinical exam that are appropriate?
The panel was most concerned that patients see their neurologist on this schedule and would leave to the neurologist the decision on what tests should be conducted during or in connection with those exams.

QUESTION 9. For subjects who received natalizumab in clinical trials, and who have not received natalizumab for at least one year (or longer), do you recommend any further monitoring?
The consensus was YES, for 2-5 years.

QUESTION 10. ***Please discuss the following:***
10A. If a patient discontinues natalizumab and plans to initiate treatment with another immune-modulating agent (e.g., an interferon beta or glatiramer acetate), do you recommend that the patient wait for some period of time before initiating the interferon beta or glatiramer acetate? If so, how long?
A Biogen official recommended a wait of 8-12 weeks, based on pharmacodynamic measures, but the FDA's Dr. Temple suggested a shorter period may be acceptable, and the panel had varied opinions.

Panel comments included:

- *Chair:* "If someone is doing badly and is stopping to shift to another treatment, there is more pressure to start another treatment as opposed to someone who is very stable and develops neutralizing antibodies, where you might be able to pause more leisurely before starting another treatment It will be hard to have someone doing badly and wait a year – or two or three years – before starting a new treatment…That is not plausible or defensible."
- "There are no data to say three months is safe but two or five months is unsafe."
- "I'd use the same protocol as the trial – two weeks."

10B. If a patient discontinues an immune-modulating agent (e.g., either an interferon beta or glatiramer acetate) and plans to initiate treatment with natalizumab, do you recommend that the patient wait for some period of time before initiating natalizumab? If so, how long?
The general consensus was two weeks, but that this should be left to the clinician's judgment.

QUESTION 11. The two PML infections observed in MS patients were both in patients receiving natalizumab and Avonex concurrently, suggesting the possibility that PML risk is greater in patients receiving concurrent treatment. Furthermore, while Study 1802 indicated that natalizumab added to Avonex provides additional benefit, it is unknown whether Avonex provides any additional benefit when added to natalizumab treatment. If, in the preceding discussion you have advised that use of marketed natalizumab be recommended only for monotherapy, please discuss if, and when, exploration of the safety and efficacy of concurrent use of natalizumab with Avonex, or any other interferon beta should be evaluated. Please include in your discussion the options of:

A. *Never risk concurrent use.*
Unanimous agreement there should never be concurrent use.

B. *Evaluation of concurrent use in clinical trials only after the risk of PML or other infections in monotherapy is better quantified.*
Unanimously YES

C. *Evaluation of concurrent use in clinical trials is acceptable at the present time.*
Unanimously NO

The FDA also asked:

1. Does anyone advocate use of Tysabri with Avonex? **NO**
2. Does anyone advocate permitting trials of Tysabri in combination with an interferon beta? **NO**

Panel members were adamant that they want experience with the re-launch of Tysabri in relapsing MS and data on Tysabri as monotherapy in other forms of MS before any combination studies are started. One said, "I definitely think monotherapy has to be tried first. There are very few other things showing efficacy in progressive disease." Another panel member said, "The priority should be to do monotherapy and trials in other MS – but as monotherapy or a head-to-head comparison." A third panel member said, "We need to allow the system to show it can work in terms of the logistics of collecting data."

♦