DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

Volume I

Tuesday, March 7, 2006

1:55 p.m.

Holiday Inn Gaithersburg
The Ballrooms
2 Montgomery Village Avenue
Gaithersburg, Maryland

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Marc Walton, Ph.D., M.D.
Susan McDermott, M.D.
Alice Hughes, M.D.
Robert Temple, M.D.
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Diane Wysowski, Ph.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. KIEBURTZ: We are going to get started, so if people would take their seats, please.

It may seem like a relatively long time, but we only have approximately 16 hours to do some serious deliberations here, and the bulk of today, we will be hearing from various presenters. We will hear from the sponsor, Biogen Idec, we will hear from the FDA, and we will hear from the public.

There is an agenda, and we will stick to the agenda. I would just like to advise all parties who are speaking that we will stick to the agenda, so please be mindful for your speakers of the time.

We will start the sponsor's presentation at 8:30, and that will conclude at 10:00, and the same for the FDA. Presentations will begin at 10:30, and will conclude at 11:45. I am sorry if all your speakers haven't had a chance to speak by

that time, but that will be the end of the presentation.

In the afternoon, we have many comments from the public, and I would point out that there are approximately 44 public speakers registered to speak, but very few of them actually have signed in. If you are registered as a potential public speaker, please be sure you sign in at the table, so that we know you are here.

The time for those presentations will be tight because of the number of people. In the interest of being fair and equitable, we will keep to the scheduled time for each speaker. More about that later.

There are also 15 seats available outside with television monitor and audiovisual information.

So, it is a long day. The committee will not deliberate today, so everybody is clear on that. The committee will begin deliberations tomorrow. No matter when we finish today, the committee will not deliberate today.

Just one last thing for the ladies and gentlemen of the press, just bear in mind it is not appropriate for committee members to speak on the record about this meeting until after the conclusion of tomorrow. Similarly, it is not appropriate to ask them to do so, so please refrain from doing so.

With those preliminaries set, I would like to go around and have people introduce themselves. Maybe we will start going clockwise. After the introductions, we will have the reading of the Conflict of Interest Statement, and then we will hear from Dr. Katz.

DR. THROCKMORTON: I am Douglas Throckmorton. I am the Deputy Center Director in the Center for Drug Evaluation and Research.

DR. KATZ: I am Russ Katz, Director of the Division of Neurology Products, FDA.

DR. McDERMOTT: I am Susan McDermott. I am a clinical reviewer in the Division of Neurology Products.

DR. A. HUGHES: I am Alice Hughes. I am a

clinical safety reviewer in the Division of Neurology Products.

DR. DAL PAN: I am Gerald Dal Pan, the Director of the Office of Drug Safety at FDA.

DR. M. HUGHES: I am Michael Hughes. I am Professor of Biostatistics at Harvard School of Public Health.

DR. COUCH: I am James Couch. I am Professor of Neurology and Chair of Neurology, University of Oklahoma School of Medicine.

DR. MOSADDEGH: I am Sohail Mosaddegh, the Acting Executive Secretary for the Peripheral and Central Nervous System Drugs Advisory Committee.

DR. KIEBURTZ: I am Karl Kieburtz. I am Professor of Neurology at the University of Rochester Medical Center, and serving as the Chair of the PCNS Advisory Committee.

DR. McARTHUR: I am Justin McArthur. I am Professor of Neurology at Johns Hopkins University.

MS. SITCOV: I am Cynthia Sitcov. I am the Patient Representative. I have been diagnosed with MS for 31 years, and I did not go to medical

school.

DR. JUNG: I am Lily Jung. I am from Seattle, Washington, and I am the Consumer Representative for this committee.

DR. SACCO: Ralph Sacco. I am Professor of Neurology and Epidemiology from Columbia University. I am a member of the panel.

DR. RICAURTE: I am George Ricaurte. I am Associate Professor in the Department of Neurology at Johns Hopkins University.

DR. SEJVAR: Jim Sejvar. I am a neurologist and medical epidemiologist with the Centers for Disease Control.

DR. DeKOSKY: I am Steve DeKosky. I am the Chair of Neurology at the University of Pittsburgh.

DR. GOLDSTEIN: I am Larry Goldstein. I am Professor of Medicine and Director of the Stroke Center at Duke.

DR. KOSKI: Carol Koski, Professor of Neurology, University of Maryland School of Medicine.

DR. PORTER: Roger Porter, Adjunct Professor of Neurology at Penn, Adjunct Professor of Pharmacology at USUHS, non-voting pharma member.

DR. KIEBURTZ: Dr. Katz, is there anyone else from the FDA you want to have introduced at this point?

DR. KATZ: We expect a few others as you can see by the name tags, but they are not here. Marc Walton is the Deputy Director of Neurology Products, and Dr. Temple is the Director of the Office of Drug Evaluation I, who will be here shortly, one hopes.

DR. KIEBURTZ: Thanks.

Conflict of Interest Statement

DR. MOSADDEGH: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee's participants, it has been determined that all interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), the following participants have been granted full waivers:

Dr. Steven DeKosky for unrelated consulting and speakers bureau activities for a competing firm for which he receives less than $10,001 per year, and for unrelated activities in a visiting professor program for a university which receives support from a competing firm for which he receives less than $10,001 per year;

Dr. Karl Kieburtz for consulting on unrelated matters for the sponsor and three competitors. He receives between $10,001 and $50,000 per year from the sponsor and less than $10,001 per year per firm from the competitors;

Dr. Ralph Sacco for consulting on unrelated matters for a competitor for which he receives less than $10,001 per year;

Dr. Larry Goldstein for serving on an

advisory board and steering committee for a competitor regarding unrelated issues for which he receives from $10,001 to $50,000 per year and for consulting on unrelated matters for a competitor for which he receives less than $10,001 per year;

Dr. Lily Jung for serving on a speakers bureau for the sponsor for which she receives from $10,001 to $50,000 per year and for serving on speakers bureau for two competitors for which she receives less than $10,001 per year per firm.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Roger J. Porter has been invited to participate as an industry representative acting on behalf of regulated industry. Dr. Porter's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Porter is a retired employee of Wyeth Research.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. KIEBURTZ: Any further comments from the committee on the Conflict of Interest Statement?

[No response.]

DR. KIEBURTZ: Dr. Katz.

Opening Remarks and Overview of Issues

DR. KATZ: Thanks, Dr. Kieburtz.

I would just like to make a very few brief opening remarks to sort of set the context for today's discussion. First, I would like to welcome the members of the PCNS Advisory Committee.

In particular, I would like to welcome our invited guests who have agreed to come here and help us with this very important issue, and especially I would like to thank the committee and guests for, at the very last minute, opening up their schedules, so that they could be here or you could be here for a second day, a second day that was necessitated by the intense public interest in this issue.

As you know, we are here to discuss the BLA for the use of Tysabri, also known as natalizumab, in the treatment of patients with relapsing-remitting multiple sclerosis.

Tysabri again, as you know, is a monoclonal antibody that binds to integrins on the surface of leukocytes and presumably, as a result, inhibits their migration into areas of inflammation, and presumably, this is responsible for its activity.

It was approved for marketing in November of 2004 on the basis of results at one year in two randomized controlled trials, Study 1801, which

examined the effects of Tysabri's monotherapy, in Study 1802, which examined the effects of Tysabri in conjunction with Avonex interferon beta 1a.

Each of these studies demonstrated clinically important effects on annualized relapse rate compared to control, and although drugs to treat MS are typically required to show effects at two years prior to approval, these effects were so robust at one year that the drug was approved on the basis of these results although the sponsor was required under the Accelerated Approval regulations of Subpart E to provide the results of two years of study after approval.

Unfortunately, as everyone in the room knows, in February of 2005, the sponsor informed the Agency of two cases of progressive multifocal leukoencephalopathy, or PML, a typically fatal viral infection of the brain in patients receiving Tysabri in conjunction with Avonex.

As a result of this, the product was withdrawn from the market in February of 2005, and the sponsor subsequently undertook an examination

of all their patients in their clinical trials and detected one additional case of PML in a patient with Crohn's disease.

The sponsor has now come back to us with the results both of their two-year clinical trials, as well as the results of their search for additional cases of PML in their patients in the clinical trials, and you will hear a great deal about the details of this over the next two days. I won't go into that.

The fundamental questions we bring to you are whether or not you believe these data justify the remarketing of Tysabri, and if you do, under what circumstances you believe it would be appropriate to do so, and in particular, we are interested to know whether or not you believe its use should be restricted in some way. For example, should it be reserved for patients who have failed other treatments, who have severe disease, who are not receiving other concomitant medications for MS or perhaps in any other way you might deem appropriate.

Importantly, the sponsor has also proposed that Tysabri be remarketed under a so-called risk minimization plan or a RiskMAP, which is a plan designed to track all patients who receive the drug with the goal of identifying, quantifying, and ideally minimizing, at least in a global sense, significant risks associated with the use of Tysabri, and if you believe that Tysabri can be remarketed under certain circumstances, we are eager to learn your views about the critical elements of such a monitoring plan, and if you have seen the revised question list, you can see that we have asked very detailed questions about the specifics of the plan. It is very important for us to know what you believe about those.

It is important to note that when marketing for Tysabri was suspended, all clinical trials in all indications were suspended, as well, and several weeks ago, as you probably know, we agreed with the sponsor that patients with MS, who had previously been receiving Tysabri in Phase 3 studies at the time of the suspension, could once

again receive treatment under the IND.

This re-initiation of treatment under the IND is being undertaken with extensive close monitoring including neurological exams and measurement of serum JC virus, the virus that is known to cause PML, prior to each monthly infusion.

It is clear therefore that the Agency has decided that at least under certain circumstances, certain patients can continue to receive Tysabri at this time, but it is important to note that treatment under these intensive monitored conditions, and again which is limited to patients who have already received Tysabri and were doing well in someone's view, represents a very different scenario than the one that the sponsor now proposes for marketing.

It is absolutely critical to state at this point that if marketing is permitted, we fully expect that additional cases of PML, many likely to be fatal, will occur. We don't know with great confidence the true rate of PML that is associated with the use of Tysabri.

Although the current IND data suggest that the accrued rate, at least in MS patients, is about 1 in 1,000, and we don't have detailed information about many of the factors that might affect the risk, including, but certainly not limited to, whether or not the risk is affected by the use of concomitant immunosuppressant or other treatments, and importantly, whether the risk increases with increasing duration of treatment.

Nonetheless, unless we can identify risk factors or tests that can reliably permit an intervention that will halt the progression or onset of PML--and I should add that we don't think such tests are available at this point--there will be additional cases of PML and perhaps many cases, and there will likely be considerable mortality associated with the use of the drug, and this is a fact that I don't believe will necessarily change based on what you hear today and tomorrow, and it is a fact that patients, their families, and prescribers will need to consider very seriously.

Against this somewhat unknown risk will

need to be considered the fact that MS in an often devastating disease for which current treatments are not always adequate, and that the treatment effect of Tysabri seems quite robust, at least certain treatment effects, and in certain respects, the treatment effect appears larger than that of available treatments, although it has to be admitted that there are no direct head-to-head comparisons in controlled trials.

So, it is the difficult task of weighing these risks somewhat unknown and benefits that we have brought you here today and tomorrow to discuss.

Let me just say a very brief word about the agenda. As you can see, and Dr. Kieburtz has mentioned the agenda already, the sponsor will present the bulk of the effectiveness and safety data, and they will also present the elements of their proposed risk minimization plan.

Following that, the Agency reviewers will present some additional effectiveness data and raise some safety issues, as well as some issues

that we believe still exist with the proposed minimization plan.

Following these presentations, as you have already heard, we will have the public session in which over 40 speakers have registered to offer their views on these issues. Again, as you know, because there are so many speakers, we have asked you to come back tomorrow and have a full, complete discussion in an unrushed way tomorrow.

Again, I will stop there, I would like to thank the committee for coming, for the work you have already done in preparation for today's meeting, and for the work that you are about to do.

Thanks.

DR. KIEBURTZ: Does anyone on the committee have any questions for Dr. Katz?

[No response.]

DR. KIEBURTZ: Well, the good news is we are ahead of schedule.

The next speaker will be Dr. Adelman.

Sponsor Presentation

Biogen Idec

Introduction

DR. ADELMAN: Good morning, members of the Advisory Committee, colleagues from the Food and Drug Administration, and members of the audience.

My name is Burt Adelman. I am the Executive Vice President of Development at Biogen Idec.

[Slide.]

On behalf of my colleagues at Biogen Idec and Elan Pharma, I want to thank you for coming here today to consider our request to return natalizumab, Tysabri, to the short list of drugs available for the treatment of relapsing forms of multiple sclerosis.

[Slide.]

Now, natalizumab was approved for treatment of MS on November 23rd, 2004, after priority review of one year of data from two ongoing Phase III clinical trials. Prior to review, an accelerated approval recognized the strength of both efficacy and safety data at one year.

Approximately 7,000 patients received at least one dose within the first three months after approval. We believe that the great demand for this new product by highly informed patient and physician groups is a clear demonstration of the significant unmet need of MS patients for more and better therapies.

In February of 2005, within a 24-hour period, we identified one confirmed and one possible case of progressive multifocal leukoencephalopathy. This occurred in MS clinical trial patients who had received over two years of natalizumab.

Within a week of identifying these patients, we chose to withdraw natalizumab from the market and stop all dosing both in the market and in clinical trials. We made this decision in collaboration with the FDA.

Our purpose was simple. We wanted to minimize any additional risk to treated patients while we undertook an extensive investigation to understand the significance of these findings.

Short after natalizumab withdrawal, we convened a meeting of PML and MS experts and invited representatives of the FDA and the EMEA to join us. At this meeting, we reviewed the pathobiology of PML and its possible relationship to the effect of natalizumab.

Although no clear conclusions emerged, a path forward was defined. We agreed to rapidly evaluate all trial patients for clinical and radiologic evidence of PML and serologic evidence of JC virus replication in plasma and cerebral spinal fluid.

A protocol was devised in collaboration with these experts and regulatory authorities reviewed the protocol. In addition, colleagues at the Karolinska Institute provided matched control and treatment-naive MS patient plasma and CSF samples for JC virus testing, truly a wonderful contribution to this effort.

These investigations confirmed that only three patients had contracted PML. Furthermore, no evidence emerged to suggest that natalizumab

treatment routinely promoted JC virus replication in blood or CSF, and just as importantly, in those samples that we obtained from the Karolinska Institute, we found no evidence that treatment-naive MS patients have increased incidence of JC virus replication in the blood or CSF.

Although the riddle of PML is not solved, we believe that our efforts enable us to define appropriate use conditions for Tysabri while we continue to assess its risks and benefits.

Most individuals diagnosed with MS suffer a relentlessly progressive disease characterized by unpredictable acute exacerbations, increasing physical disability, cognitive impairment, and often secondary neuropsychiatric complications.

The burden and disability of multiple sclerosis is certainly similar in magnitude to that of other autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, and severe psoriasis.

These disorders are effectively treated with highly active immunomodulatory agents. As we

all know, these drugs are commonly associated with serious mechanism-based toxicities including opportunistic infection and malignancy.

Patients and physicians have learned how to use these medicines successfully and maximize their efficacy and manage, but not eliminate, their risks.

We believe data you will review today clearly identify natalizumab as a highly effective treatment for MS patients. In fact, analysis of two-year data from the Phase III program has confirmed and extended the efficacy profile originally described in the label at the end of one year.

We now know that Tysabri can significantly reduce the risk of disability progression in addition to its sustained effect on relapse rate.

[Slide.]

We are now proposing the following usage statement for the package insert. Tysabri is indicated only for the treatment of patients with relapsing forms of multiple sclerosis to delay the

progression of physical disability and to reduce the frequency of clinical exacerbations.

We believe that Tysabri should be used as monotherapy in patients not immunocompromised.

Recognizing our responsibility to ensure that patients and prescribers benefit from all our current knowledge regarding risk and appropriate use conditions for natalizumab, we have designed a companion risk management and assessment program, commonly called a RiskMAP.

The RiskMAP plan is intended to exclude from treatment any MS patient with evidence of immune dysfunction consistent with our current hypothesis that risk of PML in Tysabri-treated patients is increased by concomitant immune compromise.

Further the RiskMAP establishes a comprehensive pharmacovigilance program that will enable us to proactively detect new safety signals and rapidly inform patients, physicians, and the FDA of any and all important new findings. We will present this program to you in detail today.

Biogen Idec and Elan Pharma are committed to a continuing effort to better understand JC virus pathobiology and PML. For example, we are examining the utility of various testing methods for JC virus in blood and blood constituents. Were any of these strategies to prove useful in early detection or in patient selection, we would include them immediately in the RiskMAP.

It is our intention today to ensure you that Biogen Idec and Elan, in collaboration with the FDA and prescribing neurologists, can effectively manage the use of this important new drug for the treatment of patients with MS.

[Slide.]

This is our agenda. Following me will be Dr. Alfred Sandrock, who runs our clinical development program for MS; Michael Panzara, another of our clinical neurologists, will discuss in detail the safety profile as we know it today for natalizumab. Then, Carmen Bozic, who runs our pharmacovigilance unit, will describe the RiskMAP to you.

We are also fortunate to have with us Dr. Rick Rudick, Director of the Mellen Center and Chairman of the Division of Clinical Research at the Cleveland Clinic Foundation, a well-known MS neurologist, who will speak to the risk-benefits of Tysabri.

[Slide.]

We are also pleased to have with us Dr. David Clifford, Professor of Neurology and Medicine at the Washington University School of Medicine in St. Louis.

Dr. Clifford is an eminent clinical neurologist and much of his practice is devoted to taking care of patients with AIDS and immune disorders, and the neurologic complications thereof.

Dr. Clifford was a member of the Independent Assessment Committee that reviewed all the patients that had been treated in the natalizumab trials, and was the senior author of the recently published IAC report in The New England Journal of Medicine.

Thank you very much for your time and consideration.

Dr. Sandrock.

DR. KIEBURTZ: Does anyone on the committee have any questions of clarification, ambiguity?

[No response.]

DR. KIEBURTZ: Thank you.

Efficacy Data

DR. SANDROCK: Good morning, ladies and gentlemen. My name is Al Sandrock, and I will be reviewing the efficacy of natalizumab. Before I do that, I would like to provide a brief introduction to multiple sclerosis.

[Slide.]

MS is a chronic neurological disease affecting approximately 400,000 Americans. It is a disease of young adults, mostly women, and about 85 percent of patients begin with a relapsing form.

This form is characterized by inflammation, predominantly of the white matter. It is widely believed to have an autoimmune

etiology, and the consequences of this inflammation include demyelination, axonal transection, and eventually neurodegeneration.

[Slide.]

MS takes a heavy toll on patients, progression of physical disability is a common feature. Natural history studies show that the median time to requiring a cane or crutch to walk half a city block is approximately 15 years, and that the median time to requiring a wheelchair is about 25 years.

During the relapsing-remitting stage of the disease, unresolved relapses are a major contributor to the progression of physical disability.

Cognitive dysfunction is also highly prevalent, occurring in approximately 50 percent of patients. It affects employment, activities of daily living, and family and social contacts.

Although MS is not immediately life-threatening, it is life-shortening. Studies show a 5- to 7-year decrease in life expectancy and

a 2- to 7-fold increase in the risk of suicide. About half of MS patients die of causes related to the disease.

[Slide.]

There are three principal outcome measures utilized in MS clinical trials: an assessment of clinical relapses, an assessment of disability progression, and MS lesions can be directly visualized by magnetic resonance imaging. I will take you through each of these in the next few slides.

[Slide.]

Relapses define MS during the relapsing-remitting stage. This green line shows a clinical course in a typical patient with a relapsing form of multiple sclerosis where disability is plotted with respect to time.

Relapses occur suddenly and unpredictably, and the neurologic deficits may last for weeks or months. Although patients may recover fully from relapses, about 40 percent of the time relapses result in residual disability.

Natural history studies have shown that relapse frequency in the early stages of the disease predicts future disability, thus, reducing the frequency of relapse is an important treatment goal in multiple sclerosis.

After 7 to 10 years, patients transition to the secondary progressive stage of disease where disability progression can occur gradually, even in the absence of relapse. Importantly, there are no disease-modifying therapies known today to slow the gradual progression of disability during the stage of the illness.

[Slide.]

Disability is measured in clinical trials by the use of the Expanded Disability Status Scale or EDSS. It is a 10-point scale divided into half-point increments where zero is normal and 10 is death due to MS.

A 2-step change, which in most parts of the scale is a 1-point change, is considered clinically significant.

[Slide.]

The multiple sclerosis functional composite score, or MSFC, is an alternative scale that correlates with and supplements the EDSS. It is a composite score of ambulation, upper extremity dexterity, and cognition. In this score, lower scores indicate worsening.

[Slide.]

MS lesions begin as gadolinium-enhancing lesions, which correspond to areas of acute inflammation, as shown by the perivascular infiltrate of leukocytes in the lower left panel.

Although enhancing lesions are evanescent, lasting for 1 to 2 months, they leave behind a scar in the form of T2-hyperintense lesions, which therefore corresponds to the familiar MS plaques, as shown in the lower middle panel, which is a section of cerebral cortex stained brown for myelin and where the white region is the plaque.

Inflammation can be so intense so as to destroy brain parenchyma, and when that occurs, T1-hypointense lesions develop. Non-enhancing T1-hypointense lesions correspond to areas of

axonal transection, as shown in the lower right panel, which is a high-power view in MS lesions stained green for neurofilament and where the arrows point to transected axons.

[Slide.]

Two general classes of disease-modifying therapies have been approved for the treatment of relapsing forms of multiple sclerosis in the United States - interferon-beta and glatiramer acetate.

There are three forms of interferon-beta, and they reduce the rate of relapse relative to placebo by approximately one-third. They also reduce the progression of physical disability as measured by the EDSS, the portion progressing at two years, also by approximately one-third.

These drugs result in injection site reactions or flu-like symptoms which are common adverse events. Depression has also been associated with interferon use, and there are rare cases of liver failure.

Glatiramer acetate also reduces the frequency of relapses by approximately one-third,

and the Phase III trial of this agent failed to show a significant effect on disability progression.

Because it requires daily subcutaneous injections, injection site reactions are common. Lipoatrophy and acute systemic reactions are also seen.

[Slide.]

An unmet need remains in MS because these agents are partially effective. The Phase III trials of these agents show that most patients experience disability progression while on the drug. About two-thirds of patients will have at least one relapse within two years of starting therapy, and about a quarter of patients worsen by at least 1 point on the EDSS scale within two years of treatment initiation.

Not surprisingly, adherence to therapy is poor. Fifteen to 20 percent of patients discontinue their therapy annually, and there is a cohort of about 50,000 patients in this country who have attempted one or more of these therapies, but have

quit and have chosen to remain untreated.

[Slide.]

In order to address the unmet need in multiple sclerosis, Biogen Idec and Elan sought to develop new therapies for MS, and as we did so, we were mindful of the fact that inflammation occurs early in the course of the disease.

Our therapeutic hypothesis, therefore, was that if we could suppress inflammation during the early stages of MS, we could significantly alter the course of multiple sclerosis.

[Slide.]

The biology of inflammation has been clarified over the past 15 or 20 years. An important early step is the adhesion of leukocytes to the endothelial cell wall of blood vessels, and this adhesion allows for the subsequent trans-endothelial migration of these leukocytes into inflamed tissue.

The molecular interaction of alpha-4 integrins, which are expressed on the surface of leukocytes, with cell adhesion molecules, such as

VCAM, which is expressed on the surface of endothelial cells, is an important molecular event that allows for the firm adhesion of leukocytes to endothelial cells.

[Slide.]

Natalizumab is a humanized monoclonal antibody directed against the alpha-4 chain of both alpha-4, beta 1, and alpha-4, beta 7 integrins.

By binding to the alpha-4 chain, it interferes with the alpha-4 interaction with cell adhesion molecules, thereby inhibiting the adhesion of leukocytes to endothelial cells, and inhibiting the migration of leukocytes into inflamed tissue.

Natalizumab has been studied in nearly 5,000 patients in the total clinical experience, of which about 3,000 were on natalizumab. The majority of patients were in the multiple sclerosis trials, about 2,700 patients, and 2,000 of these patients were in the Phase III program, and for the remainder of my talk, I am going to focus on the data derived from those 2,000 patients in the Phase III program.

As Dr. Panzara comes up to speak about safety, he will also include data from the Crohn's disease and RA programs.

[Slide.]

There were two, Phase III trials of natalizumab in multiple sclerosis. The first trial was a monotherapy trial, Study 1801, which was a randomized, double-blind trial enrolling largely treatment-naive relapsing-remitting MS patients.

The patients were in the EDSS range of zero to 5. All patients had to have at least 1 release in the year prior to entry. Patients were randomized to receive either natalizumab or placebo in a 2:1 fashion. 942 patients were enrolled in this trial.

The second trial was an add-on study, 1802. This was also randomized and double-blinded. It also enrolled relapsing-remitting MS patients, but this time the patients had to have disease activity while on interferon. The same EDSS range was used, and patients also had to have a relapse in the year prior to entry, this time on

interferon.

Patients continued their interferon and added either natalizumab or placebo in a 1:1 fashion. 1,171 patients enrolled in this trial.

[Slide.]

The study design was similar between these two trials. After a brief screening period, patients were randomized to either natalizumab 300 mg I.V. once monthly or placebo I.V. once monthly, and they were followed for 120 weeks, at which time they were able to roll over into an open label safety extension study of natalizumab.

Throughout the treatment period, clinical evaluations, as denoted by the C's, were done every 3 months, and MRI's were done at baseline and annually. There were two sets of primary endpoints, one at one year, and one at two years, at the end of the trial.

The primary endpoint at one year was the annualized relapse rate, and there were a number of secondary endpoints. At two years, the primary endpoint was EDSS progression, and there were also

a number of secondary endpoints. I will take you through each of these primary and second endpoints at both time points in the subsequent slides.

[Slide.]

I am going to focus on the data from the monotherapy trial because, as Dr. Adelman pointed out, we believe that natalizumab should be used as monotherapy.

[Slide.]

First, the annualized relapse rate. This was the primary endpoint at one year. Natalizumab led to a 68 percent reduction in the rate of relapse over that first year. We confirmed this effect at the end of the study, so that at the end of the study, there was 68 percent reduction in the frequency of relapses.

[Slide.]

We examined the risk of relapse by looking at the cumulative probability of having a relapse over the two-year period. These are Kaplan-Meier plots of the cumulative probability of relapse.

The hazard ratio indicates a 60 percent

reduction in the risk of relapse over the two-year time period. At the one-year mark, 60 percent of placebo patients were free of relapse compared to 80 percent of natalizumab-treated patients.

[Slide.]

Time to EDSS progression was the primary endpoint at two years. Here, we are looking at the cumulative probability of progressing over the two-year period where progression was defined as a two-step increase in the EDSS sustained for at least three months.

At the end of the two-year period, 29 percent of placebo patients had progressed compared to 17 percent of natalizumab-treated patients. The hazard ratio indicates a 42 percent reduction in the risk of progressing over the two-year period.

[Slide.]

The Multiple Sclerosis Functional Composite score indicated that natalizumab-treated patients either had no change or perhaps a slight increase in the score, which denotes improvement, whereas, placebo patients worsened.

If we break the composite score down into its three components, natalizumab showed a benefit in all three components of ambulation, upper extremity dexterity, and cognition.

[Slide.]

Turning now to the MRI endpoints, the number of enhancing lesions provides an estimate of the inflammation going on in the brain at the time of the MRI scan.

On the one-year scan, there was a 92 percent reduction in the mean number of enhancing lesions, and the same result was observed on the Year 2 scan.

[Slide.]

The number of new or enlarging T2 lesions provides an estimate of the accumulation of MS plaques over the time period studied. In the first year, there was an 80 percent reduction in the mean number of new or enlarging T2 lesions. Over the two-year period, there was a similar reduction, 83 percent in the mean number of new or enlarging T2 lesions.

[Slide.]

This slide shows the distribution of the number of new or enlarging T2 lesions over two years. If we look at the placebo group, which are the white bars, distribution is skewed toward the right, so that 68 percent of placebo patients had at least three new or enlarging T2 lesions over the two-year period.

In contrast, the blue bars indicate the natalizumab group, which shows that the distribution is skewed toward the left, so that 57 percent of natalizumab-treated patients had no new or enlarging T2 lesions over the two-year time period.

[Slide.]

T2 lesion volume is an estimate of the total burden of disease in the brain, and the change in T2 lesion volume is shown on this slide.

Over the first year, there was a decrease in the volume in the natalizumab group of approximately 1,300 cubic millimeters compared to an increase of 741 cubic millimeters in the placebo

group.

A similar finding was shown over the full two-year study period, a decrease of 900 cubic millimeters compared to an increase of nearly 3,000 cubic millimeters in the placebo group.

[Slide.]

The number of new T1-hypointense lesions is shown here. The mean number shows a 74 percent reduction in the mean number with natalizumab compared to placebo over the first year, and a similar finding was seen looking over the entire two-year study period, a 76 percent reduction in the mean number of new T1-hypointense lesions.

[Slide.]

We wondered whether the efficacy of natalizumab was restricted to certain subgroups, so we predefined a number of subgroups to look at.

This slide shows the relapse rate ratio where the vertical blue line indicates a rate ratio of 1, and points left to the 1 indicate a treatment effect in favor of natalizumab.

Regardless of age, gender, disability

status at baseline, the relapse number in the year prior to entry, presence or absence of enhancing lesions at baseline, and less than or more than 9 T2 lesions at baseline, natalizumab appears to provide a favorable benefit.

The only group in which the confidence intervals overlap with 1 is a very small subgroup, the number of patients in the less than 9 category is quite small.

[Slide.]

Turning now briefly to the 1802 add-on study, this study summarizes all of the clinical measures of all the primary and secondary endpoints of both the 1- and 2-year mark on the clinical measures.

First, in terms of the relapse rate, there was 53 to 55 percent reduction in the annualized relapse rate over interferon alone. There was a decrease in EDSS progression, so that the risk was decreased by 24 percent over the time period over interferon alone.

The risk of relapse was decreased by 50

percent over interferon alone, and the MSFC also showed a favorable benefit of combination therapy compared to interferon monotherapy.

[Slide.]

This slide shows all of the MRI measures employed as secondary endpoints in the 1802 study. The drug had a substantial effect on all the MRI measures that we looked at.

[Slide.]

So, in summary, efficacy was demonstrated on all primary and secondary endpoints at both the one- and two-year marks in both Phase III trials of multiple sclerosis.

The magnitude of efficacy as monotherapy is compelling.

The add-on study confirmed efficacy in patients breaking through active treatment.

There was strong attenuation of inflammation and accumulation of plaque burden as seen on MRI scans, and the benefit was seen consistently across subgroups.

At this time, I would like to introduce

Dr. Michael Panzara, who will present the safety of natalizumab.

Safety Data

DR. PANZARA: Good morning, ladies and gentlemen. I am Dr. Michael Panzara, and I will review for you today the safety of natalizumab.

[Slide.]

This slide provides an outline of my presentation. As has been discussed, natalizumab was approved in November of 2004 for the treatment of relapsing forms of multiple sclerosis based on one-year data from the two ongoing Phase III studies.

The studies are now complete and an analysis of the safety database has yielded no appreciable differences in most adverse events as compared with the time of initial approval.

Therefore, I will only briefly review the general safety of natalizumab. The details of these analyses are in your briefing document, and I am pleased to answer any questions that you may have about them.

The one thing that has changed since the time of initial approval is infection. Therefore, the bulk of my presentation will focus on a review of the many analyses undertaken to evaluate the risk of infection in natalizumab-treated patients.

The final portion of my presentation will focus on progressive multifocal leukoencephalopathy, or PML, and the extensive safety evaluations undertaken following identification of PML in natalizumab-treated patients.

[Slide.]

Most of my presentation will focus on the placebo-controlled MS experience. This included 1,617 patients who received natalizumab and 1,135 who received placebo. There were also patients who received natalizumab in open-label studies amounting to over 2,300 MS patients and 3,800 patient years of exposure.

I will also call upon the experience in Crohn's disease in which an additional 1,600 patients received natalizumab, amounting to 1,700

person years of exposure, and there were some differences in the safety profile in this population, which I will indicate throughout my presentation.

All together, in the combined experience, nearly 4,000 patients received natalizumab and 5,500 person years of exposure. In addition, there was a small rheumatoid arthritis experience, which I will also speak of during my presentation.

[Slide.]

This slide provides a general overview of the adverse events that occurred in the double-blind, placebo-controlled trials of multiple sclerosis.

Focusing on the first line, common adverse events were balanced between the groups. Similarly, serious adverse events were balanced, and, indeed, there were more serious adverse events on placebo than on natalizumab. This is reflective of more serious MS relapses in the placebo group as compared with natalizumab.

Moving to the next line, when these

serious adverse events are removed, the MS-related ones, the groups remained balanced.

Serious hypersensitivity reactions did occur on natalizumab treatment at an incidence of 0.8 percent. This is the same incidence that was seen at the time of initial approval, and, indeed, there were no serious hypersensitivity reactions during the second year of the trial.

Moving to malignancies, 1.3 percent of placebo-treated patients had a malignancy versus 0.7 percent of those on natalizumab.

There were three deaths on placebo versus 2 on natalizumab. The deaths on natalizumab are summarized on the next slide.

[Slide.]

The first patient was a patient who had a history of malignant melanoma, who noticed a new lesion at the time of his first or second infusion, and the diagnosis was finally made after his fifth infusion.

The next was a patient who had received 25 infusions of natalizumab, but died of alcohol

intoxication.

[Slide.]

In addition, there were four deaths that occurred in the open-label MS experience. The first was one of the cases of PML that I will describe in detail for you later in my presentation.

There was one case each of a respiratory distress in a pediatric MS patient, a patient who had a seizure and arrhythmia, and one patient suicide. Each of these last three events occurred at least five months after their last natalizumab infusion.

[Slide.]

Turning to the Crohn's disease experience, there were six deaths that occurred in Crohn's disease clinical trials, both the placebo-controlled trials and the open-label trials.

The first was a patient who died of a work-related asphyxiation. The second was a 65-year-old man with a history of hypertension who

died of a myocardial infarction. The third was a patient who developed peritonitis as a postoperative complication of a Crohn's related procedure.

The next three events were serious opportunistic infections. The first was the one case of PML in a Crohn's disease patient. The next was a patient who developed pneumocystis carinii pneumonia, and the third was a patient who developed pulmonary aspergillosis. I will describe each of these last three events in detail during my discussion of opportunistic infections.

[Slide.]

Finally, there were two deaths in natalizumab-treated patients in the rheumatoid arthritis experience. The first was in a patient who developed a renal stone and then developed E. coli urosepsis that in the process of placing a central line for antibiotic treatment, developed an intraoperative pulmonary hemorrhage.

The final case was a woman with rheumatoid lung, which was diagnosed on autopsy.

So, these slides summarize the total number of deaths that occurred on natalizumab treatment in the clinical development program.

[Slide.]

Now, I would like to turn to a discussion of infections.

[Slide.]

I would like to begin by providing an overview of the many analyses undertaken to evaluate the risk of infection in natalizumab-treated patients. This will include a discussion of common infections, as well as those reported as serious.

Then, I will review the risk of infection over time, in other words, were there an increasing number of infections with increasing natalizumab exposure.

Then, I will discuss an analysis of herpes infections. This is a relatively common viral infection that we chose to study to evaluate potential effects of natalizumab on cell-mediated immunity.

Finally, I will review opportunistic infections including PML.

[Slide.]

This slide shows the common infections that occurred in the placebo-controlled trials of multiple sclerosis, that occurred at an incidence of 1 percent or greater than placebo on natalizumab treatment.

Focusing on the first line, 74 percent of patients in each group experienced an infection. There were five infections that occurred more frequently on natalizumab than placebo using this low threshold of 1 percent.

The types of infections that developed are quite typical of those seen in this population. Similar to the incidence, the rate of infection was balanced at 1.5 per person year in each group.

[Slide.]

This slide shows the serious infections that occurred in the placebo-controlled trials of multiple sclerosis. The infections on this slide are those that occurred at an incidence of 0.1

percent or greater in the natalizumab group.

The most common serious infections were appendicitis, urinary tract infections, and pneumonia with a maximal difference between the groups of 0.1 percent.

On the middle of the slide, you can see there were three reports of what was deemed a serious viral infection. Each of these were patients who developed nausea, vomiting, and fever. The viral infection resolved spontaneously or with hydration. All patients recovered and continued in the study.

[Slide.]

Now, I would like to summarize the post-marketing natalizumab experience for infections. Approximately 7,000 patients received one or more natalizumab infusions in the three months that the drug was on the U.S. market.

Serious infections were reported in 16 patients, yielding reporting incidence of 0.2 percent. Pneumonia and urinary tract infections were the most common infections reported.

There were two reports of serious herpes infections that occurred in the post-marketing period. The first was a case of fatal herpes encephalitis that occurred three months following a single natalizumab infusion.

The second was a case of herpes simplex meningitis that occurred within hours of a single natalizumab infusion. This patient recovered fully.

There were no opportunistic infections reported during this time including no reported cases of PML.

[Slide.]

Now, turning to the risk of infection over time. We set out to determine whether with increasing natalizumab exposure, there would be an increased risk of infection.

This slide is again from the double-blind, placebo-controlled trials of multiple sclerosis. The y axis shows the cumulative probability of an infection, and the x axis shows the number of weeks in the trial.

The Kaplan-Meier curves are nearly

superimposable. This indicates an equal risk of infection over the 120-week dosing interval. Likewise, the hazard ratio was 1, supporting this conclusion.

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

[Slide.]

Now, turning to herpes infections. As I indicated, we chose to study herpes viral infections as a marker of potential effects of natalizumab on cell-mediated immunity.

These are latent DNA viruses in which reactivation leads to the clinical manifestations of disease, and these viruses have a particular tropism for the nervous system. The high rate of sporadic infection in these viruses makes it amenable to study in the clinical trial setting.

[Slide.]

This table shows the incidence and rate of herpes infections that occurred in the placebo-controlled trials of multiple sclerosis.

Infections included in this table are those reported as herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr virus, or any infection deemed as herpetic by the investigator.

7.2 percent of patients on natalizumab experienced a herpes infection versus 6.1 percent of those on placebo.

We chose to explore this further by evaluating the incidence and rate of herpetic infections in the monotherapy study, as well as those in the combination study, and that is shown on this slide.

[Slide.]

First, focusing on the monotherapy, 6 percent of patients on placebo versus 6.4 percent of those on natalizumab experienced a herpetic infection, and the rate was also balanced between the groups.

In contrast, in combination therapy, 6.1 percent of those on placebo or Avonex alone experienced a herpetic infection as opposed to 8.4 percent of those on natalizumab, and this is

reflected in the rate of 50 per 1,000 person years versus 67 per 1,000 person years.

So, this suggests that although there may be an increased risk of herpes infections that are slight, it appears to be greater in those receiving combination therapy.

So, to summarize, there was a slight increase in herpes infections of 1.1 percent in natalizumab-treated patients. It appears that this occurred primarily with combination treatment. There are no serious or disseminated herpes infections in the multiple sclerosis trials. There were the two cases of herpes infections in the post-marketing experience that I already described for you.

Although I didn't just show it, it is in your briefing document that this observation in Crohn's disease was similar. There was an increase of 0.5 percent on natalizumab-treated patients as compared with placebo.

Five of these events were reported as serious in the Crohn's disease trials. Two of the

five had onset prior to the initiation of natalizumab treatment, and all patients recovered when appropriate treatment was initiated.

[Slide.]

Now, I would like to turn to a discussion of opportunistic infections.

[Slide.]

PML did occur in natalizumab-treated patients. There were a total of three confirmed cases of PML. Two of these were in MS patients, one of these was fatal. Both patients were receiving interferon-beta concurrently at the time of diagnosis.

There was also one patient with PML in the Crohn's disease studies which was also fatal. This patient was originally diagnosed as having an astrocytoma, but later, a re-review of the pathology by an independent neuropathologist determined that the diagnosis was actually PML. This patient had pre-existing lymphopenia due to chronic immunosuppression use.

The exposure of natalizumab in these

patients ranged from 8 to 37 infusions and all of these patients presented with behavioral changes.

[Slide.]

This table shows the incidence of opportunistic infections in the placebo-controlled experience, as well as the cumulative MS experience for natalizumab.

Focusing on the righthand side of the slide, in the blue shaded area, there were a total of three patients who developed opportunistic infections on natalizumab, yielding a rate of 0.8 per 1,000 person years. Two of these were the cases of PML that I have just described.

The only other opportunistic infection was a patient who developed a cryptosporidial gastroenteritis after 16 natalizumab infusions. This patient recovered fully.

Thus, other than PML, there was only one opportunistic infection in the MS experience.

[Slide.]

Turning to Crohn's disease, this slide shows the incidence of opportunistic infections in

the placebo-controlled and cumulative experience in Crohn's disease.

Again, focusing on the righthand portion of the slide, there were five events that were characterized as opportunistic in patients in the Crohn's disease studies, yielding a rate of 2.9 per 1,000 person years. The details of these cases are shown in the next slide.

[Slide.]

Starting at the top of the slide, the first was the one PML case that I have already described. The next two cases I have mentioned when I reviewed the deaths on the natalizumab treatment.

The first was a 69-year-old man who developed pneumocystis carinii pneumonia following 34 natalizumab infusions in the setting of chronic cirrhosis.

The next patient was a 63-year-old man who developed pulmonary aspergillosis after a prolonged hospitalization that resulted from a GI bleed in the setting of chronic prednisolone and

nonsteroidal use.

The next patient is a 33-year-old woman who developed CMV colitis following a single natalizumab infusion in the setting of azathioprine. This patient recovered spontaneously.

The final case was a 65-year-old woman who developed a mycobacterium avium intracellulare pneumonia following eight natalizumab infusions in the setting of chronic prednisone use, in the setting of staph aureus pneumonia. This patient also recovered fully with treatment.

The next three events on the slide are not considered opportunistic, but are somewhat atypical and are considered for completeness.

The first is a 32-year-old man who developed a lung abscess following 13 infusions of natalizumab in the setting of azathioprine. This patient recovered fully with antibiotic treatment.

The next is a 62-year-old woman who developed Burkholderia cepacia pneumonia, also known as pseudomonas cepacia pneumonia, following

three natalizumab infusions in the setting of tobacco use and congestive heart failure. This patient also recovered fully.

Finally, there is a 20-year-old man who developed what is presumed to be tuberculosis following 25 natalizumab infusions in the setting of prednisone and azathioprine use. This developed six months following his last natalizumab infusion. Although the diagnosis has not been confirmed either by PCR or by culture, the patient remains on tuberculosis treatment.

[Slide.]

So, to summarize, natalizumab treatment is associated with an increased risk of PML. The incidence estimate is 1 in 1,000 with broad confidence intervals ranging from 0.2 per 1,000 to 2.8 per 1,000.

There may also be an increased risk of other opportunistic infections. There was one non-PML infection in MS patients. This is the cryptosporidial diarrhea.

The remaining infections occurred in

Crohn's disease patient with pre-existing comorbidity and immunocompromise. This may be reflective of any of these factors, and, indeed, there was a slight increase in infection in general in Crohn's disease patients.

[Slide.]

So, to summarize the safety of natalizumab, adverse events and serious adverse events were balanced between the groups. The hypersensitivity rate of 0.8 percent was consistent with the approved labeling and there was no increase in malignancy on natalizumab treatment.

There was no increase in the incidence or rate of common or serious infections.

There may be a slight increase in herpes infections on natalizumab treatment, and this appears to be more prevalent in the combination patients.

PML and other opportunistic infections did occur on natalizumab treatment, and these were seen mostly in Crohn's disease patients with significant comorbidity or the use of immunomodulators or

immunosuppressants.

[Slide.]

Now, I would like to summarize PML.

[Slide.]

First, PML is a rare, progressive infection of the central nervous system. It is often fatal within six months of diagnosis.

It is a lytic infection of oligodendrocytes caused by the JC virus, which is a human polyomavirus.

It is known to primarily affect immunocompromised individuals and was first described in the setting of hematological malignancies. It gained more prominence during the era of HIV infections, and most recently it has been described in the setting of organ transplantation.

[Slide.]

The cause of PML is the JC virus. This is a double-stranded DNA virus that is believed to infect the majority of individuals at an early age. However, the reported seroprevalence ranges from 30

to 80 percent depending on the assays employed.

The sites of latency of the JC virus include the kidney, the bone marrow, and lymphoid tissues.

The pathogenesis of PML is really not known, however, it likely involves a multi-step process that involves the activation of the virus from latency, a step of DNA rearrangement, interactions with the immune system, and eventual migration of the virus from sites of latency into the central nervous system.

[Slide.]

The diagnosis of PML is based on a triad of clinical, MRI, and laboratory findings. First, clinically, it is characterized by a subacute onset of progressive neurological changes. The symptoms typically localize to the subcortical region, but may also involve cerebellum.

On MRI, the lesions are T2-hyperintense and are typically non-enhancing without mass effect, and typically localized to the subcortical region as do the symptoms.

Diagnosis requires confirmation of the presence of JC virus in the central nervous system, and this is done commonly now through the use of PCR analysis of the spinal fluid looking for DNA from the JC virus.

Although there are no pathognomonic differences for multiple sclerosis, there are features that help one differentiate between the two.

First, in terms of the clinical presentation, the tempo is different. While PML symptoms typically are subacute, those of MS are typically more acute, evolving over hours to days. Likewise, the location of the lesions are somewhat different.

MS typically affects optic nerve or spinal cord, although can affect other areas, while these areas are almost never involved in the setting of PML, particularly the optic nerve and spinal cord.

On MRI, although T2 lesions develop in MS, they are typically associated with gadolinium-enhancement, edema or mass effect, and

are more typically periventricular.

In addition, JC viral DNA is not detected in the spinal fluid of MS patients.

There are currently no proven means for monitoring or predicting PML onset. A variety of methods have been explored. This includes serum, plasma, buffy coat, in white cells and urine. None of these have proven to be predictive or diagnostic.

[Slide.]

Unfortunately, there are no antiviral treatments for PML. It appears based on the literature that immune reconstitution may be the most effective treatment.

This comes from two lines of evidence. First, is the HIV experience with highly active antiretroviral treatments, or HAART. The literature shows that the introduction of HAART, at the time of diagnosis reduces the mortality of PML by half.

In addition, this literature has suggested that mild symptoms at treatment initiation, so

early in the disease, is associated with an improved prognosis.

The second line of evidence stems from transplantation. This literature has suggested that a reduction of immunosuppression at the time of clinical presentation of PML can improve survival, and survival is reported in one-third of patients in case series, although the experience is small.

The data suggest that early recognition and immune reconstitution may improve outcome.

[Slide.]

Now, I would like to review the extensive safety evaluations undertaken following identification of PML in natalizumab-treated patients.

[Slide.]

Following the suspension of dosing on the 28th of February, we evaluated the patients from the clinical trials of multiple sclerosis, Crohn's disease, and rheumatoid arthritis.

The objectives of these evaluations were

3-fold. First, to determine if additional patients had undiagnosed PML or other atypical infections. Next, to determine the true prevalence of JC viral DNA in the CSF of MS patients. There was a small literature that said that JC viral DNA can be detected in up to 10 percent of MS patients. We set out to determine if this was correct.

Finally, we set out to assess the utility of plasma testing as a predictive test for PML.

[Slide.]

All patients were required to see their neurologist as soon as possible following dose suspension for a clinical evaluation and MRI.

We encouraged CSF collection for all patients, but it was required for anyone for which there was suspicion of PML.

We also collected plasma for exploratory analyses, and we are fortunate to have CSF and plasma control samples from the Karolinska Institute. These were from patients who were naive to treatment and those who had other neurological diseases.

The entire study was done in collaboration with the NIH and was monitored by an independent Adjudication Committee of experts in virology, neuroradiology, and the neurology of HIV. The role of this committee was to determine whether there are new cases of PML.

[Slide.]

Now, to the results.

[Slide.]

3,826 patients were eligible for evaluation. Ninety-one percent of the natalizumab-treated patients participated in this assessment. We had very extensive follow-up even on those who did not participate, and vital status was confirmed in over 99 percent.

Following this detailed analysis, there were no new cases of PML.

[Slide.]

Now, in addition to determining there were no cases of PML, we learned a great deal about PML diagnosis and monitoring.

First, regarding MRI, we had approximately

3,000 MRI scans that were reviewed by our central reader centers. We found that MRI scan was very useful to exclude the diagnosis of PML in the setting of clinical change, in the setting of patients with clinical symptoms.

We found that a single MRI scan was usually sufficient to rule out the diagnosis, although if there were ambiguous lesions, re-scan was sometimes required.

When the MRI was nondiagnostic, spinal fluid analysis was required. We found during this analysis that baseline brain MRI was very important to facilitate this assessment.

[Slide.]

We analyzed nearly 800 spinal fluid samples for the presence of JC viral DNA; 400 of these were from natalizumab-treated patients. An additional 400 were the neurological controls from the Karolinska Institute.

Following these analyses, no JC viral DNA was detected in either natalizumab-treated patients and those who had never seen the drug.

We also had spinal fluid samples from the two MS patients who had developed PML, and JC virus was detected in the spinal fluid of those two patients. Thus, this data confirms that CSF testing is very specific for the diagnosis of PML.

[Slide.]

Finally, turning to the plasma analyses, plasma was collected from 2,370 patients as an exploratory analysis. Five of these patients were found to have detectable JC viral DNA in their plasma, or 0.2 percent.

There were no clinical or radiographical changes associated with this finding, and, indeed, three of these patients had never received natalizumab.

We also re-analyzed stored serum samples from the three PML patients. JC viral DNA was not detected in two of three of these prior to symptom onset. The one patient with Crohn's disease had JC virus detected about a month before clinical symptoms.

So, this suggests the presence of JC virus

or viremia is not necessarily associated with PML, but the absence of JC virus does not exclude the diagnosis.

[Slide.]

So, in closing, although there are no proven ways to monitor for PML, there are a few options that we can consider. These options extend from the extensive evaluations over the past year, opinions from consultants, and the existing literature.

We believe that clinical vigilance by the neurologists is the most important means of screening. In addition, we believe that the monthly interaction between healthcare provider and patients at the time of infusion affords a unique opportunity to enhance this vigilance through the introduction of questionnaires or checklists that have a sufficiently low threshold to prompt additional evaluations by the physician.

The three patients who developed PML in our experience each presented with clinical signs early in the course of the disease that were

recognized by the patient, physician, or family members.

Previously, such changes would have been viewed changes secondary to multiple sclerosis rather than a rare disease like PML. Now, with what we know, any clinical change on natalizumab will be viewed as PML until proven otherwise, prompting a rapid dose suspension and additional assessments.

Turning to JC viral DNA in the plasma, we were hopeful about this, however, the sensitivity and predictive value appear to be unclear. Given the presence of virus in patients without PML, and the lack of patients with PML, what the results of this test suggest are not clear. Therefore, we do not believe we can recommend widescale use at this time.

Regarding MRI, we found MRI to be quite sensitive in the setting of new changes, but not specific in MS, but helpful diagnostically. However, given the time course of PML, which is relatively short, we could think of no practical

scanning frequency which would allow its use as an effective screening tool.

Finally, regarding spinal fluid, we found spinal fluid to be very specific at the time of diagnosis, however, the literature suggests that spinal fluid tends to be negative in early disease, even in the setting of clinical changes in MRI. This, and the fact that this is an invasive test, make it a poor screening tool.

So, these are the factors that we considered when designing the risk management plan that Dr. Bozic will now present to you.

Thank you.

DR. KIEBURTZ: Any questions, clarifications from the committee? Dr. McArthur.

DR. McARTHUR: Thank you for your presentation.

I had a question about the performance characteristics of the spinal fluid JCV-PCR. You have talked about the very low rate, well, the zero rate of positivity. What about positive controls from biopsy-proven PML cases, either HIV-positive

or not?

DR. PANZARA: These assays were run at the NIH using a Gene Majors method, which has a detection of 50 nanograms or 50 copies, I should say, per ml. So, it was the most sensitive assay available, and positive controls were used. Indeed, it was the same assay in which we detected JC virus in the spinal fluid of the confirmed cases.

DR. McARTHUR: Were the positive controls re-run in this assay, or were they essentially historical controls?

DR. PANZARA: No, they were positive controls run at the time of the assay, at the time of testing of these samples.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I have a number of questions.

DR. KIEBURTZ: Just now clarifications, misunderstandings, misheards. General questions, we will get to. I just don't want to interrupt the sponsor too much.

DR. JUNG: Headaches were mentioned as

occurring in 35 percent of patients receiving Tysabri as opposed to 30 percent. Was there any concern that the presentation of headaches might serve as a precursor for HSV?

DR. PANZARA: Headache was the most common infusion-related reaction. We characterized any event that occurred within two hours of infusion as an infusion reaction. Headache was the most common event reported. It was usually reported early in the course of treatment, and then decreased over time, but it was no precursor to an infection. The patients, the vast majority continued in the trial.

DR. RICAURTE: Just following up on the issue of spinal fluid, did you address the question about high specificity in that sensitivity may be compromised particularly early on? I wondered if you could say a few more words about the extent of that and how that might or might not have influenced the evaluation of all of the cases for possible PML.

DR. PANZARA: So, there is a sensitivity of the spinal fluid. Well, the levels of DNA that

are detectable by this method, according to all our experts, is that which would be considered clinically relevant. Indeed, there was nothing detected below this very low threshold. So, we are very confident that this assay, if there was JC virus there, we would detect it.

DR. KIEBURTZ: Can I ask one last question? When you were on your slide about clinical, my attention lapsed for a moment when you said under clinical vigilance, if there is any clinical deterioration--what did you say?

DR. PANZARA: So, currently, our recommendation is clinical vigilance, and the risk management program that Dr. Bozic will describe, we will go through the steps that should be taken following the identification of clinical change, but basically, any clinical change should prompt an evaluation by a physician and which may include additional workup.

DR. KIEBURTZ: Thanks.

Dr. Katz.

DR. KATZ: I had a question for Dr.

Sandrock and I think a question or two for Dr. Panzara, if that's okay.

The first question has to do with the efficacy data. You presented the data for relapse rate or annualized relapse rate by baseline EDSS. Do you have a presentation of the accumulation of disability results by baseline EDSS as opposed to just the relapse rate outcome?

DR. SANDROCK: Yes, I believe it's 2-9, display 2-9 in the briefing document that we provided. That provides the hazard ratio on subgroups and it is broken down in the same levels that we broke them down for the relapse rate ratio, 2-10, in fact.

May I have Slide 2-16, please. Actually, could I have displayed 2-10.

[Slide.]

So, this is the hazard ratio in the various subgroups. In the third set, there are the hazard ratios based on the EDSS level zero to 1.5, 2 to 2.5, 3 to 3.5, and greater than and equal to 4.

DR. KIEBURTZ: You had some follow-up?

DR. KATZ: Yes. For either one who has the exposure data, what is the exposure, or do you have a slide for the exposure? I think you had total person years and that sort of thing, but the exposure for two years and three years, how many MS patients have gotten the drug for two years, how many have gotten it for three years?

DR. PANZARA: I would direct you to display 3-1 in your briefing document, but I do have a slide of that. That would be Slide 2-18.

[Slide.]

I direct your attention to the top portion of the table where we have number exposed to natalizumab. I would like you to focus your attention to the righthand side of the slide where you can see approximately 1,400 patients have received natalizumab for two or more years, approximately 150 patients have received natalizumab for three or more years. The bulk of that was in multiple sclerosis.

DR. KATZ: So, in MS, 1,100 patients--

DR. PANZARA: 1,121.

DR. KATZ: Exposed for two years.

DR. PANZARA: Two years, and 111 for three or more years.

DR. KATZ: Okay. And the two cases of PML occurred at two years or greater?

DR. PANZARA: Yes, one patient had received 29 natalizumab infusions, and one had received 37.

DR. KATZ: The other question I had, had to do with vital status. You said that you had vital status for greater than 99 percent of the patients, even though 91 percent participated in the follow-up study.

Could you just talk a little bit more about that? What do you mean by "vital status," just alive or dead, or do you have cause of death, if there were deaths?

DR. PANZARA: There were no deaths. The deaths that I described to you initially in my presentation are some of those patients, you know, they weren't eligible clearly. So, we had a total

of about 437 patients who chose not to participate or did not participate in the assessment.

There were a variety of reasons for that. The most common reason was most had received placebo. We had a large number of patients who received placebo, had never received natalizumab, and really didn't feel the need to come in and have this assessment.

We had about another third of the patients actively decline participation, so they had to sign that they didn't want to participate, so their vital status was confirmed. A variety of other sites, who didn't want to participate, but the physician said no PML here, but I am not participating, so there were several of those.

There were a few cases, about 60 who were considered as quote, unquote, "lost to follow-up." We actually went to each of their physicians and had those physicians make contact with them, and we found all patients except for 10.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Yes, just one question about

the MRI scan. The MRI scan is obviously one of the good ways of trying to confirm the diagnosis.

Is this an appropriate way of trying to look for early diagnosis through your IAC? Were you able to find that there were any ways in using the MRI scan to try to determine early diagnosis, so the immune system could be reconstituted early?

DR. PANZARA: The requirement was that everybody undergo an MRI scan, and what we found is that if there was any patient who had clinical symptoms that the physician was unsure of, that could be MS, could be PML, they had the MRI scan done. They referred both the MRI scan and the clinical exam to our independent Adjudication Committee.

The expert neuroradiologist on that committee and clinicians reviewed the history, and then made recommendation. In some cases, if the MRI was ambiguous, to go on to an additional MRI, approximately one to two months later, or a spinal tap. That was the diagnostic algorithm.

So, if there was any concern, they

underwent, first, MRI. If there was still concern, additional MRI and spinal tap was performed. We saw no signs on the scans that were reviewed. We were actively looking for the immune reconstitution syndrome, and we did not see any scans that would be suggestive of that.

DR. KIEBURTZ: I know the committee has further questions, but I am going to hold and let the sponsor finish their presentations, please, and we will credit you five minutes for our intervening questions.

Risk Management Plan

DR. BOZIC: Good morning, ladies and gentlemen. My name is Carmen Bozic and I am the head of Drug Safety and Risk Management at Biogen Idec.

So far this morning, you have heard this Dr. Sandrock and Dr. Panzara present on the efficacy and safety of natalizumab. In this presentation, I will focus on how we propose to minimize the risk of PML and also what we plan to do in order to better understand that risk.

[Slide.]

This is an outline of my presentation. After I conclude with the risk management plan, I will present our perspectives on the benefit-risk profile of Tysabri.

[Slide.]

So, the Tysabri risk management plan was developed based on FDA's guidance document on this topic and based on our ongoing dialogue with the FDA.

I would like to point out that the plan that I will be presenting you today is an updated version of the plan that you have in your briefing document and represents an evolution in our thinking and in consideration of several discussions that we have had with the FDA on this topic.

In developing this plan, we carefully reviewed other existing risk management plans to gain insights into the best approach for Tysabri.

We found that the approach to risk management for drugs with serious risks can vary.

For example, clozapine, which is used for severe schizophrenia, and has a risk of agranular cytosis, has a mandatory registry of all prescribing physicians and all treated patients.

On the other hand, mitoxantrone, which many of you are familiar with, and which is indicated for progressive relapsing MS, and has a risk of cardiotoxicity and acute myelogenous leukemia, does not have a mandatory registry, and while it has recommended monitoring of white cell counts and cardiac functions, these are not compulsory.

[Slide.]

Finally, and importantly, in developing this plan, we sought extensive feedback from neurologists, infusion nurses, and MS patients. We spoke to over 200 neurologists to review all the safety findings and to get their input on how best to minimize the risk of PML.

We also surveyed 225 patients and more than 100 infusion nurses, and sites regarding the feasibility of our proposal. We had the advantage

of over 10 years of experience providing for the needs of the MS community, and we understand the complexities of the setting in which MS care is delivered.

So, we considered the range of healthcare practices and diverse locales in which MS patients are treated from academic medical centers to private practice clinics in both urban and in rural settings where proximity to healthcare providers is a major factor to consider.

Thus, the plan seeks to minimize the risk of PML, but without creating unintended consequences that may obstruct patient access to Tysabri.

[Slide.]

So, our risk management plan has two sets of goals, risk minimization goals and risk assessment goals.

With respect to risk minimization, we want to promote informed benefit-risk decisions regarding the use of Tysabri in patients with relapsing MS. We also want to minimize the risk of

PML to the extent that this is possible based on currently available data, and although data on this are limited, we seek to potentially minimize death and disability if PML occurs.

With respect to risk assessment, we want to define more precisely the incidence and risk factors for PML in Tysabri-treated patients, and we want to assess the long-term safety of Tysabri in the clinical practice setting.

An important point that I want to make on this slide is that these two activities, risk minimization and risk assessment, will go on in parallel, and the data that we collect from our risk assessment activities will inform our risk minimization activities over time.

So, we will be continuously evaluating the risk management plan and make refinements to the plan, as appropriate, in order to achieve these goals.

[Slide.]

Now, I am going to talk about the risk minimization component of our plan.

[Slide.]

In designing our risk minimization program, we took into consideration some very important features about how MS patients are treated and how Tysabri is administered.

First, Tysabri has a unique mode of administration that is unlike any other drug with risk management plans.

It is administered monthly by infusion in the infusion center setting under the care and supervision of a healthcare professional, typically, an infusion nurse. This affords a monthly opportunity to reinforce the risk of PML with the patient and to screen the patient for potentially new neurological symptoms that might be indicative of PML.

Secondly, the care of MS patients is highly specialized. We know that approximately 6,000 neurologists take care of over 90 percent of MS patients in this country. What this means is we can reach virtually all prescribers and teach them about PML and about the diagnosis of PML if it

occurs.

Finally, neurologists, because PML is a disease of the central nervous system, it stands to reason that the neurologists are the best qualified specialists to diagnose and manage PML if it occurs, and it also means that they will have the expertise to apply the educational tools that we will give them about the diagnosis and management of PML.

[Slide.]

Now, I will talk about the revised labeling for Tysabri and then I will describe the risk minimization system that we are proposing to support the revised labeling.

[Slide.]

The new revised labeling for Tysabri will feature a prominent boxed warning. We are recommending the use of the box, because this is the highest level warning we can put into a drug label.

In the box, we are stating that Tysabri is associated with an increased risk of PML which

causes death or severe disability.

We are also actively warning against concurrent use of Tysabri with immunosuppressants, such as azathioprine, or immunomodulators, such as beta-interferon.

We are stating in the box that Tysabri is indicated only for the treatment of patient with relapsing MS, because it is only in those patients that the benefit has been proven.

Finally, we are highlighting the importance of clinical vigilance as a means for possibly early detection of PML, and we are instructing healthcare professionals to be alert to any signs or symptoms that might be suggestive of PML, and if they find such symptoms, they should immediately suspend dosing of Tysabri and begin an evaluation, which would include a brain MRI, as well as CSF testing for JC viral DNA.

[Slide.]

We are also including additional warnings and contraindications in the labeling. We are stating that an MRI scan should be performed prior

to initiating Tysabri, because it may be helpful in differentiating PML from MS symptoms in the patient with new neurological symptoms.

We are also contraindicating the use of Tysabri in patients who are immunocompromised, including patients who are immunocompromised due to underlying diseases, such as HIV, hematological malignancies or transplantation, or patients who are immunocompromised due to prior immunosuppressant therapies.

[Slide.]

Now, I will talk about our risk minimization system.

[Slide.]

A key feature of our program is that we will require mandatory enrollment of all prescribers and all Tysabri-treated patients into a registry, called the Tysabri Registry. All prescribing physicians and patients must complete and sign a mandatory enrollment form and send it to Biogen Idec before initiating Tysabri therapy.

We also have a new controlled centralized

distribution system that will allow us to know the location and number of all Tysabri vials that we are shipping, and we will allow Tysabri to be used and administered only in registered infusion centers.

These are infusion centers that have been trained on the appropriate use of Tysabri and the risks and benefits of Tysabri, and which have attested that they will comply with the risk management requirements.

With this system, we can deliver educational tools to all neurologists who are prescribing Tysabri, all nurses who are administering Tysabri, and all Tysabri-treated MS patients.

In the next few slides, I will cover in more detail the specific elements of our system.

[Slide.]

A key component of the enrollment form is a patient-physician acknowledgment. This records that an informed benefit-risk decision has taken place before the start of therapy.

On this form, the physicians will sign that they are aware that PML is a risk with Tysabri treatment and it can cause death or severe disability, that they have discussed the risks and benefits of Tysabri with their patient including the risk of PML, and that they are prescribing Tysabri for a patient who is appropriate for Tysabri. This is a patient with relapsing MS, not in combination with any immunosuppressant or immunomodulators, and not in a patient who is immunocompromised.

On this acknowledgment, the patients will sign that they have read the Medication Guide, they have discussed the risks and benefits of Tysabri with their physician, including the risk of PML, and that they will report any new or worsening neurological symptoms to their physician.

The signed patient-physician acknowledgment on the enrollment form must be sent to Biogen Idec as a prerequisite to starting Tysabri treatment.

Now, I will speak about the requirements

that we have imposed on infusion centers.

[Slide.]

As I said before, Tysabri can be used only in registered infusion centers. These are centers that have received educational training from our personnel and have attested that they will follow the risk management requirements.

These requirements are that they can dose only patients who have been enrolled in the Tysabri Registry, they must give a Medication Guide to every patient before every dose, they must document this in a Tysabri infusion log, and they must be willing to be periodically audited by Biogen Idec to ensure compliance with these requirements.

Another important component of these requirements is verifying the completion of a patient checklist before each dose in every patient, and I will describe this checklist on the next page.

[Slide.]

So, there are no proven monitoring methodologies for the early detection of PML. So,

in considering this challenge, we sought feedback from many neurologists.

Based on this, we determined that the best approach would be the monthly use of a questionnaire to screen patients for new or worsening neurological symptoms. If such symptoms are detected, we are instructing the Tysabri dosing be suspended immediately and that the patient be evaluated by their neurologist.

The questionnaire will be administered to each patient prior to each infusion. It may be administered either by the neurologist or his nurse in the office, or by phone, or by the infusion nurse in the infusion center setting.

We asked neurologists whether this questionnaire could always be done in person in the neurologist's office. Well, some neurologists liked this approach, others told us that in many practice settings, especially in rural areas, a requirement for a monthly visit to the neurologist would be a hardship for patients.

So, we felt that choices regarding the

mechanism for administering the questionnaire are important because not every patient has a neurology clinic nearby that they can visit on a monthly basis.

Therefore, the use of this questionnaire in the ways that I have described allows access to therapy to patients in a variety of locales and healthcare settings.

The patient checklist intent is to reinforce the importance of clinical vigilance and to facilitate a structured monthly interaction between the patient and the healthcare professional.

It is not meant to replace the neurologist's judgment, and so we are instructing the healthcare professional who administers this checklist to have a very low threshold, to contact the neurologist if there are any concerns that are detected on this checklist.

The additional purpose of the checklist is to reinforce the use of Tysabri as a monotherapy, and not in immunocompromised patients.

I will be happy to answer any questions about this checklist afterwards.

[Slide.]

So, now let me walk you through the controls that we have in our system.

Before a patient and physician begin Tysabri treatment, they will have a discussion about the risks and benefits of Tysabri. They will read and sign the patient-physician acknowledgment on the enrollment form, and they will send it to Biogen Idec.

Once we receive that form, we will verify that the patient-physician acknowledgment has been signed, and we will assign an authorization number to that patient. We will also match that patient to a registered infusion center and will notify that infusion center that this patient is eligible for Tysabri treatment.

How does an infusion center become registered? They have been trained by Biogen Idec on the appropriate use of Tysabri and the risks and benefits of Tysabri, and they have attested that

they will follow the requirements of the risk management plan.

They are now known to our controlled centralized distribution system, and we can begin shipping Tysabri to such a registered infusion center. Now the patient can begin Tysabri treatment.

So, clearly, as you can see, we have built several controls into the system. There is a control at the patient and at the physician level in terms of a mandatory enrollment into a registry.

There is a control at the infusion level because only registered infusion centers can administer Tysabri, and there is a control at the distribution level because we will deliver Tysabri only to registered infusion centers.

I should mention that we also evaluated proposals to ship Tysabri one vial at a time for each patient, and this is a relevant question, because it is a question that has been posed to the Advisory Committee.

We concluded that this would not enhance

the safety of the patients and would restrict access to Tysabri, because it would create a significant burden for infusion centers, especially those located in hospitals and in academic centers.

[Slide.]

Now, I will turn to our risk assessment plan.

[Slide.]

We have made a major commitment to further study the safety of Tysabri in the post-marketing setting. Our major studies are the Tysabri Registry and a Tysabri observational cohort study, which I will describe in the next few slides.

We also have additional studies planned that seek to understand the background rate of PML in MS patients, the impact of Tysabri on immune function, and the utility of various monitoring methodologies, such as plasma viral load testing and neurological questionnaires in clinical trials.

In the interest of time, I can't present these during my presentation, but I could answer any questions that you may have after the

presentation.

[Slide.]

So, the Tysabri Registry was designed to determine more precisely the incidence and risk factors for PML in Tysabri-treated patients and also the risk factors and incidence of other serious opportunistic infections.

Enrollment into this registry is mandatory for all physicians and all patients. We will be instructing physicians to report any PML event to Biogen Idec immediately, and in addition, we will be querying every patient, every physician on every patient every six months regarding the occurrence of any PML, any other serious opportunistic infection, any death of any cause, and any discontinuation of Tysabri treatment.

If a patient is discontinued, they must remain in the registry for a minimum of six months after the last dose, so we can collect the final set of data on this patient.

In addition, we will also collect all spontaneously reported events that occur in this

registry.

[Slide.]

We will follow up patient deaths through the National Death Index and collect death certificates on any patient that has died as an additional layer of diligence.

Noncompliance with the reporting of the data to us will result in de-enrollment of the physician and/or the patient.

So, this registry provides intense safety surveillance and tracking of all patients that exceeds routine pharmacovigilance activity.

[Slide.]

If a PML occurs in the registry, this is what we are going to do. We will thoroughly collect all data related to this case including results of clinical findings, source documentation of MRI findings, and results of CSF testing from JC viral DNA.

We will carefully analyze any PML case, looking for potential risk factors including underlying comorbidities or use of concurrent

therapies.

We will evaluate the case based on predefined criteria for PML that we have developed with PML experts, and if needed, we will seek external advice on any indeterminate cases.

We will report the case in an expedited fashion to the FDA, and because this registry will give us a complete denominator of all Tysabri-treated patients and complete ascertainment of every PML case, we will be able to assess the risk-benefit profile of Tysabri in an ongoing fashion, and if there is a clinically significant change to that risk-benefit profile, we can implement rapid corrective actions.

[Slide.]

Now, I will turn to the Tysabri Observational Cohort Study.

This study seeks to evaluate the long-term safety of Tysabri in the clinical practice setting.

A subset of patients in the Tysabri Registry will enroll into this voluntary observational cohort study.

We will enroll 5,000 MS patients worldwide, of which 3,000 will be enrolled in the U.S., and follow them for five years.

The size and scope of this study is such that it is powered to detect rare events occurring with an incidence of 0.06 percent.

In this study, we will collect all serious adverse events on all patients, as well as concomitant immunomodulatory and immunosuppressant therapies.

We will be able to assess the risk of serious infections and long latency events, such as malignancies.

Because we are collecting all serious adverse events, we will be able to investigate any potentially new safety signals that might arise in the post-marketing setting.

[Slide.]

Now, I will turn to the evaluation of our risk management plan.

[Slide.]

We have an evaluation plan that will

carefully monitor the success of our risk management efforts. It includes the analysis of data derived from the Tysabri Registry, as well as the results of surveys and audits.

We will share these data with the FDA every three months, and if needed, based on these data, we can implement rapid corrective actions to the plan, and this may include revised labeling and/or improvements in our risk minimization system or educational tools.

So, we will be continuously evaluating the success of our risk management efforts, and if we need to, make enhancements to the plan.

[Slide.]

So, in summary, our risk management plan seeks to inform and minimize the risk of PML. We are proposing mandatory registration of all prescribing physicians and all treated patients.

We are proposing monthly screening of patients in the infusion center setting through the use of a patient checklist. We have developed a controlled, centralized distribution system that

will allow us to know the location and number of all vials shipped, and we are mandating the use of Tysabri only in registered infusion centers that have attested that they will follow the risk management requirements.

We are also proposing an ongoing detailed assessment of the PML risk, as well as the overall safety of Tysabri.

We have an evaluation plan to monitor the success of our efforts, and we have designed this plan to ensure appropriate use of Tysabri without unnecessary burden to physicians or barriers to patient access.

[Slide.]

Now, in conclusion, based on the data that you have heard this morning, based on the unmet need in MS, based on the efficacy and safety of Tysabri, and the risk management plan that we have proposed, I will summarize our thoughts on the overall benefit-risk profile of Tysabri.

[Slide.]

There is no question that MS is a

devastating, progressively disabling neurologic disease with a very high unmet need.

Tysabri is a highly effective therapy with a benefit that is consistent in a broad range of subgroups.

PML is a rare but very serious risk of Tysabri treatment.

We are proposing a comprehensive risk management plan that seeks to minimize and to further assess this risk.

Based on this, we believe that Tysabri has a favorable benefit-risk profile that justifies its reintroduction into the U.S. market.

[Slide.]

Our recommendation is that Tysabri be used in the following way. It should be used in relapsing MS patients only as a monotherapy, not in patients who are known to be immunocompromised, only patients enrolled in the Tysabri Registry, and only in patients who are fully informed about the PML risk.

Based on Tysabri's benefit-risk profile

and the unmet need in MS, we believe that the use of Tysabri is justified in the following patients:

These are relapsing MS patients who either have disease activity on current therapy, or are intolerant of current therapy, or have high disease activity and our naive patients.

Now. we believe that most of Tysabri's use will occur in these three categories of patients, however, we also recognize that starting a disease-modifying therapy for MS is a complex decision, and so we think that Tysabri should also be available to other relapsing MS patients that may be deemed appropriate based on individual benefit-risk assessments made by their physician and by the patient.

Therefore, we are seeking indication for use of Tysabri in patients with relapsing MS.

On behalf of Biogen Idec and Elan, I would like to share with you that the needs of MS patients and physicians have weighed heavily on us as we contemplated the best path forward for Tysabri, and we look forward to hearing the

Advisory Committee's views on this important subject.

[Slide.]

I have the pleasure of introducing Dr. Rudick, who is a neurologist at the Cleveland Clinic, specializing in the treatment of multiple sclerosis. Dr. Rudick directs the Mellen Center, where he conducts his research and sees patients with MS referred from around the world.

He is also Director of the Division of Clinical Research at his institution, and in that capacity, he oversees clinical research programs at the Cleveland Clinic, which includes over 1,000 clinical trials involving over 20,000 research subjects.

For over 20 years, Dr. Rudick's research has focused on clinical trials, clinical and imaging outcome measures, and biologic markers of the MS disease process.

He participated in the design of the 1801 and 1802 studies. He was the coordinating investigator and chair of the Advisory Committee

for the 1802 study, and is the lead author on the recently published report of the 1802 study in The New England Journal of Medicine.

We are pleased to have Dr. Rudick with us today.

Clinical Perspective

DR. RUDICK: Good morning. Thank you for listening to my professional opinion about Tysabri and multiple sclerosis.

I am going to make three points and I will speak briefly.

First, I would like to point out from my perspective the magnitude of the unmet need in the MS field.

Secondly, I will explain why Tysabri is an important new therapeutic option in MS.

Finally, I will give my views on what constitutes responsible use of Tysabri.

I will speak about each of these in turn, again, quite briefly.

My point about the unmet need is really very simple. Despite the approved

disease-modifying drugs that we have available, MS remains in far too many patients a horrible disease, and there is a very huge unmet need.

The available drugs are effective and we are all very grateful to have these drugs, we didn't have them 10 years ago, but they are far from adequate.

The Phase III placebo-controlled clinical trials have demonstrated that the current drugs are one-third effective in reducing the relapse rate.

The effect of these drugs is so modest that we endlessly debate at our MS meetings the long-term relevance of the benefits of the current drugs, but we have used these drugs long enough to know they don't stop the progression of the disease, and we have no debates about that at our MS meetings.

In my experience during 10 years of using the MS drugs, I have noticed that most patients have relapses or eventually progression of their disability despite their adherence to the prescribed drugs.

Patients who seem stable clinically often show silent MRI lesions and too often later enter a stage of progressive disability, so the appearance of stability early on with these drugs sometimes is illusory.

These experiences are really not surprising. One only has to look at the Phase III clinical trial data. In addition to that, the current drugs cause side effects that diminish quality of life, and many patients simply discontinue their use.

My clinic is filled with patients, MS patients who report disease activity despite the current drugs, patients similar to the ones who entered the 1802 clinical trial. In such patients, our options include switching between the drugs or using our drugs in combinations.

Switching is of little benefit in my opinion given the modest differences, if any, between our available drugs. Combining interferon or glatiramer acetate with steroids, azathioprine, or methotrexate might help, but there is no data to

support this approach, and there are questions about safety.

Mitoxantrone is approved for relapsing progressive MS, but has significant cardiac toxicity, and there are cases of acute leukemia that have been reported.

The bottom line is that approved therapies don't come close to addressing our unmet need in multiple sclerosis. Many, maybe most, MS patients need better options, and we need new therapeutic products.

Now, let me explain why I think Tysabri is an important new therapeutic option for patients with MS.

The 1801 study, natalizumab versus placebo, was the first Phase III placebo-controlled, randomized clinical trial in MS in almost a decade.

The robust clinical trial results met with widespread excitement and enthusiasm by doctors and patients who viewed Tysabri as a major therapeutic advance, and you have heard that 7,000 patients

signed up for Tysabri within just a few months.

I believe there were three reasons for this widespread view which I happen to share. First, the beneficial effect on relapses, over a two-third reduction, was double what we have seen in all of the studies of the approved drugs.

Three independent randomized, placebo-controlled Phase III studies of interferon and a Phase III glatiramer acetate study, each separately and individually showed about a one-third reduction in relapses.

The difference observed in the Tysabri monotherapy study was over a two-third reduction. I am very well aware of the hazards and uncertainties of comparing results across studies, but in comparison with every other large Phase III placebo-controlled trial, the two-third reduction in relapse rate simply cannot be ignored. It is a striking result from my perspective.

Second, the 1802 add-on study enrolled patients who had experienced disease activity while using, and presumably gaining some benefit, from

standard therapy.

Addition of Tysabri to standard therapy in these patients substantially reduced clinical and MRI disease activity compared with the standard therapy alone. This indicates that Tysabri provided substantial incremental benefit over standard therapy alone.

Third, many patients simply don't perceive benefits from current MS drugs or don't tolerate them and have stopped therapy entirely. These patients need options that they will accept and that they can tolerate.

Now, in this regard, in the Tysabri clinical trials, we observed significant benefits and validated patients self-reported quality of life scales, including our pain and fatigue scales. We have never previously observed such benefits in MS studies in the past, and I found this extremely encouraging.

Tysabri really looks like a major therapeutic advance and the question then on everyone's mind is does the benefit and the promise

that Tysabri will actually help people justify the risk of PML, which is currently estimated at 1 in 1,000.

To answer this question, which is not an easy question, I believe it's important to balance benefits with the risk.

I estimated crudely the benefit that might result in 1,000 patients treated for two years compared with standard therapy. Based on the clinical trials, about 400 relapses would be prevented in 1,000 patients if they used Tysabri as opposed to standard therapy. How many of these patients would remain functional, how many would remain independent, how many would remain employed, and what would the long-term benefit be?

These estimates would really be quite speculative, but the gains could very well be substantial, and I believe gains, such as this, have to be factored in to the overall assessment.

So, I have mentioned the magnitude of the unmet need and explained why I think that Tysabri is an important new option. Let me explain what I

think about the responsible use of Tysabri.

First, I don't believe that Tysabri use should be tied to a requirement that the risk of PML be eliminated. From the data that I have seen, I don't believe this is a realistic requirement, but I do believe Tysabri should be used in appropriate patients who are fully informed and carefully monitored by an accessible neurologist.

I have subscribed during my career to a basic tenet of the therapeutic relationship with my patients. I communicate with them, and we make joint decisions about disease management. We do that together.

So, I asked my patients whether they would want to take a new drug that might be twice as effective as their standard therapy, but carries a risk of 1 in 1,000 of a fatal brain infection.

My patients had very little difficulty, surprisingly, answering that question. They gave prompt and fairly definitive answers. Some said they would welcome the chance to use a more effective therapy even under those conditions, and

others said no, they wouldn't take it.

Every patient that I talked with seemed to grasp the situation pretty easily. They weighed the options and they decided whether the benefit to them was worth the risk to them in the context of their disease state, their personal situation, their value system, their family, and whatever other factors were important to them.

I believe the neurologist has to decide whether Tysabri is an appropriate option, but I think the patient needs to be a full participant in deciding in that situation whether to use the drug.

Now, if the use of Tysabri is appropriate in a given patient, and the patient understands and accepts the risk, and agrees to monitoring, I believe treatment should proceed.

Let me sum up by just saying that Tysabri offers the likelihood of significant benefits because it is a therapeutic advance in a disease with a major unmet need. I believe it should be available to for responsible use under the conditions I outlined, because MS in many patients

is not adequately controlled on established therapies.

There really is no good evidence-based options for many of these patients, and neurologists can and will, I believe, use Tysabri responsibly.

I would just close by urging the panel to recommend the release of Tysabri for clinical use, along with some guidelines to promote its safe use, and I appreciate your listening to my opinion.

Thank you.

DR. KIEBURTZ: Thank you, Dr. Rudick.

We will now have a question period from the Committee. Just a couple of things. We will stop in 15 minutes. Just to remind members and consultants, I will read a little thing here that this is about a transparent process for information gathering and decision-making, which means outside of the context of the public hearing, we shouldn't speak with one another about our thoughts, or with people outside the committee.

The intent of the committee is that those

deliberations happen in the public eye. I mean we can certainly talk with one another, and other friends and colleagues, but the substance of the meeting is to not be conducted outside of the public hearing.

So, when we break after the questions, that is the time to stop deliberating, and then pick it up again when we join, and similarly, this evening, right through to the end of the meeting. So, just as a reminder about that.

Secondly, do remember that we won't be able to answer everyone's questions in the context of these 15 minutes. I am sure the sponsor and their representatives and the FDA will be here throughout the day tomorrow. When we have questions, they will be ready to answer them at that time, so don't think this is our last opportunity to ask questions.

Questions from Committee to Sponsor

DR. KIEBURTZ: Dr. Sacco, I cut you off. You had a question when we last opened.

DR. SACCO: I had a question for the

safety. One of the slides, I think it was Slide 50, demonstrated a cumulative risk of any infections, and I assume that was like any infection, but no cumulative risk of some composite of serious infections including the opportunistic ones.

Do you have any slide, such as that, where you would combine together some of the opportunistic infections including some of the ones you have mentioned on herpes, PML, and others?

DR. PANZARA: Yes, we do. That would be Slide 14-33, please.

[Slide.]

This slide is similar to the common infections. This is all serious infections reported in the placebo-controlled trials of multiple sclerosis. Again, the Kaplan-Meier curves represent the cumulative probability of a serious infection over the 120-week dosing interval.

As one can see, the curves are quite similar, and similar to the common infections, the hazard ratio was approximately 1, indicating an

equal risk.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I had a question about the rates of PML and other information that you might have.

Obviously, the rate that is being suggested of 1 in 1,000 person years of follow-up is assuming that the risk is independent of the duration of drug exposure, and it is notable that the two events of PML in MS patients occurred two or three years out.

So, playing the devil's advocate, the risk could be actually substantially higher than the 1 in 1,000 if the risk accumulates over time. I wondered what information you had about changes in PK or changes in immunologic status out through two or three years.

DR. PANZARA: Well, we calculated the rate in a variety of ways, and we felt that given that one of the cases that developed PML had 8 infusions, and the others had 20 to 30, that all should be incorporated, but we also calculated the

rate in terms of patients who receive combination, patients who had over two years of exposure.

The rate in all patients was about 0.5 per 1,000 patient years for PML in the whole population. It's about 0.6 if you look at the patients who have had over two years, 0.65 to be exact, so we have done that analysis.

In terms of immunological changes over two years, we haven't done longer term immunological studies at that time point, but part of what we are planning to do in the post-marketing setting is to do additional immunological testing, as Dr. Bozic indicated.

Finally, in terms of the PK, we determined that the concentration of drug in the serum of the patients who developed PML were right at the median for the overall population, so there did not appear to be an increase in drug concentration.

DR. M. HUGHES: Is the median changing over time within the population?

DR. PANZARA: No, the median remains relatively constant throughout. There is some

accumulation, but that levels off at about nine months and remains constant.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: What would be your recommendations for intravenous methylprednisolone for concurrent use of steroids?

DR. SANDROCK: So, I.V. methylprednisolone at a gram per day for three to five days was allowed in the protocol for the treatment of relapses, and we saw an increase in infections in patients who were on steroids during the time that they were treated, but the increase was similar in both the placebo group and the natalizumab, so we believe that the use of steroids for the treatment of relapses is appropriate, intermittent steroids.

DR. McARTHUR: So, in the risk management plan, will there be any monitoring of the use of steroids, any recommendations for the maximum number of annual courses of steroids?

DR. SANDROCK: Dr. Bozic.

DR. BOZIC: We are warning against the use of Tysabri with concurrent immunosuppressants, and

we would classify chronic oral steroids in that category, so we don't want people to use Tysabri in combination with chronic steroids or monthly pulse steroids. That would not be allowed.

DR. KIEBURTZ: Just a quick comment to the committee members. If you want to speak, just put your hand up. Sohail and I will make eye contact with you, and we have got you on the list, and I will run down the list.

So, Dr. Goldstein.

DR. GOLDSTEIN: I probably have 15 or 20 minutes worth of questions myself, but obviously, I won't do that.

One thing I would like to sort of flesh out a little bit. We talked a lot about risk and benefit, and it's risk for what and benefit for what is the basic issue.

Now, we know that there are other disease-modifying therapies, as Dr. Rudick had carefully pointed out, so if you could translate these data from hazard ratios into numbers needed to treat as best you can, and I realize, you know,

again, that there is a big difficulty here.

We are taking trials that were done a decade apart in different patient populations and trying to extrapolate this, but how many people would you need to treat to prevent one relapse over two years with this drug as opposed to the available other drugs?

How many people would you need to treat over two years to prevent one patient from going on to a clinical relapse? How many people would you need to treat over two years to prevent one patient from reaching disability, because I think that's the numbers that patients and we need to know as we are trying to balance these risk and benefits?

DR. SANDROCK: If I could show Slide 16-65.

[Slide.]

This kind of gets at what you would like, I think. For every 1,000 patients treated with natalizumab for two years compared to no treatment, we estimate there will 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 relapse, and 40 fewer patients requiring aids for ambulation.

That is compared to a 0.1 percent approximate risk of PML, and a 4 percent risk of hypersensitivity reaction.

DR. GOLDSTEIN: That is sort of getting what I was getting at, but not quite.

DR. SANDROCK: Okay.

DR. GOLDSTEIN: What I want to know is not compared to placebo, because the study, unfortunately, was done compared to placebo, but we are not offering it compared to placebo, we are offering it compared to other established therapies.

So, if you redid those numbers again and change it around a little bit, how many people would you need to treat to prevent 1 person from going on to each one of those endpoints. You may not have the numbers now, but if you could come back with them later, that's fine.

DR. SANDROCK: Actually, I do have a slide with the number in it to treat.

Okay. We will have to get back to you.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: For Dr. Bozic, a very practical question. You talked briefly about the patient who comes back to the clinic, who is slightly ill, and then the patient was, in your scenario, kind of assumed to possibly have PML.

Now, there is obviously perhaps only a narrow overlap between the signs and symptoms of PML and MS, but let's assume that this patient comes in with an increase in confusion, just to make the issue more difficult.

How are you going to instruct your neurologist to deal with this issue when the overlap is difficult between the relapse, which you like to treat, and the PML, which is very unlikely, but you would prefer not to treat with Tysabri?

DR. BOZIC: We will have an extensive continued medical education program directed at physicians, and a core feature of that program will

be a PML diagnostic algorithm that will outline the scenarios for the workup of a patient who potentially might have PML.

The confirmation of a PML diagnosis must rely on a triad of clinical findings, MRI findings, and then documentation of JC viral DNA in the central nervous system.

I think Dr. Panzara can speak a bit more about the diagnostic algorithm.

DR. PANZARA: As Dr. Bozic indicated, I think we learned a great deal about making the diagnosis. I think what we are trying to do at this stage is to have a sufficiently low threshold, such that we are not trying to have the determination of PML or MS immediately at the time of infusion. We are trying to find a change that would prompt the workup using the tools to make the diagnosis.

So, that has been our approach. We want to have a sufficiently low threshold to prompt physician assessments and then the additional components of the triad, such as MRI and spinal

fluid.

DR. PORTER: This means that you might treat a patient who actually has PML, and then make the diagnosis later.

DR. PANZARA: No, actually, we are asking any change at all, not making a determination of whether it's MS or PML, any suspicious change or any change at all, for that matter, that would prompt a physician assessment and an evaluation, and if there is uncertainty about change or if there is a neurological change, a physician should have a very low threshold to do an MRI, and suspend dosing is the first thing that must be done.

DR. SANDROCK: Could I add to that?

DR. KIEBURTZ: Yes.

DR. SANDROCK: Our clinical trial data indicate that the annualized relapse rate on natalizumab treatment is 0.2, which translates to 1 relapse every five years.

So, it will happen, but as Dr. Panzara and Bozic said, any new change should prompt an evaluation with suspension of dosing.

MS. SITCOV: I have just a two-part question.

Is there a recommendation for assuming, if this were approved, for how long someone should be off one of the current MS disease, modifying diseases? That is number 1.

Number 2, of the 7,000 MS patients who took Tysabri, I guess some may have only gotten 1 dose, were they given the Tysabri by a neurologist, number 1, and is it possible that of those 7,000, there was another case of PML that was not reported?

DR. SANDROCK: In terms of the washout period from a current therapy to Tysabri, we are suggesting a two-week washout period based on the PK and the pharmacodynamic effects of these drugs, a two-week washout period.

I think the second part of your question referred to the 7,000 patients and whether or not there were any cases of PML.

MS. SITCOV: Unreported.

DR. SANDROCK: Unreported. Any suspicious

case was brought forward to the IAC, and we evaluated a few post-marketing cases at the IAC level, and they were excluded.

MS. SITCOV: Right, but were those, the 7,000 that were prescribed, in all those cases, would they have been prescribed by a neurologist or sometimes by a general practitioner?

DR. SANDROCK: We believe that the vast majority--

MS. SITCOV: Who would not be as familiar.

DR. SANDROCK: The vast majority of patients were prescribed by neurologists.

DR. PANZARA: I would just like to add to that, if I could, that upon the dose suspension, anyone who prescribed natalizumab was sent a Healthcare Provider letter immediately, outlining the steps to be taken should they be suspicious for PML, and that includes referral to the IAC, as well as the clinical MRI, spinal fluid steps to be taken, so we are quite confident that if there are other cases out there, they would have been referred.

MS. SITCOV: So, that was all voluntary.

DR. PANZARA: It was a voluntary request, yes.

DR. KOSKI: I would like to actually expand on the question that was just asked. In terms of the prior therapy and selection of the patients to go on Tysabri, obviously, I think you are talking about one of the ABC drugs, but I would like to also address the issue about other cytotoxic drugs.

Obviously, the patient with Crohn's disease had been off those drugs for eight months before, and actually, although it was said that the patient had lymphopenia at the time that the patient came in with JC virus manifestations and PML, did not have lymphocytopenia, so would you handle patients on those two different types of drugs differently?

DR. SANDROCK: Yes, if a patient had been on the cytotoxic drugs, such as cyclophosphamide, the washout period would need to be longer, at least a month, and we would also recommend taking a

white count prior to starting Tysabri.

So, I think the washout period is going to depend a lot on the drug that they are washing out from.

DR. KOSKI: But I would say that in that particular patient, neither of those measures would have been adequate.

DR. SANDROCK: Well, actually, a white count and looking at the lymphocyte fraction, probably would have excluded that patient.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: MS is a long-term disease with significant survival rate over 20 and even 30 years. Do you feel that you have a decent handle on the possible genesis of malignancy by Tysabri therapy, or can you give us any additional insight on the potential for creating malignancy that is inherent in this entire group of anti-immune drugs? Can you give us any other insight about this?

DR. SANDROCK: Well, the only data we have are from our clinical trials right now, and we see a balanced incidence of the malignancy. It's a

drug that affects the immune system, cell-mediated immunity. It's possible that in the future, we will see something, but so far we have not seen a signal in terms of malignancy.

DR. KIEBURTZ: Last question is Dr. McArthur.

DR. SANDROCK: By the way, I would like to add that the observational cohort study will provide a lot more information on rare events like this over the long term.

DR. McARTHUR: This is a question for Dr. Bozic about the risk management plan, and apart from optic neuritis, I can't think of any symptom that would distinguish PML from multiple sclerosis.

So, one of my questions relates to the emphasis on the vigilance and the administration of the questionnaire prior to Tysabri, and for patients who have emotionally, psychologically bought into Tysabri, there is a strong emphasis on not reporting symptoms, because patients will know that if they report them, it might trigger discontinuation of Tysabri.

So, in your focus groups and your consideration, how have you incorporated that into your plan?

DR. BOZIC: In talking to many patients, it is very clear that they are very concerned about the risk of PML, and a primary goal of our risk management efforts is to fully inform patients about the risk of PML, not only prior to the start of therapy, but to reinforce that information at every dose.

So, the infusion centers must send out a Medication Guide that describes the risk of PML at every dose, and the patient checklist also documents that the patient has read that Medication Guide before every dose, so we are continuously reinforcing the PML risk.

So, we think it's unlikely that a patient will answer, you know, try and game the checklist, if you will.

DR. KIEBURTZ: I want to thank the sponsor for their timely and lucid presentations and answering our questions. We are going to stop

questions for now. I presume you will be available as we deliberate tomorrow to answer further questions as they arise.

We will break for 15 minutes and we will start promptly in 15 minutes from right now.

[Break.]

DR. KIEBURTZ: Our first speaker from the FDA will be Dr. Susan McDermott giving the background as a clinical reviewer.

FDA Presentation

Background, Efficacy, and PML

DR. McDERMOTT: Good morning. Welcome to Maryland. My name is Susan McDermott. I am a neurologist and a clinical reviewer in the Division of Neurology Products.

[Slide.]

Today, I am going to talk to you about efficacy and PML that is associated with natalizumab.

[Slide.]

This is an outline of my talk, and the sponsor has provided much of the background

information regarding efficacy and safety, so we thought it would be most helpful to the committee if we just gave you our view of the data and filled in some information where appropriate.

So, first, I am going to just speak briefly about the regulatory background and then I am going to touch on the pivotal trials, the efficacy results, and then mention a word or two about the antibodies.

Then, we will discuss the PML cases, and we will also talk about the safety evaluations that the sponsor has performed.

[Slide.]

So, first, the regulatory background. The first question we are asking the committee is: Has the company fulfilled their commitment to show a sustained clinical benefit for two years, or at two years?

So, I thought that it may be helpful to you to talk just a little bit about the accelerated approval and what that commitment was.

As you know, accelerated approval is

allowed under the FDA regulations, and there were many factors that went into the approval, the main one being that natalizumab effect at one year was reasonably likely to predict the effect at two years.

I also wanted to just point out that the primary endpoints for MS therapy trials, what we consider at the FDA what is appropriate from a regulatory standpoint has to do with relapse rate and disability accumulation. Essentially, we require sponsors to show an effect on relapse rate or disability accumulation.

[Slide.]

So, we will move now to the efficacy. As you know, you have heard this presentation before, so I am just going to go through this quickly.

Study 1801 was one of the big pivotal trials. That was a monotherapy trial of natalizumab versus placebo, and as you can see, the patients were randomized in a 2:1 fashion, natalizumab to placebo.

What I have on this slide is the sustained

disability progression, which was the primary outcome at two years, and I also have the primary outcome for the first year analysis. That was the annualized relapse rate.

What I should tell you upfront is that our statistician, Dr. Sharon Yan, in particular, has taken the raw data from the sponsor and has analyzed, on her own, according to the protocol, to look at the primary outcome and the top ranked secondary outcome, annualized relapse rate, and her analysis is consistent with the sponsor's analysis.

So, after they have given that exhaustive detailed presentation, I can easily now say we generally agree, so it makes my presentation much easier.

So, what I have on this slide is the absolute difference in sustained disability progression, and you will recall on their slide, they presented Kaplan-Meier curves showing a 42 percent reduction in risk of reaching sustained disability at two years, and our analysis agrees with that.

Also, annualized relapse rate, which was the primary outcome at one year, and the top ranked secondary outcome at two years, they found a relative 68 percent reduction in relapse rate. We also found the same reduction.

[Slide.]

So, likewise, 1802, that's the combination trial. You will remember all patients in this study were on Avonex and had been on Avonex for at least a year, however, they were continuing to have breakthrough relapses on Avonex, and so these patients were randomized 1:1 to receive natalizumab plus Avonex, or placebo plus Avonex.

So, again, I have the primary outcome at two years, as well as the primary outcome at one year, which is also the top ranked secondary outcome at two years, the annualized relapse rate.

Again, our analysis agrees with the sponsor's analysis. You may recall what they found, in Study 1802, is a 24 percent reduction in the risk of disability progression at the end of two years, and in the relapse rate, they also found

a 55 percent relative reduction in relapse rate, and our analysis agrees with that. So, that was relatively easy.

[Slide.]

Now, I am going to switch and just mention a word about anti-natalizumab antibodies, and the speaker to follow, Dr. Hughes, is going to speak more about the antibodies.

But I wanted to say that in the pivotal trials, the sponsor looked for evidence of anti-natalizumab antibodies, and they found that 6 percent of patients developed persistent antibodies, and what I mean by that, "persistently positive antibodies," is that they tested positive on at least two occasions.

So, an interesting finding, when they did a subgroup analysis, is that patients who tested persistently positive for these antibodies, there was an association with less efficacy compared to antibody-negative subjects.

[Slide.]

I am going to try to summarize now

efficacy, and I will start with relapse rate. That was the primary outcome at one year, and it was the top ranked secondary outcome at two years, and you will recall in Study 1801, that's the big monotherapy study of natalizumab versus placebo, there was a 68 percent relative decrease in annualized relapse rate at two years.

In Study 1802, there was a 55 percent relative decrease in annualized relapse rate at two years. The relapse rate also slightly decreased during the second year.

One thing that our statisticians have done is we looked at the relapse rate during the first year, and compared it to the relapse rate during the second year, meaning from day zero to the end of Year 1 compared to the beginning of Year 2 to the end of Year 2.

What we found is that the relapse rate during the second year actually goes down a little bit, but just by a few percentage points, but it remains statistically compelling.

Also, I would say that the relapse rates

that you have heard, these relative decreases, 68 percent and 55 percent, have been estimated approximately twice the treatment effect of other approved therapies that are available now. However, there are no head-to-head trials of natalizumab versus those approved therapies.

So, the next, my disability progression, I would like to have you recall that in Study 1801, there was a 42 percent reduction in the risk of sustained disability over two years, and in 1802, the combination trial, we found a 24 percent reduction in sustained disability progression over two years.

The treatment effect in 1801 was larger, but again, if you will recall, the populations were slightly different. The patients in 1802 had been on Avonex for at least a year and had continued to have breakthrough disease.

Now, add-on therapy. One of the most exciting potentials for natalizumab was the idea that it could fulfill an unmet need for combination therapy. As you know, I think most of the

committee members know that the currently approved MS drugs have not been shown to be effective using combination.

So, we were initially excited to think that natalizumab may show a benefit as a combination drug. So, when you look at 1802, it does win on the primary outcome, however, in one sense, we have limited data, so if you will remember the design of the study, all the patients were on Avonex, and then they were randomized to receive either natalizumab or placebo.

So, what we can say from that is we think we know a little bit about what happens when you add natalizumab to a patient who is on Avonex, but we don't know the opposite of what happens to patients who are on natalizumab and you add other therapies.

Also, if you will recall, the study was not really a factorial design. There was no natalizumab-only arm, there was no placebo arm, so it's difficult to draw a lot of conclusions about add-on therapy. One thing we can say is that we

are not really certain that the benefit of combination therapy is greater than the benefit that you gain from monotherapy.

Finally, with immunogenicity, what I would like to say is that there have been a small number of patients in the pivotal trial, 6 percent, who tested positive for anti-natalizumab antibodies, and a subgroup analysis showed a lower efficacy in these patients compared to those on placebo.

[Slide.]

So, now we are going to move on to PML. In addition to the committee members, I know there are a lot of people in the audience today, patients with MS, some of whom have been on natalizumab, and perhaps family members and friends of the three patients that I am going to discuss.

I understand that this can be a very difficult two days for you, particularly the discussion of PML, and in medicine, when we describe such tragedies, it can often appear very cold and clinical, so I certainly don't intend it to appear this way, and I apologize in advance

about the sterile nature of my presentation, but let's begin.

All committee members have received copies of the case reports, so I am just going to summarize these briefly and point out some of our thinking on these cases.

The first case was a 46-year-old lady with relapsing-remitting MS who was in Study 1802, and as you will recall, 1802 is the combination therapy trial. So, she was on Avonex, and she also received natalizumab.

She received a total of 37 infusions from April 2002 through January 2005.

In November of 2004, her PML symptoms began, and initially, they were thought to be worsening MS. This is one thing that I would like to point out to you that caught our eye initially as we began to go through the cases, keep in the back of your mind, is how are neurologists, how are physicians going to be able to discriminate MS versus early PML.

So, I will move on. The patient continued

to worsen. In December 2004, she had MRI changes that were atypical for MS. She received two short courses of steroids in December and January, and then in February, the patient passed away.

She did have positive JC virus in her CSF, and as you will recall from the sponsor's presentation, when the retrospective analysis was done on her blood, the serum was not positive for JC virus prior to diagnosis.

[Slide.]

The second case is a 46-year-old gentleman with relapsing-remitting MS, who was also in Study 1802, and he received a total of 28 doses of natalizumab from October 2002 to December 2004.

In October 2004, he was found to have an atypical frontal lesion on routine MRI. This is another thing I would like for you to keep in the back of your mind that caught our eye as we were going through these cases.

This is a patient who was asymptomatic and had a funny lesion on his--or I should say an atypical lesion on his routine MRI scan. At that

time, PML was not thought of as a possibility.

Then, in November of 2004, subtle behavioral changes were seen. The patient continued to worsen in December, and new MRI lesions were seen consistent with PML. The natalizumab was stopped in mid-December, and in February of the next year, 2005, JC virus was found in his serum, in his spinal fluid, and also in brain tissue. Avonex was stopped.

It is our understanding that the patient continued to decline. He was treated with Cytarabene, and he survived, but he is now disabled.

[Slide.]

The third case is probably the most complicated case to think about. This is a case of a 60-year-old gentleman with Crohn's disease, and he also passed away after taking a total of 8 natalizumab doses.

The subject was on natalizumab monotherapy when his initial PML symptoms developed, and he had a complicated history of intermittent concomitant

immunosuppressant use.

I will try to describe this to you briefly. You have the article in front of you, and you may read through it tonight. It's a little confusing to follow the time course.

He started azathioprine in 1998. You will remember he had Crohn's disease. He continued azathioprine until late 2002. This was eventually stopped because of immunosuppression. He had refractory anemia, low platelets.

He started natalizumab in March of 2002, and he received three doses at that time. Those three doses were given concomitantly with azathioprine. Then, the patient was randomized to receive placebo, so for some time he received placebo along with azathioprine.

He received placebo for approximately nine months and then the azathioprine was stopped late in the year of 2002, but he was still on placebo. Then, natalizumab was restarted in February of 2003, and he received five doses from approximately February to June of 2003.

He was admitted with symptoms in July, and he declined physically, and eventually, he had a brain biopsy that was diagnosed as astrocytoma. As you know, this patient was eventually found on retrospective analysis to have PML.

When the company went back and examined the pathology in the brain, they did find positive JC virus in the brain pathology. This patient is also an interesting case study because he is the only patient out of the three who, when they looked back in time, at banked serum samples, they found that his JC virus in his blood was positive in May of 2003. That is two months before he became symptomatic, a low number of copies, but the number increased in July.

[Slide.]

So, I am going to stop there with the cases and I am going to talk about the safety analysis that was done. The company has given you a detailed description of the safety analysis that was performed, and I should say, as a division, we reviewed their analysis and we reviewed the results

under the IND, and were satisfied that they had conducted an adequate review, and do not feel that there are any lurking cases of PML that we have missed.

One piece of information that we requested that I thought I would share with you, this came in under the IND. We asked them, of the patients, when you went back, of all the folks who had received natalizumab, that you went back and tested looking for more cases, we wondered how many doses had those people received.

So, this is just a breakdown, this chart, and as you can tell, I have split it into the MS safety trial and then Crohn's disease and rheumatoid arthritis safety trial.

In the MS safety trial, you can see quite a few of the patients had received, there were a total of 1,869, and over half had received 24 or more doses.

In the Crohn's disease and rheumatoid arthritis trial, more patients had received less than 12. The greatest percentage was less than 12

doses.

[Slide.]

I will summarize PML. As you know, there are only three cases identified. Again, we find that after review of their study, we think that their analysis that was done was adequate, and we don't think there are any other cases that we have missed. We have not been able to identify additional risk factors.

Most importantly, the relationship between concomitant immunosuppression and PML is unclear. I know that there has been a lot of talk in the neurology community about decreasing the risk of PML with monotherapy use, and as an agency, we do not feel comfortable in saying that you are decreasing your use with monotherapy, because we feel as though we don't have enough information to really tell patients that and give them that confidence.

So, we are in quite a conundrum and we are hoping that the committee will be able to help us. As you delve into this, you realize that there are

only three cases, and it is hard to draw a lot of conclusions when you only have three cases.

However, to get more data, you essentially have to expose more patients to natalizumab, and so how to do that, if we should do that and how we should do that, that is really where we are seeking your guidance.

I am going to stop here and I guess I will take clarification questions and then Dr. Hughes will come up to the microphone.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. McDermott, in the first case, the woman, the 46-year-old woman with multiple sclerosis, the autopsy findings were overwhelmingly consistent with PML, but were there any autopsy findings of multiple sclerosis?

DR. McDERMOTT: I have not seen the autopsy report. You may be alluding to an article that was recently published that suggested that the patient did not have MS, and I don't think that I can comment on that. I haven't seen the autopsy report. I don't have any basis to tell you one way

or another.

Let me go back. I missed the most important slide, my acknowledgment slide. I apologize to my colleagues. The review team is a very large team, and if I listed every person on the review team, I would have to pass out binoculars to the committee.

Our next speaker is Dr. Hughes, and she is going to talk to you about safety.

Safety

DR. A. HUGHES: Hi. Thank you very much.

[Slide.]

In this talk, I am going to discuss our view of the major safety concerns associated with natalizumab outside of PML. My goal is to allow you to consider natalizumab's risk-benefit profile more fully as you consider the questions that we have posed to you.

[Slide.]

I will focus here on just three major safety issues. First, infections, again, my discussion is limited entirely to infections other

than PML. Second, immunogenicity and hypersensitivity reactions, which Dr. McDermott has talked a little bit about in her presentation. Third, carcinogenicity.

My focus on these three concerns is driven both by the serious adverse events that were observed in the clinical trial development program, as well as by theoretical concerns based on natalizumab's mechanism of action. There is, of course, an overlap between these two things, but not a complete overlap.

In addition to discussing these three major safety issues in the context of the natalizumab clinical trial program, I will, if time allows, briefly review serious adverse events that were reported in the brief post-marketing interval.

[Slide.]

So, the first issue that I am going to talk about is infections, and just as natalizumab blocks the migration of leukocytes to sites of inflammation in the central nervous system, it may also impair the recruitment of lymphocytes and

monocytes to sites of infection.

You have heard a lot already about natalizumab and infections from the sponsor. I will present data regarding infections in a slightly different way than you saw it presented in Dr. Panzara's presentation, that I think is also useful to consider.

In clinical trial, cases that appear to represent the same type of infection were often categorized under numerous umbrella terms, and these distinctions were often helpful, but sometimes probably not clinically meaningful.

For example, an upper respiratory tract infection might be classified as upper respiratory tract infection not otherwise specified, nasopharyngitis, or pharyngitis viral not otherwise specified, to name just a few of the many terms denoting upper respiratory tract infections.

So, I will consider cases of upper respiratory tract infections together, as well as cases of all lower respiratory tract infections together, as well as all cases of gastroenteritis

and vaginal infections to give you a better understanding, I hope, of the incidences of these infections.

So, after this long preamble, in placebo-controlled multiple sclerosis studies, natalizumab and placebo-treated patients had similar incidences of infections overall and serious infections.

Incidences of upper respiratory tract infections, which I just talked a lot about, were similar, as you can see. Incidences of urinary tract infections, both overall and serious, were similar in natalizumab and placebo-treated patients, and this is a safety concern with data through one year, but it wasn't borne out with the two-year data.

Incidences of gastroenteritis were similar. That was another concern based on data just through one year.

[Slide.]

Infections in which there was a slightly greater degree of difference between natalizumab

and placebo-treated patients in incidence, as you can see on this slide, were all lower respiratory tract infections, 13.3 percent of natalizumab-treated patients had infections categorized as any type of lower respiratory tract infections, compared to 12.2 percent of placebo-treated patients.

0.4 percent of patients treated with natalizumab had serious pneumonias, and this is compared to 0.2 percent of placebo-treated patients.

I would like to point out again that natalizumab-treated patients had a slightly higher incidence of herpes infections compared to placebo-treated patients, 7 percent compared to about 6 percent.

In terms of atypical infections--and I use this term on purpose rather than opportunistic infections--there was one case of cryptosporidial gastroenteritis in the monotherapy Study 1801.

This case is interesting in that cryptosporidial gastroenteritis can occur in

immunocompetent patients, but usually resolved in a couple of weeks without treatment. This patient, who was otherwise healthy, 31 years old, again not on concomitant Avonex, developed diarrhea after the 17th natalizumab infusion, and it didn't resolve for about 70 days.

There was also an acute CMV infection with transaminitis in the open-label Study 1808. This, though, is a typical presentation of an acute CMV infection in an immunocompetent patient.

[Slide.]

Turning to Crohn's disease studies, there was a similar incidence of serious infections in placebo-controlled Crohn's disease studies, 2.5 percent versus 2.6 percent, but there was a slightly increased incidence of infections overall in the natalizumab-treated patients compared to the placebo-treated patients, as you can see, 40 percent versus 36 percent.

As listed, the incidences of selected infections on this slide, you can see that in the Crohn's disease studies, there was an increased

incidence of upper respiratory tract infections, but not lower respiratory tract infections in natalizumab-treated patients.

On this slide, I would like to note that herpes infections occurred in 1.6 percent of natalizumab-treated patients compared to 1 percent of placebo-treated patients.

I should point out here that the placebo-controlled Crohn's disease studies were much shorter. Patients received from just 1 to 3 natalizumab infusions.

There were two cases of serious viral meningitis in natalizumab-treated patients in these short-term, acute treatment, placebo-controlled Crohn's disease trials, no cases in the placebo-treated group.

These cases were fairly typical for viral meningitis although they were serious adverse events and the patients were hospitalized.

There were two serious UTIs in natalizumab-treated patients, none in placebo-treated patients in the placebo-controlled

Crohn's disease studies. Again, this is considering all UTIs together.

In the short-term, placebo-controlled Crohn's disease studies, there was one serious CMV infection, a case of CMV colitis. The patient was also receiving azathioprine.

[Slide.]

In long-term Crohn's disease studies, that is where we saw the atypical infections, as the sponsor noted. There were six serious atypical lower respiratory tract infections, and I call these infections atypical either because of the passage it involved or because of the features of the case, such as the pneumonia with lung abscess, a pathogen was never identified in that case.

There was a case of pulmonary aspergillosis, a case of pneumocystis pneumonia, a case of varicella pneumonia, a case of mycobacterium avium intracellulare complex pneumonia, and a case of Burkholderia cepacia infection, which is a concern in cystic fibrosis patients, generally not seen or very, very rarely

seen in immunocompetent patients.

I should mention that of these six cases, two of the patients were not on any immunosuppressive medications or any other immunomodulatory medications. The rest of the patients, though, were on corticosteroids or azathioprine, or a combination of those two.

I would also like to note that these infections occurred after varying numbers of natalizumab infusions, ranging from 3 to 34, and there was not a clear relationship between the number of natalizumab infusions and the risk for atypical infections although that is certainly based on a very small number of cases or infections overall, as the sponsor pointed out.

There was a case of possible tuberculosis infection, which you heard about. This is an interesting case, and based on the information that we have, I don't think is terribly compelling for being a TB infection, although it is certainly concerning with a product like natalizumab.

It was a patient who after receiving 22

infusions, two and a half months later--and I should note he had a history of multiple prednisone courses, and was also taking azathioprine and had been on that drug for a year and a half--about two and a half months after 22 natalizumab infusions, he had surgery for Crohn's disease flare.

A couple of months later, he had an ileostomy takedown, and at that time it was noted that his peritoneum was studded with granulomas, and the pathology revealed granulomatous inflammation with confluent caseous necrosis, and, of course, Crohn's disease is associated with non-caseating granulomas, so it was thought to be representative of a tuberculosis infection, but AFB staining and PCR testing for mycobacterial DNA were negative.

[Slide.]

In terms of immunogenicity, which is the second major safety concern that I am going to turn to, treatment with therapeutic proteins can lead to the formation of antibodies against the product, and that is why we considered this as a major

safety concern, and why the sponsor monitored anti-natalizumab antibody formation every 12 weeks in the Phase III multiple sclerosis studies and in selected Crohn's disease studies, as well.

Ten percent of patients had a positive antibody titer at least once. I should mention that anti-natalizumab antibody formation is of great interest because it is associated with potentially hypersensitivity reactions, decreased efficacy, and potentially other adverse events.

So, getting back to the incidence formation, 10 percent of patients has a positive antibody titer at least once. As Dr. McDermott mentioned, 6 percent of those patients were persistently positive, so they had at least two positive antibody titers.

Four percent of patients were transiently positive meaning they were positive once, or they were positive on their last assessment.

The incidence of anti-natalizumab antibody formation was higher in Study 1802. It was 12 percent compared to Study 1801, and it was 9

percent. Actually, I take back what I just said. The patients who were positive on their last assessment and weren't followed up again, I believe those patients were characterized as being persistently positive.

Now, there is a concern, a historical concern with therapeutic proteins that intermittent, irregular infusions may lead to a higher incidence of antibody formation against the product. We don't have enough information from the natalizumab trials about whether intermittent, irregular infusions, so not monthly, could lead to a higher incidence of antibody formation than was seen generally, about 10 percent.

These was a study, Study 251, a Crohn's disease study, in which patients were dosed when they had flares, and that study has the potential to give us some information about this issue, but the numbers are really too small to draw any conclusions about them.

[Slide.]

Anti-natalizumab antibody formation was

strongly associated with infusion reactions and hypersensitivity reactions.

Infusion reactions occurred in 77 percent of persistently antibody-positive patients. Again, infusion reactions were defined as adverse events that occurred within two hours of the start of the natalizumab infusion.

So, they occurred in 77 percent of persistently positive antibody-positive patients compared to 20 percent of antibody-negative patients and 29 percent of transiently antibody-positive patients.

So, the profile of the transiently positive patients was actually very close to the profile of the antibody-negative patients. It was really the persistently antibody-positive patients that stood out in terms of the infusion reactions and the increased multiple sclerosis relapses, which I will talk about in the next slide.

Anaphylactic reactions very notably occurred in 5.3 percent of antibody-positive patients in the Studies 1801 and 1802, in which

anti-natalizumab antibody formation was assessed, and it occurred in no patients who were antibody-negative throughout these studies.

In the Crohn's disease studies, which again were much shorter, anaphylactic reactions occurred in 1.3 percent of antibody-positive patients, and again in no antibody-negative patients.

[Slide.]

Multiple sclerosis relapses and also Crohn's disease exacerbations were reported more frequently as adverse events in antibody-positive patients compared both to transiently positive patients and antibody-negative patients.

Again, this is just adverse events that were reported, not relapse defined by any meaningful criteria. Fifty-seven percent of antibody-positive patients had adverse events of multiple sclerosis relapse compared to 35 percent of antibody-negative patients.

The incidence of infections, interestingly, was lower in persistently

antibody-positive patients compared to antibody-negative patients.

Overall, infections were reported in 69 percent of persistently antibody-positive patients compared to 82 percent of antibody-negative patients. This pattern was seen for many of the individual infections, as well.

Just to select herpes infections, which are of concern to us, they were observed--and this is simplex and zoster, all herpes infections--they were observed in 2.7 percent of persistently antibody-positive patients compared to 8.4 percent of antibody-negative patients, and this is in the two pivotal studies, 1801 and 1802.

[Slide.]

Just briefly to talk about the overall population of patients, again not getting away from antibody-positive versus antibody-negative patients, anaphylactic reactions were observed in multiple sclerosis placebo-controlled studies in 0.4 percent of patients treated with natalizumab compared to 0.2 percent of patients treated with

placebo.

In the shorter Crohn's disease placebo-controlled studies, there was one anaphylactic reaction in a placebo-controlled study. In long-term studies, there was one additional case of anaphylaxis.

This case is interesting. The patient had received four infusions in a prior study, had an interval of 300 days before receiving his first infusion in Crohn's Disease Study 251, and had an anaphylactic reaction. This is interesting to us because of the theoretical possibility that the antibody formation might be higher in patients who are not dosed regularly.

I have talked a lot about or some about anaphylactic reactions. I should mention that skin and subcutaneous tissue disorder reactions were actually the most common hypersensitivity infusion reactions in the multiple sclerosis studies.

They occurred in 4.6 percent of the natalizumab-treated patients compared to 2.2 percent of the placebo-treated patients. Of the

reactions categorized under the broad umbrella of the skin and subcutaneous tissue disorder infusion reactions, urticaria was the most common, 1.6 percent of patients in the MS studies who were treated with natalizumab had urticaria compared to 0.3 percent of patients treated with placebo.

Per protocol, those patients had to discontinue from the trial.

There were a few delayed hypersensitivity events. Events reported as serum sickness in multiple sclerosis studies were actually balanced in the natalizumab and placebo treated groups. There was also, in the Crohn's disease studies, a case reported as a Type 4 hypersensitivity reaction, and there was one case of leukocytic classic vasculitis.

Most hypersensitivity events occurred during or immediately after the second infusion, but some occurred later. One case of anaphylaxis occurred in association with the 13th infusion.

I should mention now, this wasn't observed in the clinical trial setting, but in case I don't

have time to talk about it when I talk about post-marketing events, there were some events reported in the serious hypersensitivity events reported in the post-marketing setting in association with the first natalizumab infusion. That was not observed in the clinical trial setting.

[Slide.]

The third and final major safety issue I am going to discuss today is carcinogenicity, and that is a concern, more a theoretical concern at this point. Tumor immunosurveillance is mediated by T-lymphocytes because natalizumab interferes with their trafficking. We are concerned that it has the potential to increase the risk of cancer.

In the multiple sclerosis placebo-controlled studies, malignancies were balanced in natalizumab and placebo-treated patients. I have listed on this slide the types of malignancies that were observed just in natalizumab-treated patients.

You can see there were no cases of

leukemia or lymphoma, no particularly unusual types or patterns of malignancies. In Crohn's disease studies, malignancies were more frequently reported in the natalizumab group compared to the placebo group, 0.6 percent versus 0.2 percent, but as you will remember, the number of infusions the patients received was small. Biological plausibility I think is quite low.

[Slide.]

I have listed again the types of neoplasms observed in natalizumab-treated patients. In the Crohn's disease studies, I listed all neoplasms on this slide rather than just malignancies.

I thought it was of note that a meningioma and a craniopharyngioma were picked up during the dose suspension safety evaluation study when all patients were assessed to see if there were any additional cases of PML.

Now, I have saved the most concerning case potentially, I have listed it last. There was one case of a lymphoma, and this is the only case of a leukemia or lymphoma that has been observed in all

the clinical trials, and basically, in all patients treated with natalizumab, there were no leukemias or lymphomas observed in the post-marketing setting, the brief post-marketing setting.

[Slide.]

Just a little bit about this case. It was a 49-year-old man who had received six infusions of natalizumab in the course of two Crohn's disease studies, from September 2004 to February 2005.

On his screening examination in September of 2004, it was noted that he had submandibular lymphadenopathy. Subsequent examinations, though, this lymphadenopathy wasn't noted.

He had a history of infliximab therapy. He had received eight doses, and he was taking 6-mercaptopurine at the time that he was taking natalizumab.

In August of 2005, he presented with enlarging lymph nodes that were painful, and he was diagnosed with a B-cell lymphoma. He had a CT and a biopsy that established this diagnosis. The histological type, though, is not known to us. At

this point, clinical details beyond what I have told you are pending on this case.

[Slide.]

I think that I have a minute to talk about serious adverse events that were reported in the post-marketing setting.

Primarily, I want to emphasize the two cases of herpes central nervous system infections that were reported. These are concerning to us particularly because of our concerns about cell-mediated immune compromise and because consistently, although the incidence difference was small, we observed an increase in herpes infections in the placebo-controlled trials in natalizumab-treated patients in both the MS and the Crohn's disease trials.

So, there were two herpes central nervous system infections. One case of herpes, HSV-2 encephalitis, and the patient died. It was a patient with secondary progressive MS who had a history of methotrexate therapy lifetime and Novantrone therapy, actually had received a

lifetime maximum dose. Had one infusion of natalizumab, had viral symptoms.

Three months later, presented with seizures, was diagnosed as HSV-2 encephalitis by the appropriate CSF studies. Acyclovir was initiated, but the patient died the next day. The temporal relationship in this case is not typical certainly given that there was a three-month interval.

The temporal relationship in the second case is also a little bit interesting. This was a patient, a healthier patient, not on any other immunosuppressive medications, who was diagnosed with herpes meningitis basically right after receiving her first natalizumab infusion.

She had a history of migraine headaches, received natalizumab dose I believe in the morning, later that day had a headache, thought it was her usual migraine, but it didn't get better with her usual treatment.

Two days later she was admitted, diagnosed with herpes meningitis, but she recovered and did

well with appropriate treatment.

In terms of the malignancies that were reported in the post-marketing setting, again, no leukemias and lymphomas, which is an important point. There was a case of ovarian cancer, a case of endometrial cancer, three cases of skin cancer including one case of melanoma.

Hypersensitivity reactions and infections were the most commonly reported serious events, but they don't shed any more light on natalizumab's risk profile than the clinical trials did, so I am not going to discuss those cases any further.

[Slide.]

I would like to summarize briefly the three key safety issues starting with infections other than progressive multifocal leukoencephalopathy.

The types of infections that we observed suggest the possibility of a compromise in cell-mediated immunity. The herpes infections, the lower respiratory tract infections that were observed in both the multiple sclerosis trials,

although there weren't atypical pathogens, there was an increased risk of all lower respiratory tract infections and serious pneumonias, and, of course, the atypical lower respiratory tract infections that were observed in the Crohn's disease trials are of concern to us, and the cases of viral meningitis that were observed.

The role of concomitant medications and intercurrent illnesses in the pathogenesis of these infections is unclear, and, of course, that's the huge and difficult question before us.

I would like to mention on the summary, this summary slide, that the relative risk for infections was similar with monotherapy and combination therapy. In the combination therapy studies, patients tended to get more infections, but it was balanced in the natalizumab and placebo treatment groups.

As I mentioned, there was no clear association between increasing numbers of natalizumab infusions and the risk for infection.

[Slide.]

In terms of immunogenicity, antibody formation to anti-natalizumab occurred in approximately 10 percent of patients. Persistently positive antibodies were associated with infusion reactions, hypersensitivity reactions, increased multiple sclerosis relapses and Crohn's disease exacerbations, and a decreased incidence of infections supporting that natalizumab is associated with an increased risk for infections.

Anaphylactic reactions occurred in 0.4 percent of natalizumab-treated patients with multiple sclerosis overall and in 5 percent of antibody-positive patients, a striking difference.

Hypersensitivity reactions were most common with the second infusion, but may occur much, much later.

[Slide.]

In terms of carcinogenicity, there was no evidence of an increase in risk for malignancies in the multiple sclerosis studies. There was one lymphoma observed in a patient who participated in a long-term Crohn's disease trial. It should be

noted he was also on 6-mercaptopurine and had a history of infliximab therapy. Those medications are associated with an increased incidence of malignancies themselves.

There have been no leukemias observed in the clinical trial setting or the post-marketing setting, but this is really the key point in terms of carcinogenicity, and it's a fairly obvious one, but I think it is worth making, that longer exposures will be needed before the risk for malignancies can be adequately assessed.

So, this is something that we are going to have to keep our eye on in addition obviously, to infections and hypersensitivity reactions if there is market reintroduction of natalizumab.

[Slide.]

I would also like to acknowledge--I will say Tysabri for the first time in the presentation--the Tysabri Review Team. Everyone has contributed to my understanding of the safety profile, and I would just like to acknowledge everyone, and apologize to people I have left off

the slide.

And I would like to introduce our next speaker, Dr. Diane Wysowski from the FDA's Office of Drug Safety unless there are, first, points of clarification for me. I don't know if we have time for that .

DR. KIEBURTZ: Dr. Hughes.

DR. A. HUGHES: Yes.

DR. M. HUGHES: I have a question about mortality. As I understand it, there are two PML-related deaths, but I want to try and put that in the context of other mortality that was seen in the overall experience with this drug.

What I am not clear about is how many total deaths are we talking about amongst drug-exposed subjects, how many are related to other infections, non-PML, and are any of the deaths related or thought to be related to MS?

DR. A. HUGHES: I would like to answer this question, if I may, at my seat where I have my notes.

In the development program overall, the

clinical trial development program, there are 17 deaths overall. Thirteen of them were on natalizumab-treated patients, the rest obviously were in placebo-treated patients. Five of those were in multiple sclerosis studies, six were in Crohn's disease studies, and two were in the rheumatoid arthritis studies.

In terms of causes of death, I can briefly run through them. There was one malignancy, a melanoma. There were four infections, the two cases of PML, the case of pulmonary aspergillosis, the case of pneumocystis pneumonia. There was also a suicide.

There was an acute myocardial infarction with left ventricular rupture, a case of accidental carbon dioxide asphyxiation, respiratory distress secondary to multiple sclerosis progression. This was in a 5-year-old girl who received natalizumab in a compassionate use study.

There was a case of severe Crohn's disease exacerbation with multi-organ system failure. There was a case of respiratory failure due to the

procedural complication that occurred after a central line insertion, and there was the case of end-stage rheumatic pulmonary disease.

That was in the trials. There were five deaths in the post-marketing setting through the safety cutoff date, one case of suicide, one case of ovarian cancer, the case of herpes encephalitis, a death due to a motor vehicle accident, and a urinary tract infection in a very sick patient with multiple sclerosis who had other medical problems, and that case was actually reported by a family member, and there aren't too many details about that.

DR. SEJVAR: Just a real quick question. The cases of viral meningitis, were they substantiated cases of viral meningitis, or was there the possibility of aseptic meningitis from the agent entertained?

DR. A. HUGHES: I believe that they were substantiated cases of viral meningitis although I will have to look. I will have to get back to you on that tomorrow.

MS. SITCOV: Are the number of deaths in these studies, 1801 and 1802, separate from the PML, are those high numbers for studies like this, or are these conservative numbers? I mean how many people die from these kinds of studies?

DR. A. HUGHES: Dr. Katz and others, and Dr. Walton may be able to give a better perspective on this than I can. I think it's fairly typical, but--do you have anything to add?

DR. WALTON: We were not impressed that the overall mortality rate was markedly different than we might expect in MS studies. Of course, different studies use different populations, so it is not possible to really compare the precise mortality rates, so we tend to focus more on the nature of the mortality, but the absolute rates did not strike us as notably different.

MS. SITCOV: So, you don't look at this and say it's striking.

DR. WALTON: No.

DR. A. HUGHES: I think that the fact that the deaths were not notably increased in

natalizumab-treated patients compared to placebo-treated patients is informative, and not for that question.

Risk Minimization Action Plan

DR. WYSOWSKI: Good morning. My name is Diane Wysowski and I am an epidemiologist in the Division of Drug Risk Evaluation, Office of Drug Safety, FDA.

I am here to review and discuss the Tysabri Risk Minimization Action Plan submitted by the company sponsors Biogen Idec and Elan. The information presented is based on our understanding of several versions of the plan and on discussions between the sponsors and the FDA.

Some of the changes in the plan came in yesterday, and I will mention the changes that have been made although my slides have not been updated.

[Slide.]

In this presentation, I will review the main features of the plan including its goals, its methods, the Tysabri Registry that is primarily for PML surveillance and opportunistic infection

surveillance, and the Tysabri observational cohort study, and I will present issues and questions relating to each.

[Slide.]

First, I think it's worth considering the sponsors' goals for the Risk Minimization Action Plan. They are: To promote informed risk-benefit decisions about Tysabri use in the treatment of multiple sclerosis patients; to minimize the risk of PML by contraindicating Tysabri in immunocompromised patients, and by ensuring that physicians know that Tysabri is contraindicated in these patients; and to minimize the health consequences of PML including disability, and death through early diagnosis.

[Slide.]

The plan features the use of a Medication Guide provided by doctors for patients to read about Tysabri, the risk of PML, other safety concerns that the patients should know, and instructions on the importance of reporting new or continuously worsening neurological symptoms

lasting over several days.

It requires mandatory enrollment of prescribers and patients.

[Slide.]

The plan also requires a mandatory Patient-Physician Acknowledgment Form, similar to an informed consent form, that is to be completed and signed by the patient and the physician.

The forms and the Tysabri prescription are to be sent to Biogen Idec where the patient and prescriber information are entered into the Tysabri Registry.

[Slide.]

On the Patient-Physician Acknowledgment Form, the prescribing doctor acknowledges and signs that he or she has read the full prescribing information, is aware of the risk of PML including disability and death, has discussed the risks and benefits of Tysabri with the patient, is prescribing the product for relapsing multiple sclerosis, confirms that the patient has no contraindications including immunosuppression, has

told the patient to report any new or continuously worsening neurological symptoms lasting over several days, and is enrolling in the Tysabri Registry.

[Slide.]

Similarly, the patient acknowledges and signs that he or she has read the Medication Guide, is aware of Tysabri's PML risk that includes disability and death, has discussed the risks and benefits with the doctor, understands the importance of reporting to the doctor any new or continuously worsening neurological symptoms, and is enrolling in the Tysabri Registry.

[Slide.]

Following the receipt of the forms and the prescription, the sponsors plan to enter the patient and prescriber information into the Tysabri Registry, match the patient to a registered infusion center, notify the infusion center of patient authorization to receive Tysabri, and provide the infusion center with the patient authorization number.

The plan does not require that the patient be reassessed by the prescribing physician and reauthorized at regular intervals to receive Tysabri.

[Slide.]

Tysabri will be shipped from a centralized distribution system consisting of one distributor, and less than or equal to 12 specialty pharmacies. It will be sent only after the shipping company has received the patient authorization code from the company sponsors.

[Slide.]

Tysabri will be administered only at registered infusion centers that attest to compliance with the risk management program. Infusion centers can be a hospital clinic, a stand-alone clinic, or a doctor's office.

Biogen Idec and Elan estimate that 2,000 infusion centers will be registered to administer Tysabri.

[Slide.]

Before Tysabri is administered, the

infusion center nurse is to confirm that the doctor and patient have been enrolled in the Tysabri Registry.

Using the patient checklist, the nurse also is to confirm that the patient has multiple sclerosis, has a copy of the Medication Guide and has read it, is not known to be immunocompromised by HIV, hematological cancers, organ transplants, and anti-neoplastic and immunosuppressive drugs, and that the patient has not experienced any new or continuously worsening neurological symptoms lasting over several days.

The checklist provides the following examples of the neurological symptoms that would require a hold on Tysabri administration: new or sudden decline in the patient's thinking, eyesight, balance, or strength.

Also, the nurse is to document Tysabri administration on an infusion log.

[Slide.]

Although there is contraindication of Tysabri, if the patient is immunocompromised, the

plan does not state whether Tysabri is contraindicated with concomitant or recent use of immunomodulators, such as interferon-beta, with the systemic corticosteroids, such as methylprednisolone, and with other steroid and immune suppressant drugs.

[Slide.]

Currently, the patient checklist that the infusion center nurse is to use to determine if the patient is immunocompromised includes only a few diseases and six drugs that can induce an immunocompromised state.

The six drugs currently named on the checklist are azathioprine, Cytoxan, methotrexate, Novantrone, CellCept, and Rituxan, however, we note that the sponsors' focus group composed of doctors, patients, MS nurses, and infusion nurses, requested that all drugs and diseases that could induce an immunocompromised state be clearly spelled out.

[Slide.]

The sponsors also plan to provide ongoing educational information for physicians and infusion

center nurses that will be delivered via mailings, a website, a toll-free help line, and continuing medical education programs.

They will conduct a survey of physician prescribers and infusion center nurses about their knowledge of Tysabri's PML risk and appropriate use conditions.

[Slide.]

An important feature of the plan is the Tysabri Registry whereby all patients who receive Tysabri will be systematically followed for the development of PML and to determine the PML incidence rate.

Patients will also be followed for the development of serious opportunistic infections.

The sponsors plan to ask prescribing doctors every six months if the patient is continuing on Tysabri and if the patient has PML. They also will ask the physician if the patient has developed any serious opportunistic infections and if the patient has died from any cause.

The sponsors recently added that follow-up

patient deaths will be accomplished through the National Death Index with collection of death certificates from state health departments.

While the former version of the plan did not specify the length of patient follow-up after Tysabri discontinuation, the sponsors now state that the patient will remain in the registry for a minimum of six months after the last dose of Tysabri.

They also state that noncompliance with the requirements for patient follow-up would result in de-enrollment of the patient to receive Tysabri.

The plan does not specify if the Tysabri Registry will contain a dosing history for all individuals who receive the drug in the clinical trials and in the previous post-marketing period.

Adding dosing history to the Tysabri Registry would enable the prescriber, the patient, the infusion nurse, and the registry to track the cumulative number of doses the patient has received, and would be important for clinical and risk assessment purposes.

[Slide.]

The sponsors plan special assessment of suspected PML cases for early diagnosis of PML. This would include administering a PML specific questionnaire, obtaining clinical details, and confirming the diagnosis based on an MRI and cerebrospinal fluid, JC virus testing.

For uncertain diagnoses, they plan to submit the data to an external PML expert. The sponsors will report confirmed cases to FDA within 15 days of receipt. On a quarterly basis, they plan to provide to FDA the PML incidence rate and a qualitative analysis of risk factors.

[Slide.]

We have the following questions for the Advisory Committee which are simplified versions of the questions they will be asked to answer.

To maximize the benefit and minimize the risk of Tysabri, should there be restriction of Tysabri by MS disability severity? Should there be restriction of Tysabri to patients who experience failure of other MS therapies?

[Slide.]

To minimize the risk of PML, should Tysabri be contraindicated with concomitant or recent use of the immune modulator drugs, systemic corticosteroids, and immune suppressant drugs?

[Slide.]

Regarding patient assessment, should prescribing physicians reassess and reauthorize patients on a periodic basis to receive Tysabri? If so, how frequently should this be done?

Along these lines, should the assessment of neurological symptoms and patient immunocompromise before Tysabri administration be performed by an infusion center nurse or by a doctor? Is this an assessment that a nurse should make?

Should the patient checklist include a longer, more comprehensive list of diseases and drugs that are known to induce an immunocompromised state?

[Slide.]

Concerning tracking of Tysabri use, should

there be one-to-one patient to vial distribution, such that each vial is associated with an individual patient for tight control of Tysabri distribution and tracking?

[Slide.]

Concerning follow-up of patients, would patient follow-up be aided by collection in real-time of Tysabri administration, discontinuation, and reasons for discontinuation?

As mentioned earlier, the sponsors recently added follow-up of patient deaths through the National Death Index and collection of death certificates from the state health departments.

This should aid collection of information on patients who have discontinued Tysabri and are lost to follow-up. However, we note that the National Death Index has an important limitation in that there is a lag time in getting deaths into the National Death Index.

[Slide.]

For the Tysabri observational cohort study, Biogen Idec and Elan plan to enroll 5,000 MS

patients from the Tysabri Registry in the United States and Europe, including 3,000 U.S. patients. They will follow patients for up to five years after the Tysabri start date.

The companies plan to assess the incidence and nature of all serious adverse events including serious infections and malignancies. The study will also help them investigate potential signals of unanticipated adverse events.

The study will collect information on concomitant immunomodulator and immunosuppressant therapies.

[Slide.]

We have the following comments about this study. Regarding ascertainment of deaths and causes, we think that the National Death Index should help identify deaths in the cohort, and this will be especially useful for patients who have discontinued Tysabri use or are lost to follow-up.

Following the NDI search, death certificates would need to be collected from state health departments.

We believe that inclusion of all patients in the Tysabri Registry would provide complete ascertainment and avoid selection bias. If not all patients are included, the subset of patients to be included in the observational cohort study should be selected based on statistical survey sampling procedures.

The lack of a non-exposed MS control group could pose problems in the interpretation of etiology. If the companies need to rely on population controls, the outcomes of interest may not be available from population databases.

Also, the study does not specify if previous Tysabri exposure accumulated in the clinical trial and in the previous post-marketing period would be counted towards the five-year follow-up time.

Further, is five years sufficient time for follow-up?

[Slide.]

The most important issues and questions concerning the Tysabri Risk Minimization Action

Plan that I raised above have been rephrased as questions for the Advisory Committee.

If the committee votes to have Tysabri reintroduced to the United States market, we believe that the issues and questions outlined in this presentation should be carefully considered by the committee in an effort to maximize the benefits of Tysabri, while minimizing its PML risk.

[Slide.]

Finally, I want to acknowledge my colleagues in the FDA's Office of Drug Safety who participated in the review of this Risk Minimization Action Plan.

Thank you.

DR. KIEBURTZ: Thank you, Dr. Wysowski.

Questions from the committee? Dr. Goldstein.

Questions from Committee to FDA

DR. GOLDSTEIN: Dr. Hughes, you went through all these individual numbers. Have you synthesized these, can you give us like what the total rate is or frequency is of serious and

opportunistic infections combined in treatment versus control, because we have seen all of these things in pieces, and I don't know what the unique rates are?

DR. A. HUGHES: I can give you an idea, I believe, of serious infections. Well, I believe that serious infections in the multiple sclerosis and Crohn's disease studies were on the slides. I am not sure if this is exactly answering your question.

But in the multiple sclerosis placebo-controlled studies, 2.4 percent of the natalizumab-treated patients had serious infections categorized as serious, compared to 2.3 percent of placebo-treated patients.

Again, in the MS studies, there was only that one atypical infection, the cryptosporidial gastroenteritis, and then in the placebo-controlled Crohn's disease studies, again, very short, just 1 to 3 infusions, serious infections occurred in 2.5 percent of natalizumab-treated patients and 2.6 percent of the placebo-treated patients.

So, that is overall. I could give you, if you are interested later, if there are any specific serious infections that you are interested in, I could give you the incidence differences.

DR. GOLDSTEIN: What I was interested in is what the combined rate was of opportunistic and serious infections, for example, the herpes that we are concerned about, other viral infections combined, and they may balance out, and that's fine. I am just not sure what the numbers are.

MS. A. HUGHES: In terms of the herpes infections, that's in the multiple sclerosis placebo-controlled studies, it was about 7 percent versus 6 percent, natalizumab versus placebo. In the Crohn's disease placebo-controlled studies, it was 1.6 percent versus 1.0 percent, and this is all herpes infections.

In terms of the opportunistic infections, there were--it sort of depends on your definition of opportunistic--there were those 7, I considered 7 atypical infections, the 6 lower respiratory tract infections and the extra pulmonary TB

infection may or may not actually be tuberculosis. Those all occurred in the long-term Crohn's disease trials.

There was just the case of CMV colitis in the placebo-controlled trial. That was the only one. And in the long-term Crohn's disease trials, there were approximately 1,500 patients, so that's, you know, 7 divided by 1,500. Is that helpful? It doesn't look like it.

DR. GOLDSTEIN: Again, you just went down the list again. I just wanted to know what the bottom line total number was in the two groups. Maybe you can calculate it for me afterwards and give it to us later.

MS. A. HUGHES: That might be more efficient.

DR. GOLDSTEIN: That would be helpful.

MS. A. HUGHES: Thanks.

DR. GOLDSTEIN: Sorry.

DR. KIEBURTZ: Any further questions?

DR. M. HUGHES: I don't know if it's good sense in these sorts of programs if there is any

potential for off-label use in a RiskMAP program.

DR. KIEBURTZ: Again, in the risk minimization program?

DR. M. HUGHES: Well, as I understand it, the physician has to sign that their patient has relapsing- remitting MS, so if they are telling the truth, it would exclude all patients without.

DR. WALTON: It also depends upon how tightly written the RiskMAP is.

DR. COUCH: Will this RiskMAP program need to go through human subjects or be, for instance, in academic centers or in private centers? Is there going to be any anticipated need for doing that?

Secondly, from a legal standpoint, will the procedure of discussion with the patients who are signing the appropriate forms take care of the legal aspect of it, or is there an anticipation that the judicial aspect of this, somebody can always come back and say, well, my client developed PML and you are still going to be at risk regardless of what papers you signed.

DR. TEMPLE: This is not an investigation. We will fight to the death to insist on that. It is part of how to use the drug safely, and you can't opt out of it, and will not go to IRBs.

DR. KIEBURTZ: So, it's not a research tool.

DR. TEMPLE: It is not a research tool. We religiously won't learn anything from it, and I am not sure we can comment on the law.

DR. KIEBURTZ: Issues of legal tort issues.

DR. TEMPLE: Can I make one comment that came up previously? How you write one of these things can determine how possible it is to use a drug off label, and that is one of the things you are going to be asked.

For example, the doctor could sign something that says I know this drug is indicated only for MS. Well, fine, you can know that and still prescribe it for something else. He could also be asked to say my patient has MS. That's a different level of assurance, and those are the

very things that you need to think about when you think about what to write.

DR. WYSOWSKI: I just had a comment about off-label use. If you track the vials and link them to a patient, you are less likely to have off-label use I think, because otherwise, you might have some stockpiling in the infusion center, in the doctor's office, or whatever, and then with that, unless that excess gets sent back to the company, then, there is always that possibility that it could be used off label.

But that is one point for the committee to consider is about tying the vial to the patient.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Could I ask you, Dr. Wysowski, have you reviewed the checklists that have been mentioned several times? I don't see them in the documentation.

DR. WYSOWSKI: Right. I have looked at the checklist, and as I mentioned in my presentation, there are only a few diseases that are on that checklist, and six drugs, and I think

it's important for the committee to consider whether there might be a more comprehensive list of immunosuppressive drugs and diseases.

DR. McARTHUR: How about the checklist for new or continuing neurological symptoms?

DR. WYSOWSKI: They are very nonspecific, change in eyesight, change in balance, new or sudden change in eyesight, balance, strength, and thinking. So, you know, I am not a neurologist. I would assume that that might produce a large number of potentially false positive suspected PML cases.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: Just to clarify for myself, so the idea of the use of the NDI would be to cross-reference these folks and do annual cross-referencing with all-cause, all death causes?

DR. WYSOWSKI: I am sorry. Could you repeat the question?

DR. SEJVAR: The use of the National Death Index, basically, you would be performing annual cross-referencing of these enrolled or registered patients with the all cause of death data, is that

correct?

DR. WYSOWSKI: Right. That is my understanding.

DR. TEMPLE: That would be for people they can't find in the ways they are going about finding them, right, or not?

DR. WYSOWSKI: In think initially, what you do is you run the index, you know, and compare it with all the cohort patients, and then later on, you know, subsequently, you would just include the ones that you can't find or that have been discontinued on Tysabri and lost to follow-up.

But there is that lag period, so it's not--I don't know exactly--can you speak to that, the lag period, do you know what it is now?

DR. SEJVAR: We do similar assessment for CJD, and it's about anywhere between two and three years.

DR. KIEBURTZ: Ms. Sitcov, please.

MS. SITCOV: I am wondering, it sounds like if this drug gets approved, PML is a possibility in terms of occurrence, but I am

wondering what sort of adverse reactions, both qualitative and quantitative, if Tysabri gets approved, would cause Tysabri to be removed from the market.

DR. WALTON: Are you asking for a nature of events or a frequency?

MS. SITCOV: Well, I guess what has to happen if Tysabri gets approved, do 20 people have to die from PML, or what has to happen?

DR. KIEBURTZ: That may be a tomorrow question.

MS. SITCOV: Okay.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Could I ask Dr. McDermott the experience with other risk management or minimization programs, you mentioned clozapine, or maybe it wasn't you?

DR. McDERMOTT: That wasn't me.

DR. WYSOWSKI: Claudia Kawolski [ph], who is the Scientific Coordinator for Risk Management Plans, could probably speak about, you know, what has happened with our--

DR. McARTHUR: Well, that was the question, what have we learned from the clozapine mandatory registration that we could apply to Tysabri.

DR. WYSOWSKI: Gerald Dal Pan, our office director--

DR. TEMPLE: Well, Rusty can add. We can say a few things about clozapine. Of course, each one of these is unique. For clozapine, you have to bring in a white count from the week before in order to get the next dose.

The result is that agranular cytosis is discovered much earlier than it ever was before, and the mortality from the agranular cytosis that is indeed seen is much lower than people expected, a couple of percent instead of the 10 percent that was anticipated.

In addition, the registry assures that no one who gets a white count problem ever gets the drug again. The registry has been used by all of the generic makers, as well as the original maker, and so on.

Now, to be fair, and not to overstate it, it's a fairly simple question that is being asked. It is just about white count, relatively simple, not so complicated. It's a simple lab test.

But I would say we feel quite good about that. There has been a gradual rollback of how frequently you have to have the test after you have been on the drug for a certain number of years, your chance of getting it decreases, so the frequency has dropped back.

There are other similar ones. There is a similar program for a drug called bosentan for pulmonary hypertension that Doug knows more about than I do. That one is designed to prevent pregnancy, so you have to bring in your pregnancy test and your test of liver function, because those are the two things you are worried about there.

There have been some pregnancies. That is not good, we think fewer than otherwise, and there hasn't been a fatality due to liver disease yet, a relatively low use drug, but each one sort of has to be looked at.

They vary in stringency, they vary in how much you have to say and do. Each one is sort of targeted, and that is why a lot of the questions tomorrow are going to be about how to target this one.

DR. KIEBURTZ: About the clozapine one, too, it was modified. I think that is another important thing. It existed and then was modified based on the initial results of that.

DR. TEMPLE: Yes, absolutely. The frequency of testing is modified if you have been on it, I forget, more than six months, more than a year, or whatever, based on observed data.

DR. KATZ: It is not just the frequency, but the criteria that serve for deciding what to do have actually altered it, as well, so many things about it have been changed over time based on the data that has been accruing.

DR. KIEBURTZ: Last question.

DR. JUNG: I think it is clear that neurologists use drugs off label frequently as part of our practice. Given the fact that there is a

change in the indication to remitting-relapsing MS, do you think that there is any need to clarify the diagnosis of remitting-relapsing MS?

That seems fairly elementary, but if the drug is released, will there be pressure on physicians by their patients to expand the definition of remitting-relapsing to patients with primary progressive or secondary progressive? All of us who take care of MS patients know that there is a lot of overlap there, and how do we clarify that?

DR. KIEBURTZ: I think that is a question to us to discuss tomorrow quite specifically in terms of the nature of the severity and the characteristic of the patients.

It looks like I said the last question, but I will take two more from Dr. Goldstein and then Dr. DeKosky, and then we will stop for lunch.

DR. GOLDSTEIN: Thanks. This may also be some information that needs to be gathered for us for tomorrow, but in the background information, one of the things that was talked about is the

dropout rate on other established therapies of 15 to 20 percent dropout rate.

What I was interested in is what the dropout rate was in this clinical trial for people who were enrolled in the clinical trial as compared to the dropout rates in the other clinical trials where these other therapies have been used. Are we expecting a difference, or are the dropout rates going to be similar to one another?

The second thing again may require some looking into is one of the things that we are being asked to do is, well, what group, if it is going to be restricted, should we consider, and one is treatment failures.

So, what definition is going to be used for treatment failure, and is there any data aside from this combined data that we know about from 1802 that switching the patient to this drug as compared to a different immunomodulatory drug results in further improvement.

DR. KIEBURTZ: Again, I think we are edging into tomorrow.

DR. GOLDSTEIN: No, this is for tomorrow, but they may need to get some data together to be able to address those, so I wanted to ask them now for tomorrow.

DR. KIEBURTZ: Thank you.

DR. WALTON: If I may respond in part to your first question about the dropout rates. I am sure it is in here somewhere, although I cannot find the page in the briefing document, but in the natalizumab studies, the dropout rates were relatively small.

There was very good follow-up on almost all patients, but that is not really I think the question that you are trying to get at. The question is what will be the experience in clinical practice.

I would be very wary about trying to reach insight into that question based upon the clinical trials. Clinical trials are so different, such different circumstances than clinical practice is.

It is clear to us from the clinical trials with the beta-interferons that there was a much

better sustained compliance, sustained use within the clinical trials for the beta-interferons than is reported to be the experience in clinical practice.

So, based on that, I would be very wary about trying to reach conclusions about what the clinical practice experience in the future will be.

DR. GOLDSTEIN: That is exactly what I was trying to get, and probably dropout rate wasn't maybe the best term to use. What I meant is drug treatment discontinuation rates, and as you correctly point out, looking at clinical practice compared to clinical trials are looking at apples and oranges, but again, as part of the background information, we were told that 15 to 20 percent of MS patients stopped these interferons or whatever during their clinical care.

So, the question was within the clinical trials that were done for these drugs, what was the drug discontinuation rate in those trials compared to this. That way, we at least have apples and apples to look at.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: This may also be for tomorrow, but the issue of who gets this drug and how we define relapsing-remitting would also have to deal with a first episode of likely MS with or without a clinical history, as Dr. Jung talked about, of episodes that did not reach the attention of a physician, but were part of the history, as well as initial optic neuritis and suspicion that there are other lesions in CNS, and whether that would meet the criteria for relapsing-remitting.

DR. KIEBURTZ: Thank you.

Russ, you get the final word.

DR. KATZ: Maybe to address Dr. Goldstein's second question, if I understood it, which was what do we know about if you switch from one interferon to another interferon, what is the response compared to if you switch from an interferon to Tysabri, somebody can correct me if I am wrong, but I don't think there is any reliable data that speaks to that question.

DR. WALTON: We have no data about that

sort of a crossover.

DR. KIEBURTZ: That concludes this morning. I would remind open public hearing speakers to check in at the desk if you intend to speak. We will start the open public hearing promptly at 1 o'clock.

Let me just remind folks there will be a set period of time, so that it is fair and equitable. It looks like committee members can leave their things here.

[Whereupon, at 12:05 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. KIEBURTZ: The schedule for this afternoon is slightly more flexible in the sense that we will take the break if and when it seems appropriate, the one of the few things I get to decide today.

Just to remind people that there are two forms of public comment, individual and group. Individuals have three minutes to speak, groups have five minutes to speak. When your time is up, someone somewhere in this room will turn off your microphone, so when the three minutes is up, you are done.

This may seem overly restrictive and harsh, but there are a number of people who are scheduled to speak, and it only strikes me as fair and equitable that everyone gets the same amount of time to speak, and I believe people knew about this in advance. So, we will stick with that plan.

Before the beginning of the open public hearing I need to read the following.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning

of your statement, it will not preclude you from speaking.

That's the end of that. We will now commence with the open public hearing, which is in a particular order of speakers as per the slide.

The first is Jason Mark.

Open Public Hearing

MR. MARK: Good afternoon. My name is Jason Mark. Both myself and Alex McDonald, the next designated speaker, will be ceding our time to representatives of the family of Anita Smith.

MS. SMITH: Thank you for the opportunity to speak to you today. My name is Beth. Anita Smith was my mother.

I am here with my brother Jason and my father Walt. My father prepared his statement to read to you, however, this is a very emotional, difficult time for him, and he has asked me to read his statement on his behalf.

I am here to briefly tell you about my wife, Anita Smith. Many of you have read about Anita in medical journals and newspaper articles.

Anita died from PML caused by Tysabri. Tysabri was withdrawn from the market because of Anita's death. I lost my wife, my best friend in the whole world because of this drug. My children lost a mother they loved, who loved them dearly.

Before she took Tysabri, Anita worked full time. She was an active, fully functioning person. She was not disabled, she did not appear ill. Anita was basically fine.

Beginning in 2000, Anita was prescribed Avonex. It cost us $1,000 a month. In 2002, we were told that if we participated in a study, Anita would receive Avonex and another drug, Tysabri, that we wouldn't have to pay for any of the treatment or medications.

We were told that Biogen would pick up the tab for us. We were never told that Tysabri could result in Anita's death. If we knew this, we would have happily stayed away from the study.

I understand that this meeting is to determine whether Tysabri should come back onto the market and whether clinical trials of Tysabri

should be permitted to resume beyond what has already been permitted.

I am here with Dr. Gregory Shoukimas from Boston who can speak to you about my wife's medical history better than I can. The one thing he cannot describe for you is how broken my family's heart is over ever having Tysabri enter our lives.

I ask that Dr. Shoukimas speak to you now.

DR. SHOUKIMAS: Good afternoon. My name is Dr. Gregory Shoukimas. I am a neuroradiologist and have been practicing for 20 years, and I am here at the request of the Smith family. I am not sponsored by Biogen, and I am not sponsored by any competitors.

I am here to address primarily the issue of the raw data, that is, the individual data that a patient presents with and was enrolled in the study, the Tysabri study. That is, how did Anita Smith present clinically, what was her symptomatology, what was her physical examination, and what tests aided in making the diagnosis of multiple sclerosis.

In the talks that you have heard this morning, it is assumed that Anita Smith had remitting-relapsing multiple sclerosis, and that has been called into question. I have no time to go into the details of her physical examination, but suffice as to say that her clinical symptomatology was benign, relatively benign, was not disabling, and certainly did not contribute to her disability scores.

Her physical examinations for the most part were normal. She showed very minimal signs of decreased leg strength, spasticity, and slight hyperreflexia.

In December of 2001, her physical examination was entirely normal. She had reported to her neurologist she was doing well, and she had normal muscle strength in all major muscle groups, but despite all this clinical information that was available, she was being considered by her neurologist for the Antegren or Tysabri study, which she was told would be starting shortly, that is, within three or four months.

I had the fortune of talking with the Smith family for about an hour, and it was related to me by Mr. Smith and his daughter, Beth, that from the time of her visit to enrollment in the study, that is, the time of her first visit to the neurologist to enroll in the study, she thought of her problem as an annoyance.

She worked, carried the laundry up and down stairs, clearly not indicative of a disabled patient. She didn't get worse, and she didn't get better. There was some indication that she had visual problems, but this was never tested formally with electrophysiology tests to confirm that she had optic neuritis.

Her magnetic resonance imaging study in 1999, which I have reviewed, showed some nonspecific white matter changes, and, in fact, given her previous history of migraine, may have reflected previous migraine. The changes were nonspecific, and while demyelination was considered criteria for this, for the diagnosis of MS was not fulfilled.

She had a cerebrospinal fluid analysis, which was normal, including IgG assessment, oligoclonal bands were nonexistent, and had one lymphocyte, which is nonspecific.

Electrophysiology studies were not performed especially visual, evoked potentials, which would have been helpful in making the diagnosis of optic neuritis.

Her clinical examination, as briefly, very briefly detailed, but more fully talked about by Dr. Godec later today, showed that she did not really have two clinically symptomatic attacks and that her objective lesions were not clearly defined.

So, the question really is did Anita Smith have multiple sclerosis. The talks again have assumed that she had relapsing-remitting disease, but, in fact, this was not ever clearly established. If, in fact, it was present at all, it was mild and stable with minimal neurological manifestations, and any objective tests that might have been helpful were ignored.

These are the MRI scans, which were not available when the New England Journal of Medicine published its clinical pathological study detailing the effects of MS on Mrs. Smith, and the Tysabri results and the progressive multifocal leukoencephalopathy which ensued.

These were the lesions that were described as 9 lesions. These are two illustrative MRs. There is a lesion back here. These are not very typical of MS. They are nonspecific findings.

These are two patients that have MS, similar in presentation, a little bit more severe, more objectively defined disease, but these MR scans are clearly contributory. There are some lesions in the periventricular white matter, close to the cephalo-junction region. In the Annals of Neurology 2001, the McDonald criteria were published, and clearly defined how MRs should be interpreted with respect to MS. The MR scan that Mrs. Smith underwent did not meet that criteria.

After her enrollment with two potent immunosuppressant and modified immunomodified

drugs, she was a minimally symptomatic patient whose diagnosis was questionable, and yet she was given the drugs, and progressive multifocal leukoencephalopathy ensued, causing her demise.

The enrollment of Anita Smith into a clinical trial of these two drugs is almost incomprehensible and certainly raises grave ethical concerns about Biogen Idec's process of enrollment.

The FDA has already decided that new clinical trials can proceed with Tysabri. As we examine the enrollment process for Anita Smith, we must question and examine the serious concerns that Biogen Idec is incapable of proceeding in a safe manner with future clinical trials. Obviously, they admitted, enrolled Mrs. Smith into this trial.

Anita Smith's enrollment process may represent a systematic approach to enrollment of questionable patients. Therefore, if the enrollment process is put into question, then the study findings that Biogen Idec has publicized widely in recent reports must also be put into question.

Anita Smith's death has caused close

examination in the literature. Her autopsy report was published in the New England Journal of Medicine in 2005, and the results of that autopsy report indicate that she did not have any histopathological evidence of MS. In fact, the report showed widely disseminated PML and evidence of possible vasculitis.

The enrollment MRI I obtained on court order was not available to the New England Journal of Medicine at the time that the report was made regarding her clinical history and ultimate demise.

The British Medical Journal and Lancet have recently published articles also questioning whether or not, in fact, Anita Smith had MS, and the possibility that this drug will be continued to be used in patients who may not be suitable candidates for its use given the possibility of mortality.

Why Anita Smith's case is so important to the panel today, the panel must question, as many other experts have, the serious implications of how and why Anita Smith was enrolled and possibly how

other patients were enrolled as well, especially since new clinical trials by Biogen Idec are anticipated and possible approval of Tysabri for clinical use is anticipated.

Thank you.

MS. CASANOVA: My name is Lisa Casanova. My trip here is not sponsored by anyone. I am speaking only for myself.

I was a participant in the Phase III and open-label trials of Tysabri for Crohn's disease, which I have had for 20 years, since I was 7 years old.

I know that this committee is not considering bringing back Tysabri for the treatment of Crohn's, but the benefits I got were so great, and I believe that this is so important, that I am here to ask you to bring this drug back on the market for the people it can help.

Before I went into the trial, I was facing a major surgery to remove part of my large intestine that has been damaged beyond repair by this disease. Tysabri allowed me to delay that

major surgery for almost three years. For a Crohn's patient, that is a long time.

It allowed me to live with less pain, it improved my quality of life. I went into the Tysabri trial to test an unknown drug with unknown risks, because I firmly believe that that is the only way we are going to see progress.

I thought the risks were worth it, and my heart goes out to the people who suffered as a result of their choice to participate, but I still believe those things. I am willing to take the risks and I can only imagine how much more willing these MS patients are who have such a terrible disease and so few choices.

I understand the place that they are in. When you live with life-long debilitating disease, all of your choices are tradeoffs. No one can tell you, you just need to do this one thing, and everything is going to be okay.

Right now I control my disease with drugs that put me at risk of lymphoma, of infections, of liver damage. My other options carry similar risks

with them.

For us, it is a series of tradeoffs between drugs, surgeries, between the quality of life that we want to have for ourselves, and the chances that we are willing to take to get that quality of life. That is the reality that we live with every single day of our lives, and it is not a reality that is ever going to be made better by having fewer options.

I know that this drug is not going to come back for Crohn's patients. When it comes to real therapeutic progress, our day hasn't come yet, but I am always hopeful that it will, and in the meantime, I believe that you need to do the right thing and bring this drug back to the market for the people it can help.

Thank you.

MS. CLARK: Thank you for listening to my personal experience with Tysabri. My name is Pamela Clark, and I have had MS for 10 years. I have progressed from relapsing-remitting to secondary progressive.

My mother and I traveled here from Phoenix and Salt Lake City respectively. We paid for our own ticket, and we are not sponsored by any organization.

It was important that my mom be here, because she has two daughters with multiple sclerosis, and she was the one who held my hand during my first Tysabri infusion. In the weeks after the infusion, she witnessed the improvement in my gait and my energy level. We were ecstatic and we were filled with hope.

You see, she fought her own battle with cancer 15 years ago, using then risky and then experimental drugs. Today, she is cancer-free and those experimental drugs are widely used by people with cancer every day. As a family, we understand the risks of using experimental drugs, but we also understand the risk of doing nothing.

The risk of doing nothing for me is too great. The risk of doing nothing, which for me means continuing to take ineffective drugs, is too high for me to ignore. I must fight for the right

to have the opportunity to live life to its fullest. I owe it to myself and I owe it to my family.

I attend a MS physical therapy group three days a week. It is comforting to be among people who have the same affliction, and they understand my struggles completely. It is not comforting, however, to watch my friend's health falter and fail. It is not comforting, however, to watch my friend, who walked in on a cane last year, roll in in a wheelchair.

This disease and its symptoms are progressive and they will not wait for anyone's approval. The drug they take do not stop or even slow the progression of MS. Finding an effective treatment seemed hopeless. That was I felt hopeless until I found Tysabri last January or January of 2005.

In January of 2005, I had two infusions of Tysabri and I got better, not miraculous jump up and run a race better, but I did walk to the duck pond with my two, five-year-old boys. I did stand

up and cook dinner, stand up long enough to cook dinner, and I did smile more often. That is what hope does. That is what Tysabri did for me.

On the issue of risk management that you have been talking about this morning with Tysabri, I received monthly Solu-Medrol infusions at the infusion clinic in my neurologist's office, and there, Julie and Martha, who I know from being there monthly, every month, they sit down with me, and they have a questionnaire already, and they say, "What are your symptoms like? What have changed?"

This new reporting mechanism will be no different for them, and I know that they will gladly do it.

The cost of getting here is high for me, both the cost of our travel expenses and the cost to my health. The stress--.

DR. HUGHES: Thank you for allowing me to speak. My name is Chris Hughes. I am a board-certified neurologist, and I have been in private practice for 12 years.

Within the past year, I have signed consulting agreements with Biogen, Berlex, Serono, and Teva, but I am here today at my own expense to state that in my opinion, the current state of therapeutics for multiple sclerosis is remarkable, and the future with new drugs in development is even more encouraging.

Through the 1990s, beta-interferon and Copaxone were FDA-approved for the treatment of MS. We now have over 10 years of experience with both of these agents, and numerous studies demonstrating their safety and efficacy in slowing the progression of the disease.

We are just now learning from new studies that early initiation of these established therapies further improves their effectiveness. Today, with the use of these medications, the severely affected multiple sclerosis patient is still part of our clinic, but make up a smaller percentage than they did in the past.

Yes, interferons and Copaxone have revolutionized the state of our MS patients for the

better. Further, we hope that combining these two agents proves synergistic and studies addressing this subject are planned. Further, the higher dose interferons and study of this are also underway.

For interferons and Copaxone, in my opinion, the best is yet to come, and for those patients with aggressive disease, we have another FDA-approved drug, obviously Novantrone, which is a highly effective agent.

Regarding Tysabri, in the initial New England Journal report, investigators identified 4 out of 142 patients that had serious side effects related to Tysabri, one of which was anaphylactoid, a state that most community neurologists are not well equipped to treat in an office setting.

Since its withdrawal, I have attended many scientific meetings in which the issue of Tysabri and PML has been discussed. Many of us fear that with the reduced immune cell migration effect of this drug, longer exposures to Tysabri could exponentially increase the risk of opportunistic infection or latent virus reactivation, and I have

seen no data to reassure that concern.

So, in summary, beta-interferons, Copaxone, and Novantrone are highly effective agents. High-dose interferons and combined therapy hold additional promise for new agents, and also we have new medications in development.

In this context, I would argue that there is no crisis in MS therapeutics, and therefore no need to rush back to the market a drug that has serious proven hazards given the lack of safety data in longer term use.

I would urge further study of Tysabri and its relationship to PML. Only with longer term safety data can neurologists feel comfortable using this drug in the future.

MS. LADD: Mr. Chairman and members of the Advisory Committee, thank you for the opportunity to address the pending biologics license application for Tysabri. My name is Virginia Ladd, and I speak as President and Executive Director of AARDA, the American Autoimmune Related Diseases Association.

AARDA maintains strict and transparent guidelines for commercial contributions. Neither I nor AARDA have received financial relationship or funding from the sponsors of Tysabri, Biogen Idec, or Elan Pharmaceuticals, nor does AARDA endorse any product or services.

AARDA is the only national voluntary health agency advocating for all of the more than 22 million Americans afflicted with 100 autoimmune diseases. We do this through education and research and patient services.

On behalf of AARDA and its members, I thank this committee for its critically important work. Tysabri is an important new therapy for multiple sclerosis. FDA's decision on this application will directly affect hundreds of thousands of MS patients nationwide and have important implications for patients with other autoimmune diseases.

That is why we are pleased that FDA emphasized last year that it places particular importance upon patients' views of Tysabri.

AARDA urges the committee to keep the question of patient choice uppermost in mind as it proceeds with its important work. The potential reintroduction of Tysabri to market with appropriate safeguards would enable fully informed patients to make reasoned decisions about their own health care.

FDA made this point forcefully when the Agency explained its decision to permit the market reintroduction of Lotronex in 2002, quote, "Physicians are essential in determining the benefits and managing the risks of an individual patient for whom the drug is prescribed. Ultimately, the patient, once informed, is the definitive decisionmaker concerning the benefit-risk balance."

Our members have made clear that decisions like Tysabri should only be made when the decisionmakers understand fully that patients with chronic diseases may view the balance of risk and benefits differently from physicians, regulators, and other stakeholders, not simply because they are

not informed or because they cannot fully understand the issue at hand, for a patient with a chronic illness, the potential value of a therapy that allows him or her to leave their wheelchair behind or go back to work may make that patient willing to take risks that would be unacceptable to someone else.

Just as the generalization cannot be made that no one drug will be effective for everyone, neither can it be said that a drug will have the same safety issues in all treated individuals. With the right information and advice of their caregivers, it would be a grievous mistake to underestimate the capacity of MS patients to recognize, understand, assess, and assume the risk or the potential benefits of a product like Tysabri.

This is not a novel point, but it bears emphasis in this proceedings. I have submitted for the record, AARDA's position paper, "A greater Need for Patient Voice and Choice," that addresses the vital importance of patients participation in the

clinical, as well as the regulatory, decisions that determine the therapeutic choices available that determine our health and our quality of life.

AARDA believes that Tysabri's effectiveness is well established and it is a very important as a first in class novel therapy for MS. We believe that Tysabri's market experience, clinical investigation, and reports from patients and providers demonstrate its important clinical benefits.

Effective new therapies are few and far between for autoimmune diseases generally and specifically with MS. Therapeutic regimes for autoimmune diseases are clinical juggling acts of multiple medications that must constantly be fine tuned to avoid and manage relapse and flare-ups.

The availability of novel, new therapies is critically important to our members.

Finally, AARDA recognizes that FDA has been under intense public and congressional scrutiny in relation to post-market safety of drugs and biologic products, but we urge the committee

and FDA to act strictly on science, clinical evidence, and availability of appropriate labeling, risk management controls, and post-market studies in deciding whether Tysabri should be returned to the market.

MS. CANAVAN: Hello. My name is Emily Canavan. I have no financial ties with any pharmaceutical company, and no one contacted me to come here today.

I am 27 years old and I was diagnosed with MS in 2003. My mother was diagnosed in 1999. I was 24 years old when my life as I knew it ended. It was a life where I was a hiker, an athlete, a teacher, and an adventure traveler.

My health has declined rapidly. For someone like me, time is precious. I have never experienced any real period of remission and no medications have stopped or slowed my MS from progressing.

I cannot convey to you how difficult it is to watch my friends travel, work, and excel while I am held hostage by multiple sclerosis. In 2002, I

received a Master's Degree and teaching students with emotional and behavioral disabilities.

During the 2001-2002 school year, I taught every day, had class four nights a week, and at 23, I had found something I loved and I was good at. After graduation, I began teaching fifth grade. Four months later, I had to go out on disability. By then I had daily headaches so bad that I could not get out of bed.

My mother had been diagnosed with MS four years before, but I kept telling myself I am just stressed out, this is not MS. I clung to this statement as hard as I could, but in the next six months I developed painful muscle cramps, constant urinary problems, tingling, cognitive problems, and my mobility became very limited.

Some days it's two steps, and some days it's two blocks. These new symptoms and an ever-growing number of lesions on my brain finally confirmed the diagnosis of MS. To add insult to injury, last year I was diagnosed with ulcerative colitis. Colitis and Crohn's disease both involve

inflammation in the intestines, and Tysabri during trials gave many Crohn's patients an improved quality of life.

Less than a year after leaving my job, I had to move out of the city and closer to my family, because I need help so often. My headaches continue to be debilitating and other symptoms persist. I have had to adjust to using an electric scooter. I have to consider how to transport it, investigate each location's accessibility, and deal with the reality that when you are in your 20's and on a scooter, people are going to stare.

I have exhausted most MS treatments already. AVCRs, IVIG, methotrexate, Solu-Medrol, LDN. I am not currently on any MS treatment drug. I had one dose of Tysabri the week it was taken off the market. I am reluctant to take strong chemotherapy drugs because of the risk of infertility, but that's the point. Every patient has to weigh the benefits and risks of every medication.

I haven't been willing to risk

infertility, but if nothing else helps, that risk will become worth it to me. All medications have risks, even over-the-counter medications can be deadly if taken inappropriately or by people with certain conditions.

I will be extremely disappointed if Tysabri doesn't help me, however, I will be glad I came to this hearing because it will help so many people whose lives have been turned upsidedown by MS. It may help me, it may help my mother.

DR. STUART: My name is Bill Stuart. I am the Medical Director at the MS Center of Atlanta, which is a foundation-run public charity center. We see over 100 patients with MS a day, five days a week.

I have been in neurology practice for 36 years. The last 16 years I have done almost exclusively MS, so I have an intimacy with this disease that I would like to share with you.

That is, that it is a disease. When my center was at the Shepherd Center, which is a large spinal cord treatment center in Atlanta, one of the

things that became apparent to me is that spinal cord injury patients and MS patients with comparable disabilities function differently.

The MS patients never took advantage of the therapeutic recreational facilities, whereas, the other group did. They had vigor, they had interest, and it dawned on me that MS is more than just a disability, it is also an illness, and it is the illness part we don't measure very well.

In my observations through the years, I think that the reasons people leave active life because of MS are largely due to cognitive change, excessive fatigue, pain, sleep disorders, bladder and bowel issues, and sexual dysfunction.

The second point I would like to make has to do with how we would enter a person into the study, relapsing-remitting has been proposed. I would suggest that that will create a number of problems. First of all, recordkeeping will be fudged. Every patient will have relapsing-remitting disease if the doctor treating the patient desires to try Tysabri.

I would suggest that you consider a term called "worsening MS," and work at trying to define what worsening MS is.

The third issue is a socioeconomic issue. In our center, the actual day-to-day medical care of the MS patient is in the red. If we add onerous risk management type efforts to this in the opportunity to give Tysabri, we won't be able to use the drug, it will be impossible, because it will drive our losses even higher. The losses now are overset by contributions and other collateral revenue streams.

I think that the Biogen plan for monitoring patients was quite a reasonable plan, and I would favor that you endorse that.

Finally, there is a crisis in MS care, and it has to do with compliance. We currently have compliance rates that are terrible. We have as many patients going off of the medicines that we have today as are going on them, so that we are a steady state in trying to treat these patients, and that steady state is well below where we should be.

Thank you very much.

MS. COOKSEY: My name is Christy Cooksey. I have traveled here from Coos Bay, Oregon, to represent my mother, Janet Russell, in Klamath Falls, Oregon, who is too disabled to make the trip due to her MS disability.

I would like to disclose that I have no financial interest in either Biogen or Elan, nor have I received any financial support from either company.

My mom has written a letter to this committee, which you all have in your packets, and I hope that you will read it. You will hear her words, but I would like to describe to you what it is like to watch your mom be destroyed by this horrible disease.

My mom is my hero. She is one of the strongest people that I know. She jokes about her disability saying things like "I'm going to be the first disabled stunt woman," referring to her constant falling.

My mom is my best friend and I have been

devastated having to watch her quality of life diminish so rapidly. Her inability to travel has impacted our entire family. I currently live four and a half hours away from my mother. For my mom to travel to visit me and my two children, it takes her two days as she has to stop halfway to rest.

If she were to attempt the trip in one day, she would be so fatigued the next day, all she would do is to sleep to recover.

I have witnessed many of my mom's symptoms and also her sometimes horrible reactions to at least three different, quote "treatments" she has been on. These include flu-like symptoms, uncontrollable shaking, injection site reactions, and possible bone loss.

At one point, she experienced a total loss of control of her legs and an actual increase in her relapses while on these treatments. Tysabri has been her miracle, and she needed it back a year ago.

With only one infusion, her muscle spasms all but disappeared, allowing her to walk without

her walker, and without falling. She was less fatigued, her cognitive abilities improved, her speech was less slurred, and her beautiful singing voice, which she lost in 1999 due to her MS, was finally coming back.

On a follow-up visit with her neurologist, he saw her improvements and stated, quote, "If you think the first infusion helped, just wait until you get the second or third." She never got the chance to get her second.

The MS community has a tremendous unmet medical need for effective treatments for this horrible disease. Every day my mom suffers the risk and the reality of her disability progressing. This is a much greater risk than Tysabri if it was used in compliance with the risk management plan.

My mother is more than willing to participate in any form of risk management program approved by this committee. My mom and our family, along with her neurologist, want to have a choice in which treatment is most appropriate for her to slow, stop, or possibly reverse the progression of

her disease.

MS. LYONS: I don't own stock in Elan, I don't own stock in Biogen Idec. I occasionally speak for Biogen Idec as part of a voluntary group.

I am K.T. Lyons, and I am an MS survivor. I am one of those who was first diagnosed by a general practitioner, just kind of had an idea that I might have MS from my on and off symptoms, and his idea was since I have had these on and off symptoms for more than eight years, why didn't we just watch it.

So, indeed, that is what we did. I continued my job in a Fortune 500 company, and I continued running two miles a day until that one day in 1977 when I woke up, blind in one eye, completely unable to speak, and having great difficulty in breathing.

I was hospitalized and finally a neurologist was called in, and they came in with the permanent diagnosis that I did have MS. So, I had steroids for my eye and some physical therapy, and I was put on an interferon and sent home.

I am one of those who had sickness and depression on the interferon, but nonetheless, I continued with my life. My disease continued to worsen, so they tried IVIG, they tried another interferon, and then finally, they tried Novantrone. None of this worked, and I continued to have relapses more often and more often.

Finally, just to try to improve the other part of my wellness, I began an involvement with the Bureau of Vocational Rehabilitation, and found out there might be a way that I would go back to work.

They enabled me to start my own business, which I did start, and got on my way to at least beginning to feel better. Then, in 2005, the level playing field that I thought I had gotten onto changed again.

I am in severe pain and have difficulty talking all the time from a little known symptom of MS called trigeminal neuralgia, and I take a drug for that, that is an anti-seizure drug, and the drug had built up in my system way too much, and I

went unconscious.

I remained unconscious in the hospital for more than nine hours, because the combination of my MS lesion and the tegretol had placed me in such a dangerous position. When the hospitalist came in and when the neurologist came in--.

MS. LAWSON: I would like to disclose that I have received remuneration in the past from Biogen Idec. My expenses associated with this open public hearing are being paid through personal and private funds.

Thank you very much for this opportunity to speak with all of you. My name is Sonda Lawson. I am a licensed counselor and director of MS Clinical Research and Services at the Michigan Institute for Neurological Disorders MS Center.

MIND has a comprehensive MS care facility servicing over 2,000 MS patients. I am speaking to you today from both a personal and a professional perspective.

I was diagnosed with MS 10 years ago, but have really been living with the disease for over

15 years now. Although outwardly no one would know that I have MS, there isn't a day that goes by that I don't have some reminder whether it's residual visual deficit from multiple bouts of optic neuritis, bladder issues, numbness, weakness, clumsiness, or seeing how my MRI continues to worsen.

Although I try not to live my life wondering what could happen to me, the reality is that in the back of my mind, I do fear that today or tomorrow the disease could manifest into something very significant.

It is very real because the threat is present and looming on a daily basis. I watch this disease slowly or aggressively destroy people's lives.

When I was diagnosed, the images that were portrayed were those of essentially a wheelchair sentence, and Dr. Kevorkian was helping MS patients commit suicide because they couldn't bear to live as essentially vegetables.

I distinctly remember all the literature

indicated that a cure was 5 to 10 years away. Well, here we are now, 10 years later, and we are not even close to a cure.

I started working in MS Research in 1999 in an effort to help in any way that I could find more options for our patients in the fight to end the devastating effects of this illness.

Over the last four-plus years, I have had the unique opportunity to serve as the research coordinator in four different Tysabri clinical trials with a cumulative total of 56 patients.

In addition, I personally received four doses of Tysabri, and after taking injections for over 10 years now felt so liberated to not undergo the myriad of side effects and dosing regimen involved with injections.

For the first time, I felt more in control of my illness, and so the impact it had on my emotional and physical wellbeing was profound. My experience is not unique. Virtually, every one of our patients is eager to resume taking Tysabri.

Although Tysabri doesn't represent the

answer, it represents better preservation until we can find the answer. Unfortunately, no matter how the data is tweaked, the current approved medications used to treat MS today are only about 30 percent effective.

Tysabri has been shown to be far more efficacious than any of the current options. Yes, there is a risk, but if you look at the biologic pipeline, are we ever really going to take away the element of risk.

Furthermore, having MS is our biggest risk. I understand we live in a litigious society. The FDA, pharmaceutical companies, and physicians are appropriately concerned about patients overall safety.

As a research coordinator, I have reviewed the new safety measures and consent documentation required from each candidate that will receive Tysabri in the reinfusion trial.

Furthermore, I can speak at least on behalf of our facility. There will be a treatment algorithm that we will follow in order to minimize

and manage the risk to the extent that we can.

Thus, I am confident those that wish to receive this therapy will be well informed of the potential risks, and as their healthcare provider, we will be hypervigilant when it comes to monitoring our patients and managing their care.

In conclusion, I sit before all of you today as a clinician and a patient of MS. I am in the unique position of intimately knowing the risks and benefits of this disease and its medications. We live in a world where many neurologists view the treatment of this disease as one that should be without risk because MS is not terminal, but rather a manageable disability.

So, I ask you how can any physician, pharmaceutical company, or governmental organization determine my/our disability as acceptable or manageable? We, as patients, should be able to decide.

My final note that I leave with you today is an analogy I often use in regards to MS. Any of us can get hit by a bus. The difference is those

of us affected with MS see the bus coming. The bus for us represents disability, and it's imperative that we have as many choices as possible to slow the bus down.

I truly believe that Tysabri represents a better alternative to slowing the bus down. Tysabri may not be for everyone, but it is another option to add to our armamentarium.

Thank you.

MS. CROOKS: Good afternoon. My name is Barbara Crooks and I am here to defend Tysabri, and I have not been paid by anyone to be here.

Life is all about tradeoffs. I was diagnosed with MS eight years ago, and at that time I was a very active 40-year-old, married, mother of two, who had a very fulfilling job as a registered MRI technologist, working in the neuro field for over 25 years.

I have a wonderful family who all had their input as to what I should talk to you about today. My father wanted you to know that I was district champion in hurdles in high school. I ran

cross country in college, survived a 50-mile bike race, did hours of aerobics, weight training, and probably walked 473,000 miles in my neighborhood.

I played basketball with my son and rode horses with my daughter, and then the MS monster hit. I have traded my active lifestyle for a life of isolation in my home as you can see by the way I walk.

Throughout the years, I have struggled just to keep my legs under me going from one FDA-approved drug to another. I have been on hundreds of steroids - Avonex, then, I doubled Avonex, which after relapsing again, I traded double-dose Avonex with single-dose Avonex and Copaxone, only to relapse again.

I then traded that combination for Avonex with Mitoxantrone, and most recently I had to trade Tysabri for Imuran. All of these drugs with their side effects of flu symptoms, nausea, and weakness only helped temporarily.

This, combined with my underlying MS symptoms of back pain, hip pain, right foot drop,

balance, and vision issues, and fatigue contributed to the decline of my wonderful life and the loss of my job. My patients walked better than I did.

Then, there was Tysabri, absolutely the easiest and the only positive treatment that I have ever taken. With the one-hour injection time and only slight nausea, I was able to return home feeling great, slept great, woke the next day with no pain.

This shocking discovery led to improved walking and mobility for the first time in over a year. Had I been able to continue the Tysabri treatment, I believe that I would have been protected from further attacks and given the improved quality of life that I strived for.

After my third dose, Tysabri was pulled from the market. While I understood the decision, I told my husband, Dave, that I would sign a waiver to continue the drug even with the risk of PML. Naturally, my comment upset him, fearing of losing his wife of 24 years.

As a Christian, I am not afraid of dying,

but I am afraid of living as a burden to those I love. Soon afterwards while running a couple errands, he was struck by my difficulty in performing simple, everyday tasks, which are taken for granted by the average person.

This realization led him to understand why I would risk taking this drug in order to regain the basic quality of life that I crave. The technicalities of how Tysabri binds with the potentially damaging immune cells from the bloodstream and interferes with crossing the blood-brain barrier can be left to all the experts in that area.

I am coming to you humbly, as a wife, a mother, a daughter, sister, sister-in-law, and a friend--.

MR. LORE: My name is Steve Lore and I have no financial interest in whatever outcome comes about because of today's hearing.

I was diagnosed with MS in 2001, not a great year for the country, and not a great year for me. But after diagnosis, I went through a

whole regimen of treatments I did the ABCs, Rebif, Avonex, Copaxone, and all without really much improvement in the disease.

So, my doctor then put me on Solu-Medrol, and then we tried different things, IVIG. We have finally, most recently, done Novantrone and Retuxan. Now, those are drugs that have potential side effects that are not very good, but they are just potential side effects, just like with Tysabri. PML is a potential side effect, and I choose to take that risk of that side effect, because I had one dose of Tysabri, and with that one dose, I felt like my life had been given back to me.

I felt so much better after just one dose, and it was pulled before I got the second dose. Who knows what would have happened had I had two or three doses. Hopefully, I will get a chance to do that before very long.

It all comes down to a risk versus benefits, and I think the benefit of having it out there for people to have the choice to take it,

because the choices are very limited in scope. There are not that many choices out there, so this was a huge advance for the treatment of a very debilitating disease. It is like looking down a well. If you fall into the well, you are not going to get out of it very easily, and MS is like that. It is not a disease that has many ups.

There are not many high points in the disease of multiple sclerosis. It's all of aggression that gets worse and worse and worse, and, you know, hope is a great thing, and I felt that with Tysabri, there was hope.

Thank you.

MS. BLOOM: My name is Cheryl Bloom and I live in Idaho, and I am disclosing that I own 300 shares of Elan stock, and I am here on my own.

"But you look so good." That is what people tell me all the time, but I don't feel good. On a daily basis, I fight fatigue, dizziness, spasticity, permanent numbness, and pain. I was once an aerobatic pilot.

Since my diagnosis of MS in March of 2001,

at the age of 48, my life altered drastically. I am here today to talk to you about how my life changed for a few short months when I had the choice to have Tysabri infusions in early 2005.

I have a very active case of relapsing-remitting MS in which I have exacerbations every three months. None of the current disease-modifying drugs nor therapies have done anything to slow down this exacerbation rate.

I have been on Betaseron, Betaseron combined with methotrexate, and Copaxone. To control these exacerbations, I must have I.V.-administered Solu-Medrol for a minimum of three days. The long-term adverse effects of Solu-Medrol are not reversible.

If you add up all of the three-day Solu-Medrol infusions I have had over the past five years, that is a lot of steroid damage to my body. The short-term side effects of infused Solu-Medrol are life altering for me.

I cannot work, nor perform such simple daily tasks as cooking dinner for my husband due to

debilitating fatigue. It takes almost two weeks for my life to get back to my normal after an exacerbation and I.V. Solu-Medrol.

When my neurologist recommended that I try Tysabri, I was ready to try anything. The first two infusions in January and February 2005 went very well with no side effects. Amazingly, I felt like a normal person again, like a person without MS.

I was scheduled for the third infusion on March 3rd, 2005. Unfortunately, I was unable to have this infusion because Tysabri was pulled from the market, but the effects of the drug were enough that I had no exacerbations for five months.

Tysabri is the most effective disease-modifying treatment currently known for relapsing-remitting MS, and people with MS should have the choice of Tysabri available to us as long as we have all the information known about the potential risks and benefits.

Every drug carries risks of side effects, even Zantac, a drug to which I had an acute

anaphylactic reaction. People with MS have a right to decide what risks are acceptable to us for an effective treatment as long as information about the risks is not concealed.

I assure you I will adhere to every element of any risk management plan implemented. Please do not make us wait any longer for Tysabri.

MR. BARRON: Hi. I am Mike Barron. I am 48 years old. I proudly served my country as a nuclear engine room supervisor aboard the nuclear-guided missile cruiser USS Texas, CGN39.

I was honorably discharged from the U.S. Navy and began a civilian career in the nuclear electrical generation industry. In December of 1985, I developed severe optic neuritis of my right eye, but continued to qualify until I received my nuclear reactor operator's license for Pala Verde nuclear generating stations Units 1, 2, and 3.

I safely and effectively operated all 13 nuclear plants until I suffered another major exacerbation and was officially diagnosed with multiple sclerosis on February 28th, 1995.

In mid-1995, I was found medically disabled by MS and placed on Social Security and private pension. My specialist prescribed me interferons for over nine years. During that time, I found out about Antegren as a MS drug showing great promise.

Because of my belief in that new hope for my MS, I took a small position in Elan stock in 2002. In late 2003, I began having severe abdominal lower extremity spasticity attacks as very painful charley horses.

After studying the drug with the help of my doctor, I began preparation for getting my first dose. In October of 2004, I quit Betaseron without telling my doctor because I felt it was making me sicker, and it wouldn't interfere with the Tysabri.

On January 5th, I received my first Tysabri infusion. I received my second infusion on February 4th. I started feeling so good about myself, I started doing more things around our home. I started taking walks with my wife again. I started feeling so good about myself, I couldn't

feel like I had MS anymore basically. It was going away.

Not only was I feeling better, I was sleeping better at night. then, on February 28th, 2005, they took my Tysabri away. I decided to get actively involved to find out why my Tysabri was taken away.

I even volunteered and became a non-paid Biogen MS patient advocate, and after contacting the FDA and figuring out what needed to be done to improve the patient feedback to the FDA, I quit my Biogen patient advocacy, which leads me to why I am here today.

I want to let you know that I am fully capable and willing, with the help of my chosen professional, to engage the possible risk of 1 in 1,000 in order to achieve a much higher quality of life for me and my wife.

I truly believe that Tysabri is the cure for the active component of my dynamic MS. I would really like to become productive again and give up my 24/7, 365-day job as an MS patient and get a

working man's job to pay taxes again.

Thank you.

MR. RICHERT: Thank you for the opportunity to speak at this hearing. My name is Dr. John Richert and I serve as the Vice President for Research and Clinical Programs at the National Multiple Sclerosis Society.

Prior to assuming this position one year ago, I was on the faculty at Georgetown University Medical Center, where I served as an investigator in the Sentinel trial of Avonex plus Tysabri. I currently serve on the Data and Safety Monitoring Boards for the Phase III trials of Novartis' FTY720 and Acorda's Fampridine.

The mission of the Society is to end the devastating effects of multiple sclerosis. It is essential that people with MS have more choices for safe and effective treatments. We are grateful to the FDA for granting expedited review of this application.

Determining the relative risks and benefits for Tysabri is a complicated matter. Data

are being considered by the Advisory Panel that have not generally been in the public domain. There are also issues of risk for which there are no answers at this time.

The National MS Society has pursued all possible avenues to assure that the FDA brings together the expertise required to evaluate all of the data and to come to the best possible decision.

In this effort, we submitted a recommended list of potential panelists who, in our opinion, bring to the table a comprehensive and balanced understanding of the issues associated with the return of Tysabri to the market. We also provided recommendations on clinical and scientific experts, as well as people with MS, to speak at this open public hearing.

In order to assure that the FDA heard from every interested individual, we dedicated a month-long front-page link from our website to the FDA comment page. We also provided information on submitting testimony and participating in the hearings in person.

In December 2005, we commissioned an online survey of a random sample of over 800 people with MS, with particular emphasis on determining the amount of risk that they would be willing to accept and still take this drug.

The study was coordinated by International Communications Research with Harris Interactive Online and has a margin of error of plus or minus 3.4 percent.

We have made the results of this survey available to the FDA. Of those who had heard of Tysabri, approximately 25 percent had a positive impression of the drug, 25 percent had a negative impression, and approximately 33 percent expressed a neutral opinion, wishing to have more information before making up their minds.

Twenty-six respondents had received Tysabri during its period of availability. Of these, approximately 76 percent wished to receive it again, 12 percent did not wish to receive it again, and 12 percent were undecided.

Among all survey respondents,

approximately one-third wished to have Tysabri available and half wished to have more information before making a decision.

In this survey, questions about acceptable degrees of risk were phrased in a manner such as: Would you wish to take this drug if the risk of dying from PML within 3 years is one in a thousand, or it's 1 percent, or 10 percent, and so on, right up to a 100 percent risk of dying from PML.

The responses were spread relatively evenly throughout the range, without a cutoff at any particular degree of risk.

We have been extremely fortunate that the approved disease modifying agents for MS have been extraordinarily safe. Similar degrees of safety are not seen among the medications available for treatment of most other autoimmune diseases.

Medications approved by the FDA for use in the treatment of rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, psoriasis, and ulcerative colitis, include those with degrees of known risk that include fatalities. These

medications include Enbrel, Humira, Kineret, Remicade, methotrexate, azathioprine, and Celebrex.

Patients suffering from these autoimmune diseases, along with their physicians, are learning to weigh the potential risks and benefits when making their treatment decisions. It is likely that our frame of reference for MS drugs will need to change to be more in line with the toxicity risks that are recognized in the treatment of other autoimmune diseases. The risks of the medications will need to be weighed against the risk of doing nothing.

If, after the safety review is complete, the FDA recommends Tysabri's return to the market, we will applaud the addition of this treatment to our arsenal.

If the FDA does not approve Tysabri's return to the market, or if it does so with significant restrictions, we will work tirelessly to find ways to satisfy the safety concerns so that more effective treatments can be readily available for the benefit of people with MS.

Thank you.

DR. KIEBURTZ: We have videos now.

MS. ROBERTS: Good afternoon, ladies and gentlemen. Thank you for allowing my videotaped testimony today. I had planned on being there in person, however, due to a recent exacerbation of my MS symptoms, I am no longer able to travel, and for the same reason, please excuse my slurred speech.

My name is Lauren Roberts. I am 51 and I live in California. I have been living with MS for 30 years. As a long-time MS patient, I can tell you that there is a tremendous unmet medical need when it comes to MS therapies, because what is available to us today is ineffective for a large population of people with MS like me.

My MS started out 30 years ago being fairly mild with only numb hands and a slight drop foot on the right, and I was able to remain a productive member of society working as a certified paralegal for 26 years. I enjoyed hiking, camping, dancing, swimming, et cetera.

However, in 2001, I had to retire due to

the worsening of my cognitive problems, and in the past two years, my disability has progressed very rapidly. MS has taken away my ability to work, destroyed my finances, destroyed my health, and is rapidly destroying my ability to remain independent.

Since the worsening of my MS, I have been on Avonex, Copaxone, oral and I.V. steroids. Novantrone was not an option for various reasons. I actually got worse on these therapies. None of them stopped my attacks, and now I have an overall decline in strength and coordination. Only Tysabri stopped my attacks and gave me hope with the improvement in my symptoms.

The issue here is having the option of a choice, which we currently do not have without Tysabri. The FDA's over-caution is not warranted here. It is only hindering our hopes of a recovery and a future.

Regarding PML, most well-informed patients know that Tysabri is safe as a monoclonal therapy, and we have taken steps to clear our bodies of

medications in anticipation of Tysabri's return.

As a Tysabri patient, I would be more than willing to undergo regular medical testing including MRIs and a regular blood test to minimize any possible risk of PML. These are our bodies and our lives, and the unmet medical needs of the MS patients are staggering. There is a much greater risk presented by not having Tysabri available to us as a choice.

Give us back the right to make our own fully informed choice and give us back the tools to do so. Put Tysabri back in the arsenal of therapies to choose from.

I gratefully thank you for this opportunity to address the AC panel. I pray that you never have to experience this dreadful debilitating disease called multiple sclerosis. Do the right thing and give us Tysabri back now until something better comes along.

Thank you.

MS. FUQUAY: My name is Carol Keller Fuquay. I have had primary progressive MS for over

30 years. It is the most severe form of the disease, and there are no disease-modifying drugs at all to treat it.

I am speaking to you on video because it is difficult for me to travel. I have been in a wheelchair since 1995, and in 2001, I lost function in my right hand. My disease was moving quickly, and in 2004, I became a full-fledged quadriplegic.

I had two Tysabri infusions when the drug was available, and I feel that it helped me. I can still speak and swallow, and I hope Tysabri will be available soon, so that I have the best possible chance to retain these valuable functions.

Please bring Tysabri back, so that it will be available for all who need it.

Thank you for your valuable time.

MR. RICHARDSON: My name is Charlie Richardson. For full disclosure, I have absolutely no financial interest in any pharmaceutical company including the ones involved here.

I was diagnosed in 1988. I have had a relapsing and progressive course ever since then.

I have been in a wheelchair for about three years. I am sort of a classic non-responder. I have gone through therapy with all the popular drugs.

Betaseron treatments produced nothing but bad side reactions, spiking liver enzymes and continued relapses. Avonex, the persistent flu symptoms and chemical depression was too much to handle, even with single dose and double dose both tried.

Mitoxantrone, and multiple steroid treatments have given me incredible osteoporosis that I now have to treat with parathyroid hormone injections. I tried IVIG and it gave me an anaphylactic reaction on the second dose.

Nothing has stopped the relapsing and the progression.

I may be stable today, but as you can see, I am a Kurtzke 8, I don't want to become a Kurtzke 9, and what I would like to do is to have all the options on the table. Let my neurologist and I decide what the risk and benefit ratios are. It may turn out that Tysabri has limits to its

duration of use where recommendation is to get one dose a year. More experience is necessary in order to be able to determine that.

MS is not a monolithic disease. I would like to advocate with the people, the researchers that are here, that there is some effort being made to determine what the subgroups are and responders and non-responders to MS drugs.

I believe that as a biostatistician that you can certainly stratify by HLA markers and by MRI type whether you have T1-hypointense gadolinium enhancing lesions. You certainly ought to be able to stratify the data in order to be able to get more information about which patient subgroups respond to these drugs and which ones don't.

In my biostatistic lectures, I often say and teach that, quote, "Given enough opportunity, uncommon things happen commonly, but not specifically."

There is 1 in 1,000 chance of developing MS. After winning that lottery, I am fully prepared to be one of the 999 out of the 1,000

patients who don't develop PML when taking Tysabri.

Thank you for your consideration.

MS. KUTLER: My name is Alison Kutler. I am not sponsored by any organization. I was diagnosed with MS almost 12 years ago at the age of 23. I have relapsing-remitting MS, which manifests in intermittent exacerbations and a wide array of baseline symptoms which have increased significantly over time.

I am an attorney at a large law firm, which sometimes requires long hours. I also exercise intensely six days per week, and I am an avid tennis player. I maintain an active social life and travel frequently for both business and pleasure, and I serve on the board and work daily to expand a national nonprofit organization which provides recreational opportunities to severely disabled children.

My days begin at 5:00 a.m. and oftentimes run well into the evening as I try to balance the many things on my plate. I participated in the Tysabri combination trial. As you are aware, the

first phase was complete after 26 months, and the second phase was open-label with the option to discontinue Avonex, which I did.

I was on Tysabri alone for five months before the drug was withdrawn. I started taking interferons nine years ago and have remained on the therapy without any breaks beyond the five months of the clinical trial.

Although I am a big believer in the interferons positive impact in limiting my exacerbations and slowing my disease progression, it has resulted in a significant decrease in my quality of life as I have severe side effects which last for 48 hours each week.

The challenges presented by being sick two days out of every week, but continuing to lead an active and productive life are great. Imagine having one chance at a meeting with a member of Congress to advocate your client's position with a burning fever, or attending your father's surprise 65th birthday party with a headache so bad you cannot even see straight, or playing a big doubles

match with aches and chills throughout your body.

During the five months that I was on Tysabri alone, I felt terrific. My baseline symptoms all but disappeared, and I did not have any exacerbations, and I had two days of each week returned to my life.

I also had the comfort of knowing that I was on a drug that is profoundly more effective than any of the other medicines available. It was an amazing five months in all respects.

I would like to commend the FDA for its quick action and would urge the committee to make the recommendation to bring Tysabri back to the marketplace. I believe that patients, in conjunction with their doctor, should be given the opportunity to conduct a risk-benefit analysis for their individual situation.

I have closely reviewed the available data over the past year, as well as the recently released reports in the New England Journal of medicine, which clearly suggest to me that Tysabri is an incredibly effective drug and the risk is

manageable at this time.

There will be a growing body of knowledge regarding the drug's effectiveness and the potential causes of PML, and my ongoing decision-making process will continue to take this new information into account.

I would also urge the committee to make Tysabri available to newly diagnosed patients and others, such as myself, who have worked hard over time to limit disease progression. I think it would be the absolute wrong approach to make Tysabri only available as a last resort to patients who have not had success with other treatments and who have more severe progression.

The best advantage to Tysabri is that it may be able to slow disease progression to prevent thousands of patients from developing more severe and debilitating cases of MS that will diminish their abilities to be healthy and productive members of society.

Thank you for the opportunity to testify.

MRS. MILLER: Good afternoon. Thank you

for allowing us to speak today. Neither my husband nor I have any financial interest in, nor have we received any financial help in being here.

My name is Karen Miller. I have multiple sclerosis. What you should also know about me is that I do not take risks easily. I floss daily, I buy products with the Consumer Reports Seal of Approval. I intentionally overpay my estimated taxes. I drink milk only after double-checking the sell by date. And I want to take Tysabri again.

I would prefer not to risk coming here to speak publicly. I would prefer not to risk being in a drug trial with--and I quote from the standard consent form--"Risk including the possibility of death and side effects not currently known."

I would prefer not to risk having PML. So, why, in order to speak here for two and a half minutes, would I spend three days resting, have my husband work on my muscles and tendons from 3:00 a.m. to 7:00 a.m. this morning, and risk the next weeks bedridden?

Why, on November 4th, 1997, did I consent

to be the 32nd human being to participate in the early Phase II trial for what was then called the Antegren?

Why, on February 28th, 2005, did I spend $15,000 from my savings to buy bottles of a drug that was being removed from the market?

So, why would I take Tysabri and why would I be here today? To help the medical science of multiple sclerosis, to aid the MS population, to have a chance to teach legal ethics again, to take a shower without anybody nearby in case I fall, to swallow confident that I will not choke on my own saliva, to read and to remember, to feel my niece's hug.

Yes, there is risk, but with the medical information from my wise and caring neurologist, Dr. William Sheremata, and with the support of my husband and family, with prayer, I took Tysabri in 1997 and again in 2004, 2005, and I will do everything I possibly can for those who want to, and for myself, to have the chance to take it again.

Off Tysabri, on a good day, I am a 5.5 on the disability scale, on my crutches for about 10 feet, facing chemotherapy.

On Tysabri, it's a whole new day. I am a 1.5 on the EDSS scale. I have been on my bike for 10 miles facing the road ahead.

MR. MILLER: My name is David Miller. For the last eight years I have looked at Tysabri through three different lenses: as a former business executive, now as a pastor, a theologian, and a Professor of Business Ethics at Yale Divinity School and Yale School of Management, and most importantly, as the husband and caregiver of a woman with MS.

As a former business person, I want companies to develop and make a good profit. As a pastor, a theologian, and an ethicist, I raise questions of justice, compassion, and integrity.

Finally, as a husband of 26 years, and now a caregiver, every day my wife is without Tysabri I see her ability to function running out like sand granules in an hourglass. Without Tysabri, she is

at greater risk of ending up in a wheelchair and becoming a cognitive shell of the women she once was. This is real risk.

I have this image. I enter an old-fashioned bank and walk up to the counter. Behind the inch-thick bullet glass stands a doctor in a white lab coat. In front of him is a small glass vial of Tysabri. The doctor does nothing. I shout, asking for the Tysabri. "I will pay anything," I weep. He does nothing. I am not sure if he can hear me. I pound against the glass, trying to get it to break to get at the vial. Of course, the glass window is bulletproof and the shield easily withstands my blows. But finally, the doctor moves and reaches for the vial, and the question is will be break through the glass barrier or will he turn away.

Let me show you another piece of glass, this small, triangle glass was once part of the North Tower of the World Trade Center in New York. I had the privilege to serve as a chaplain at Ground Zero for nine months.

Early one morning as we left the pit to go to the morgue, a fireman gave this chard of glass, this once clear, strong, impenetrable glass. Imagine people like you and me, that morning peacefully looking out their window, out that glass. Suddenly the planes hit and this glass shattered as did their lives.

I am reminded by these images that nothing in life is fully safe or 100 percent risk-free. Not the bulletproof windows in an old bank, not the impenetrable glass from the North Tower, and not even exciting new advances in medicine.

Too often all we do is sweep up the broken glass of our life, but today, you, you have the rare privilege to break through a barrier for the good, and restore thereby the shattered chards of our lives - not just for my wife, but also for the countless others impacted by this invidious disease.

Please return Tysabri to the market.

I thank you.

MS. SALES: Hi. My name is Barbara Sales.

I am from Raleigh, North Carolina. I have no affiliation with any company. I am here on my own behalf.

I was diagnosed with relapsed-remitting MS in March of 2000. I am a pediatric nurse and was able to work until February of 2003. At that point, my most significant symptoms were extreme fatigue and migraine headaches for three years.

I had tried numerous prescription and over-the-counter medications with no relief. I even went as far as having Botox injections and sinus surgery. I participated in a double-blind drug study starting August 25th, 2003, and continued on Tysabri with my daily injections of Copaxone until the Tysabri was taken off the market. My last dose was on February 21st, 2005.

I found out I was on the Tysabri during the study, after the drug was pulled from the market. I had done very well on the Tysabri with no side effects or exacerbations.

From August 25th, 2003, until February 21st, 2005, while I was on the Tysabri, I had an

average of 5.3 headaches per month over 19 months compared to daily headaches before that, and the fatigue was noticeably improved.

Since stopping the Tysabri, there has been an increase in my headaches and fatigue. The headaches have increased to 6.6 per month, and I now have daily headaches continuously since December of 2005.

I am hopeful that all we learn from new medications, there will be a cure in my lifetime, and I am requesting that Tysabri be brought back on the market and let the patient and their physician decide if this drug is the drug of choice in treating their MS.

Thank you.

MS. SMITH: Good afternoon. My name is Heather Smith. I am 36 years old and live in Indiana. I was diagnosed with MS in 1998. In full disclosure, I bought 100 shares of Biogen stock after realizing that Tysabri was a miracle drug. I also provide my views as an MS patient to Biogen on an advisory panel as a volunteer.

Today, you will hear requests, such as please return Tysabri to MS patients, let patients evaluate their own risk versus quality of life.

I, too, am motivated by these requests and bring them to you as my own, but as I sit here, because I cannot stand for the duration of my allotted time, I am motivated by other requests that I hear every day, requests, such as "You dance with me, mamma", "You chase me now, mamma", "You carry me, please."

These requests from my son, Ezra, that I cannot fulfill are the key to my risk-benefit equation. In the five short years since my diagnosis, I became disabled. I struggle to walk with the help of a walker. I am constantly fatigued and I am incontinent.

I have taken Avonex and Rebif while watching my disease progress. These drugs were obviously failing me, yet, out of fear and lack of alternatives, I continued these shots, waiting for a new choice.

That choice came in January of '05, when I

received my first infusion of Tysabri. After only one dose, I felt that Tysabri was a miracle for me. I was able to make outings on my own. My mobility drastically improved, and I transitioned from my walker back to using a cane.

The best reward was that I had more energy to spend with my son. By my second infusion, in February of '05, I started to focus on my future. I no longer had to budget my energy and choose between playing with Ezra or taking a shower. I could freely enjoy each moment of his life with a renewed hope.

On March 1st of '05, my hopes vanished and my MS has continued to progress. Interferons were not helping me, so I began taking Copaxone. I am no longer able to drive, I cannot go anywhere unassisted.

With all this considered, my risk-benefit analysis is quite clear. I know Tysabri worked for me when all other MS drugs failed. Each MS patient has the right to make an informed choice and create their own risk-benefit analysis. Each patient will

have a different equation and a different answer at different stages of their life.

It is easy for me to see that five years ago, I would not have taken Tysabri. I would have, however, lived with a greater peace of mind knowing that there was another choice available for me when I was ready and my need for benefits outweighed the risks.

I may never be able to carry my son, Ezra, or chase him, or dance with him, but he deserves a mom that is as healthy as possible. Each day without Tysabri is a day without hope, a day closer to my permanent disability.

DR. WADE: Good afternoon. I would like to thank the committee for allowing me to speak today. I have a consulting agreement and speak on a speakers program for Biogen Idec. I speak for Serono. I speak for the makers of Copaxone, Teva, and I also speak for Berlex.

I have approximately 150 MS patients that I follow in my office. In the fall of '05, I began to treat MS patients with Tysabri and treated about

15 patients. My patients found the medicine very, very effective. I have one patient that found she was able to get up and clean her house for the first time in four years. She can't take any of the interferons, she has depression, and she has skin reactions to Copaxone therapy.

With the withdrawal of this medication from the market, there was a significant amount of despair in my patients. They again had to live more with the fear of the next exacerbation, about getting worse on this disease.

I live with the same fear. I had optic neuritis when I was in college. I developed intranuclear ophthalmic plegia, had double vision in medical school, and was diagnosed with multiple sclerosis.

I was treated a little bit of low-dose prednisone, but it didn't do much, but I did recover enough to complete medical school and started internal medicine training. During that time, I had a significant exacerbation where I couldn't walk for a month. I was home in bed.

I recovered, finished my medicine training, and went on to training in Neurology. In Neurology, I had another significant exacerbation and back home in bed, but took intravenous Solu-Medrol and got better in a week.

I completed my training and started in practice in Hartford, Connecticut in 1990. I have had several exacerbations over the time. One in the mid-1990s left me so that it wasn't all better. I finally took my head out of the sand and said I might as well take one of these medicines.

I took a daily injection medication because it seemed easiest. I found after taking that medicine for about a year and a half I had another attack, and at the end of the month, there was about 10 doses left in the refrigerator, because taking a shot every day reminds me I am sick every day, and I try to deny being sick.

I switched to weekly interferon injections and have taken that medicine on a regular basis. I have had one attack in the past four years.

Unfortunately, I have flu-like reactions

for two to three days after every injection. I am still not feeling well today. I take the injections on Sunday.

When Tysabri came out, I took three doses of the medication and then it was withdrawn from the market. I am back on weekly interferon therapy, back having flu-like reactions. My patients and I live in fear of the next attack, live in fear of losing my ability to help my patients, to be with my family.

I understand there is a risk to taking Tysabri, but there is a real risk to not taking it, having more attacks, and getting worse and worse and worse and worse.

I have a great deal of empathy for all the patients that have spoken here today. I understand how they feel. I am asking this committee to allow me to treat my patients with this very, very effective therapy.

Thank you.

MS. GREENFIELD: My name is Audrey Greenfield and I am 49 years old. I have no ties,

financial or otherwise, to either Elan or Biogen Idec.

I was the girl who had everything - ivy league education, successful career as a real estate partner in a prestigious law firm, beautiful family, and multiple sclerosis.

This insidious disease that progresses daily has robbed me of almost everything I once had. Even my choice for treatment has been taken away from me. I am appearing here today as my own advocate to have my right of choice restored to me.

I have always been proactive when it came to deciding on a course of treatment for my MS. I have tried all available treatments - Novantrone, Cytoxan, cladribine, methotrexate, steroids, IVIG, the ABC drugs, and Rebif.

With each of these treatments, my doctor required me to have monthly blood tests, periodic liver and kidney function tests, EKGs, and MRIs. Unfortunately, the side effects with each treatment were debilitating, and for what. There was not one bit of improvement in my level of disability or in

the progression of my disease.

Then, I heard about Tysabri. I discussed it with my doctor, who said the drug was well tolerated in clinical trials. In January 2005, my health insurance provider pre-approved payment for 12 treatments of Tysabri. I had my first and only infusion in February 2005. Then, the drug was pulled from the market.

I had no adverse reactions or side effects. I was even able to ride the bus home on my own after treatment. That alone was a huge step forward for me in this disease.

It has been over a year now and I haven't had any treatments of any kind because nothing has worked for me. I feel as if I am losing my battle against MS. I have no other options. Without Tysabri I don't even have hope.

I have no illusions. Tysabri was never marketed or hailed as a cure for MS, however, the clinical trials proved conclusively that the drug halted the progression of the disease and, in some cases, lessened the degree of disability.

It is wrong to think that MS is not a life-threatening disease. My quality of life is threatened every day that I go without a treatment that I deserve.

My daughter is graduating from high school in June. Before I know it, she will be getting married.

I would like the chance to halt the progression of my disease and walk down the aisle with her. Please allow me the chance to see if Tysabri can make my dream come true.

MR. FRANKLIN: Good afternoon and thank you for the very important work you are doing on this subject today.

I am Doug Franklin. I am the President and CEO of the Multiple Sclerosis Association of America.

We were founded in 1970. For 35 years, we have had only one goal, and that is to help people deal with this dreaded disease. All of our efforts are aimed at the patient and their care partners. That is all we do.

Our mission is to enrich the quality of life for individuals with MS. We receive funding support for some of our services in public education outreach from pharmaceutical companies. We support the FDA position that all currently approved MS drugs have value for MS patients.

We speak to all of our patients about all of the therapies. Informed consumer consent is our objective. The funding we receive from pharmaceutical companies makes up less than 10 percent of our total funding. We receive no government funding. The remaining 90 percent comes from the public through donations, through gifts, through special event fund-raising.

We remain a strong neutral advocate for patient education, and we are very pleased to be able to be here today to respond, to be able to share our views on the reintroduction of the drug Tysabri.

When I say "we," I am speaking for MSAA. I am speaking for the charity, our Healthcare Advisory Council, our board of directors, and in

particular, our Chief Medical Officer, Dr. Jack Burkes, who had to leave today.

Dr. Burkes is a clinical Professor of Medicine, of Neurology, at the University of Nevada, School of Medicine. He is also a member of the Medical Advisory Board of the National MS Society. He has edited two textbooks on multiple sclerosis, and in the 1970s, he established the Rocky Mountain MS Center in Colorado, one of the nation's first comprehensive MS centers.

His input into this brief today represents MSAA's thoughts. He believes people's lives are at stake and he has been serving MS patients for more than 30 years.

We all know this drug was approved for the treatment of relapsing-remitting MS and released into the marketplace in November of 2004. In our winter edition of our quarterly newsletter, The Motivator, Dr. Burkes had the following to say in the Ask the Doctor section.

He said discussing the role of Tysabri with your doctor is an excellent idea. Only one

year data is available on adding Tysabri to Avonex and no data is available for combining Tysabri with Betaseron, Copaxone, or Rebif.

Tysabri plus Avonex was more effective than Avonex plus placebo at one year in a group of patients on Avonex who were having attacks or new MRI activity. In my opinion, this is a very selected group of patients, may not be relevant to Copaxone or high-dosed interferons. More studies are needed before the effectiveness and/or potential complications of combination therapy using Tysabri are known.

Two months later, the drug was voluntarily suspended, and based on reports of the dramatic events that we are all well aware of, including the events in Anita Smith's death.

The MSAA welcomes the development of newer and more effective medications to treat MS, but we believe great care must be exercised when bringing a new drug with potential serious side effects to market.

In our experience, most of our MS patients

do very well on currently available medications with minimal side effects in the long run especially if started on treatment early in their disease course.

As a charity, we struggle with the concept of a possible black box warning label sufficing as a caution to physicians and patients. Caveat emptor, buyer beware seems to run contrary to sound medical treatment based on first do no harm principles.

We strongly believe that patient safety must be a primary consideration as the FDA proceeds with the process of analyzing all of the available data. If Tysabri is reintroduced, precautions should be taken to protect the patient until long-term safety can be evaluated.

These include strong scientifically-based protocols to ensure the patient's understanding of the treatments versus the risk-benefits. This can be problematic.

Can this be assured if more than 50 percent of patients have cognitive dysfunction,

which includes reduced executive function, which may make it difficult to completely understand the consequences of decisions?

Two issues predominant are patients' perspectives on Tysabri, the relative strength of the drug over current treatments and toxicity. Many patients are convinced that Tysabri is twice as effective as any other treatment available today.

For example, a website mspatientsforchoice.org has developed a positive portrait of the benefits of Tysabri over currently available treatments. Does the FDA agree with these conclusions? This type of information will likely become accepted by MS patients who are always looking for the cure.

We need the FDA's position on relative efficacy. Who more credible than the FDA to address these issues?

Also, the MS patient's risk of PML are perceived as rare. Counter to this, we hear concerns of 1 in 1,000 death rates associated with

this. What is the truth? Are there potential risks other than PML, cancers or infections? Can PML be detected before damaging the brain? Dr. Burkes insists that by the time PML is detected, every single cell in the brain has been affected.

MS. CANAVAN: Hello. My name is Marcy Canavan. I have no ties, financial or otherwise, to any drug company.

I led a pretty charmed life up until a few years ago. Then, one day MS hit me with a bang. Within two months of the initial attack, I couldn't walk across my yard. In less than a year I was using a scooter, retired on disability, and drove my car with hand controls.

I have taken Solu-Medrol many, many times, Betaseron, Copaxone, methotrexate, and finally, Novantrone. That was the only drug that helped. The fast downhill spiral stopped, and I actually improved, but I have exhausted my lifetime limit.

The downhill spiral is starting again. I risked congestive heart failure and leukemia to take the Novantrone. Before the Novantrone, aside

from the physical problems, I had very serious cognitive difficulties. I stopped reading anything because by sentence two, I couldn't remember what sentence one said anymore.

My memory disappeared. I found myself forgetting where I was, where I was going, and how to get where I had been on decades. I can't tell you how many times I just sat on the beltway lost. Simple words eluded me. My IQ dropped 25 points, and that was before I hit bottom.

My reason for being here today is simple. I have no treatment options left, and at the rate I am losing ground again, in a few years, my life won't be worth living.

I am willing to take a chance on a drug that shows as much promise as Tysabri, and according to the data you have in front of you, it is much safer than the one I have already taken anyway.

When I was a kid, I had my life saved twice by drugs, once when I had blood poisoning and once with pneumonia. Those same two drugs almost

killed me as an adult, when I had full-blown anaphylactic shock attacks after taking them.

Am I mad because the FDA approved a drug that nearly killed me? No. If you hadn't approved them, I wouldn't be here at all today anyway.

The risk of death is not a reason to deny a desperately needed drug. What you have to do is weigh the risk of the death against the need for the drug.

I want to see my grandson grow up. I would rather be able to enjoy things now and take a chance that I won't live that long than miss enjoying life and live to be 100. Quality is important, and it is more important than quantity. That applies to lots of things, but especially to life.

I ask you to approve Tysabri for me, for the other people here, but even more for my daughter, Emily, who has already spoken to you today. Compared to her, I still lead a charmed life. I was 46 when MS hit me. She was 24. All of her plans and hopes for a life are in shambles

thanks to MS.

Several days a week, she is in bed all day because of intractable pain. She has all the same problems I do, and she is only 27 years old. I had a normal life for 25 years after finishing school. She had a normal one for 4 months. I want Tysabri badly, but for my baby, I want it desperately.

You have the power to give her a chance, and I would ask you to do it. When you make your decision, please think about how you would feel if Emily was your child.

DR. KIEBURTZ: I thank all the speakers who have spoken so far. We are going to take a 15-minute break before we go on with the rest of the speakers.

We will reconvene right at 3 o'clock.

[Break.]

DR. KIEBURTZ: We will begin the open public hearing now, please.

MR. CROYDON: Good afternoon. My name is Stan Croydon. No one has paid for me to be here today, and I have no financial interests in any

drug companies. They, however, have a whole lot of my money and a big interest in me keeping using their medications.

Before I left home this morning, my wife said to me, "Why are you speaking today? You never took that drug." I said, "You are right, but if someday I or my doctors think I should be taking it, I want that option. I want people to know that we are the ones who ought to making the decisions on the pros and cons of medication."

I have had multiple sclerosis symptoms since 1967. For the mathematically challenged, that is 39 years, but it took me eight years to get an accurate diagnosis. Then, it was one made by a psychiatrist who I was seeing. I had gone to my regular doctor one visit, and said give me the names of a good psychiatrist and a good neurologist. One of those two has to have the answer to what is wrong with me.

Guess what. He gave me the name of his psychiatrist.

Well, back in 1975, steroids were about

the only thing available to help a person with MS, and when I took mine for the first time, I felt like I was walking around with my finger plugged into a light socket. I also began to worry that I might wind up pumping iron or even worse by the time I got finished taking those drugs. Ever since I have tried to avoid those.

It was a decade ago I first learned how to give myself a daily subcutaneous shot of Copaxone, but when my insurance company looked at the fine print of what my doctor had written, they realize I had the wrong kind of MS to be taking that drug.

Consequently, I had to switch to Avonex three months later, and instead of giving me those shots, I decided to let the nurses at work give me my weekly intramuscular injections for the next seven years.

Today, I am using Rebif at the recommendation of another MS patient who is a nurse and an expert in her field. She saw improvement in her condition after taking that subcutaneous medication, and my doctor concurred with my

decision to change.

I like to think of myself as a well educated medication consumer. I ask my doctor plenty of questions about the course of my MS, ask for an MRI if I feel I need it, and he thinks I am getting better, and if I hear about new therapies, I go and investigate them.

I even read the sheets you get at the pharmacy that come with your medications. I have been doing that ever since one neurologist prescribed an antidepressant for me when I told him I was depressed. I called him back three days later and said, "I have stopped your drug." I said, "When I first came to see you, I was depressed, now, I am impotent, and frankly, I would rather be depressed."

[Laughter.]

MS. TIBURTIUS: Good afternoon. My name is Bartira. I was diagnosed with a mass in March 2001. I was on the Tysabri starting combination with Avonex for 28 months. In the past, I did some educational programs coordinated by Biogen. The

company paid for my expenses and my time. I spoke about my experience with MS, not about Biogen drugs. Biogen did not encourage or pay for me to be here today.

I am a language teacher and I need to be alert all the time, but four years ago, I had two very bad relapses that put me in the hospital. I had all the symptoms in the book including loss of vision, and the worst of all, I had cognition problem.

I can handle everything even a wheelchair, if I have to, but I cannot handle to lose the ability of thinking, and I had some very bad cognition problem.

I was switching letters, I had difficulty remembering simple words. I was getting lost in conversation. I used to wake up in the morning and not having a clue where I was. I was spacing out. I didn't know if I was dreaming or it was a reality. I was confused between where reality and a dream. I was like a nightmare.

When I start on the Tysabri study, it was

a double-blinded study, but it seems the first infusion, I was so sure that I was getting the real thing, not the placebo because the way I was feeling. Little by little I started to feel healthier and healthier.

The fatigue was gone, I had my brain back 100 percent, but a couple months ago, I started to have problems again. The fatigue is back, my left arm is numb, my face is numb, and again sometimes I cannot remember simple words.

I am very scared. I am a teacher. I cannot afford to lose the ability of thinking again. I don't want to go back there. I want to be able to walk, to speak, eat and drink, and the most important, I want to be able to think. I want to know when I am dreaming or when I am awake.

I do understand that there is a small risk with Tysabri, but the risk that I am willing to take. If someone tells me that Tysabri is going to take 10 years off of my life, but I will have the quality of life I had a year ago when I was in the study, I would take it.

If I have Tysabri back, I will have life. If I don't, I don't even know if I am going to have a future.

Thank you for listening.

DR. GODEC: I am Dr. Mark Godec, a physician in private practice in the Washington, D.C. area. I have no financial interest in Biogen and Elan, and I have not received financial support from any competing companies.

I would like to thank the committee for the opportunity to speak today.

Anita Smith was a healthy, active woman until her final months and untimely death from PML arising from Tysabri therapy. She was the wife of Walter Smith and the mother of two children.

She worked daily in her family's business and lived a full life without restriction or disability. At the request of Walter Smith, I reviewed Anita Smith's medical records. She was in good health until June 1999, when she developed minimal neurological symptoms that were eventually attributed to multiple sclerosis.

However, the medical evaluation that led to the diagnosis of MS was incomplete and produced results that were not diagnostic of MS. At most, only her presenting episode provided objective clinical evidence of a CNS lesion that might be due to MS.

An MRI of her brain revealed only a small number of nonspecific lesions that did not enhance with gadolinium. Her CSF never showed oligoclonal bands that are characteristic of MS.

EP studies were not performed and she was not evaluated by a neuro-ophthalmologist. Her symptoms were mild and her EDSS score remained between zero and 2, indicating that she had no significant disability. At most, she should have been considered to have possible MS.

Despite a questionable diagnosis of MS, Biogen and Elan enrolled Ms. Smith into the Sentinel study in April 2002. It is likely Biogen and Elan offered substantial monetary awards to physicians for each patient they enrolled in the study.

Biogen and Elan reported in the New England Journal of Medicine that Ms. Smith's enrollment MRI showed nine lesions consistent with MS to justify her enrollment in the study. This enrollment MRI actually shows only four or five nonspecific lesions per Dr. Greg Shoukimas, who you heard earlier today.

In November 2004, Ms. Smith developed much more serious neurological signs and symptoms. Tysabri was eventually discontinued, but her condition continued to deteriorate.

Anita Smith tragically died on February 24th, 2005, from PML at the age of 46. Neuropathological examination of her brain and spinal cord revealed only PML lesions, and no MS plaques, verifying that she did not have MS.

Had Biogen and Elan not inappropriately enrolled her in the Sentinel study, she would be alive today.

Ms. Smith's case dramatically demonstrates the danger of Tysabri therapy. As a physician, I would like to see effective and safe drugs

available to all MS patients. Unfortunately, Tysabri is not the miracle drug for MS that everyone is hoping for. Returning Tysabri to the market will only put more people's lives in jeopardy.

I strongly encourage this committee to carefully consider the risk that Tysabri poses to the public. Despite the recent clearance Tysabri received for human clinical trials, I strongly believe that Biogen and Elan should be required to conduct additional animal studies to fully define Tysabri's safety before it is again given to humans.

Thank you very much.

MS. ROGERS: Hello. Thank you for the opportunity to testify before you today. My name is Martha Rogers and I just turned 53 years old. I am a wife, a mother of two teenage daughters, and a teacher working 30 hours a week, and I have MS.

I was once asked to speak about Avonex and was paid $300, but I am here today on my own to speak about my experiences with Tysabri. My world

as I knew it changed two years ago, when I was 50, and initially diagnosed with MS.

At that time, I was happy, working full time, getting into shape and feeling great. Every day was a joy to live, and I was thankful. I was diagnosed in February 2004, after an attack of optic neuritis, which my doctor first thought was a brain tumor.

An MRI showed my condition to be multiple sclerosis. My neurologist allowed me to choose Avonex, because I felt that that was the best disease-altering drug for me. At that time, I was also encouraged about the news of future release of Tysabri. I think they called it Antegren at that time.

My first relapse occurred in the spring of 2004. I was one of the very first patients in the Norfolk area to receive an infusion of Tysabri in January 2005. I was so excited about going on this drug, and I knew it was so important that I was able to get two local TV stations to film me getting my infusion.

I received two infusions and felt fantastic within 24 hours of my infusion. I knew the drug was working. I knew that I could face any obstacle with this disease as long as I had my Tysabri. My fatigue went away, I felt steadier on my feet, and my concentration improved.

Since February 2005, when the drug was pulled from the market, my MS has progressed and I have had three more relapses. My symptoms have returned and I have gone on steroid therapy. I have had to adjust my life in many ways in order to manage the various symptoms of this devastating and unpredictable disease.

My particular symptoms include balance and gait issues, constant fatigue, memory and concentration problems, impaired vision, and depression. I have also had to cut back on my hours at work, which has been causing my family financial difficulties.

The progression of my disease has consumed my thoughts, challenging me to overcome my anger of having MS.

I urge you to consider the results, the clinical results proving that Tysabri can have a profound ability to stop MS. I believe that this drug can prevent my disease from getting any worse. It's all about maintaining a quality of life.

I believe Tysabri is the best drug available today for people like me.

Thank you.

MR. KELLER: Thank you for your time today. I have received no financial support or interest in any of these pharmaceutical companies in question today or competitors.

My name is Larry Keller and I would like to tell you about my sister, Carol Keller Fuquay. For about 30 years, Carol has had MS, the most progressive kind of MS. We witnessed her testimony during the second video here earlier before the break.

Being her younger brother, I have always looked up to Carol as the model of success. She completed her Bachelor's Degree after only three years of study, followed with a Master's in

computer science, and became one of the first female project engineers at Hewlett-Packard in the early 1970s.

Carol has always been at the forefront of technology, has been blessed with a supportive family, but at the point in her business and family careers, where she should have been most active, she noticed the muscles in her legs weren't responding the way she expected. Yes, she was experiencing the onset of MS.

The reason I tell you this story is that my sister, after having poured her energies into a successful career, redirected them to find out everything she could about this debilitating disease. At that time, no one even knew the cause of MS.

Over the next three decades, she learned everything she could about the current research into the disease, she came to know many of the nation's leading MS researchers, neurologists, and immunologists.

She learned, as they discovered, the

causes of the disease, but the cure remained elusive. Over the last 15 years, she tried every imaginable treatment, even a hyperbaric chamber, all in an effort to arrest the progression of her MS. None of these were truly successful.

Over time, she lost the use of her legs, then, her right arm and hand, then, finally, her left. If only she could stabilize the progression of her MS. She fears the next step is that she will lose the ability to speak and swallow. You can imagine her long-term prognosis.

However, during this slow decline, she decided to share this knowledge she acquired on MS and help others who have been unable to converse with those at the forefront of research. She decided to offer this knowledge in a book, which she published last year, "Understanding MS Builds Hope." You can imagine the difficulty she had trying to put this together in the condition that you witnessed on the video.

During her research, she became aware of the clinical trials of Tysabri, and once it was

approved for use in late 2004, she was able to receive two treatments prior to the drug's removal. As Carol has always been a close monitor of her condition, she noticed that during the year of 2005, she experienced no progression of her MS.

This is quite exceptional since she had had the most severe and progressive form. Tysabri works for my sister. It has arrested the progression of her disease.

Consider Carol's case, consider her condition, consider her prognosis. Tysabri is the only hope she has.

I ask, as my sister asks, for the committee to recommend that Tysabri be returned to the market. How fitting an end to my sister's book that not only does understanding MS build hope, but that there is real hope that we have a cure for this disease.

Thank you.

DR. SMITH: Hello. I am David Smith, Rochester, New York. I am a board-certified neurologist and neuro-ophthalmologist. I have a

private practice and care for several hundred active MS patients.

I would like to speak from my own experience to you today. I diagnosed my wife's MS 15 years ago.

When I go to the meetings, it seems like the discussion always revolves around the relative merits of the ABCR drugs, neutralizing antibodies, and things like that. When I am in the office, I am saying to a young lady, look, in order to preserve your quality of life, we have to arrest your MS, and I am thinking in my own mind that those ABCR drugs that we have are only about 30 percent effective.

Now, there is a spectrum to severity in MS. There are aggressive cases and there are mild cases. In my own experience, if you take one of the milder cases and put them on any one of the ABCR drugs, they arrest, and those people go on and live happily ever after.

But most people, I would say about 80 percent will break through and continue to

progress. What that means is that it is just a matter of a few years before those people go into a wheelchair.

So, our goal in treating relapsing-remitting MS must be to arrest, not to slow the disease. What I am suggesting is that 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-to-risk ratio here becomes enormous. Do you see what I mean?

We have never had a benefit-to-risk ratio in a drug like this before. I was talking to my wife, Mary, about four years ago. She was having a crescendo pattern of attacks, three attacks a year, and she was on steroids all the time. I said, well, there is this new drug called CellCept out. She couldn't tolerate Imuran because of hepatotoxicity. I said it looks like it ought to work better than Imuran and safer.

So, she says, well, what do I have to lose? And I read her the riot act - lymphoma, leukemia, sepsis, all kinds of weird infections.

She says what do I have to lose, I am going into a wheelchair now, and at that time, she was talking to me about the ways that she would take her life if she went into a wheelchair.

Mary hasn't had one attack since on the CellCept. That is four years without an attack.

Thank you.

MR. BURROUGHS: I am Frank Burroughs, President of the Abigail Alliance for Better Access to Developmental Drugs. We don't take any money from the pharmaceutical industry. We represent patients who are fighting for their lives.

The Abigail Alliance paid my expenses to be here today.

Before I get to my talk, I just had one comment, and that is I am a little confused. Was Speaker No. 32 a patient advocate?

Today's issue is yet another example that patients are not being put first in the drug development process. By the way, I am sitting sideways because I can't turn my back on MS patients.

This slide illustrates that there is a 100 percent chance that multiple sclerosis patients will perish with the ship. Out of what are now thousands of patients treated in trials with Tysabri, there are still only three confirmed cases of PML.

The reports vary a bit, but there is one-tenth of 1 percent chance one of the lifeboats will sink, one of the lifeboats. Tysabri never should have been taken off the market. It was a severe overreaction to the drug safety hysteria caused by the Vioxx issues, and the overreaction by the FDA, also, the media, the FDA Advisory Committees, and certain politicians played a role.

Many thousands of MS patients have progressed and become more disabled as a result of the overreaction to these mostly false and ill-considered magnifications of drug safety concerns.

The FDA Advisory Committees have regressed from a stance that was already too cautious into an extreme harm the many to protect the very few

posture, that simply must be reversed.

The people who run the current system must realize that it should be the individual patient's decision as to whether or not they get a new therapy, such as Tysabri, having the current information about known risks/benefits.

The patients, in consultation with their physicians, should have greater control over how they fight for their lives. Ask Parkinson's patient Robert Suthers. Robert and others will tell you that MS, Parkinson's, and other illnesses can be a living death.

Let me share a huge catastrophe. Please listen to this. It was in Fortune magazine last month. Let me share a huge catastrophe due to the current system of overreaction due to our current antiquated method of statistical analysis.

Launched in 1998, RotoShield was a lifeboat for millions of children. It was virtually 100 percent effective in preventing rotovirus, a deadly diarrhea-causing virus that leads to 600,000 deaths worldwide a year, mostly in

developing countries.

Because there was a 2 chance in 10,000 that there was a bowel obstruction, the drug was pulled off the market at the urging of the FDA and the Center for Disease Control. The result of that was that there was not a new--Wyeth dropped the vaccine--there was not another vaccine on the market for six years, and 3.6 million children died worldwide.

This is what happens when government, individuals get in the way of the rights of patients and overreact to statistics. What's so incredible about the rotovirus was that they found there was a statistical error. We have seen that over and over again.

Here is vivid proof of what I am saying today, and the Abigail Alliance has been saying for over five years. Every drug the Abigail Alliance has pushed for earlier access to is now approved by the FDA. In this case, we have one, like Iressa, one that has been pulled back, that needs to be brought forward.

Let me leave you with four things that are so important. FDA and others must understand patients need to be put first. There is a difference between an MS patient, a cancer patient, Parkinson patients, and somebody with an allergy or arthritis. Contrary to what an FDA Associate Commissioner said to me in a meeting, there is clinical pressures involved in this.

Thank you very much.

MR. MILTON: My name is Clive Milton. I represent my wife who has had MS for eight years, cannot be here today. She was part of the Phase III placebo-controlled, double-blind study for Tysabri in the Affirm group.

My wife had a very serious side effect, which could probably have been avoided had a series of simple allergy tests been performed prior to acceptance in the study.

We discovered after she was unblinded from the study, and without much help from Yale University School of Medicine or Biogen, that she was allergic to polysorbate 80, an ingredient that

is used in the delivery solution.

She is now hypersensitive to anything that contains polysorbate, and she has been suffering from intense itching, severe rash over her arms, back, and scalp, which results in bleeding and loss of sleep, loss of work, and quality of life for the past three years since she was involved in the study.

There is no cure to this type of hypersensitivity and no one knows the effect of the additional illness on her MS.

No one at the Yale University School of Medicine or Biogen cared to investigate or help her once she was unblinded from the study. Where was the protection, care, and treatment that Biogen, Yale University School of Medicine, and New Haven Hospital, and the IRB promised to give her?

I have several questions. Why has the FDA allowed polysorbate 80 to be used in an I.V. solution especially as it is not recommended as an injectable by at least one of the manufacturers?

Polysorbate is also used in Avonex, also

made by Biogen, and as a result, my wife cannot use this or any other MS medication that may contain esters of any kind because of the likelihood of serious adverse reactions.

All the information issued by the FDA and Biogen seems to be looking at the study drug Tysabri alone or with Avonex, but could it be possible that the culprit that forced the closure of the Sentinel study two weeks before the conclusion of the Phase III stage, and the issues found in the Affirm study is not caused by either drug? Has any testing or research been conducted to rule out the possibility that one or more of the constituent components used in the delivery solution may be the problem?

Why did Biogen get to review its own data when Tysabri was removed from the market? There appears to be a slight conflict of interest here. The FDA should mandate the use of an independent body to review such data to avoid potential cover-ups or bias in reporting and findings.

MR. KAHN: I have made many public

presentations during my 30-year career as a General Electric executive, and in the last 20 years, as an active participant in my local community. Not one of these presentations was as important to me personally as this one is today.

I am here in my role as the father of a daughter whose life is at stake. Without access to Tysabri, her quality of life is rapidly declining.

I do not have a relationship or financial interest with any company involved in this issue, nor have I accepted any financial help from any interested party. I am here solely as a father.

In 1996, I went with my daughter for the first time in 30 years to a doctor. When the neurologist told us that she had MS, I had to ask him what MS was, because I knew so little about the disease.

In nine years, I have learned a considerable amount about MS. I have educated myself through research, listened to dozens of MS doctors, attended over 100 MS meetings with expert speakers, I met with many other MS sufferers and

caregivers. I have learned much about MS from riding the roller coaster of the disease along with my daughter.

Eight year ago, I accompanied my daughter as she walked with great difficulty into a single infusion, early Phase II trial for Tysabri, and I was heartened when I saw her walk briskly as she left the infusion trial.

When my daughter took Tysabri, she had MS, but she was remarkably stronger and had an improved quality of life. My daughter is unable to tolerate the other standard therapies, and therefore, she has no other viable treatment option.

When Tysabri has been unavailable, I have witnessed her painful suffering and have helped to move her stuck toes, feet, arms, and fingers, and helped her eat and walk just as I did when she was a baby. Certainly, I do not need to tell you there is not a cure for MS. If there were, we would not be here today. Until there is a cure, patients have to choose what treatments, if any, to take to try to alleviate the symptoms and to stem the

course of their diseases.

If there were an effective drug that was risk-free, then, we would also not need to be here today. I understand that your role as the FDA Advisory Committee is to ascertain the benefits and risks of a drug, and to communicate that valuable information to doctors.

This then allows the patients to receive information and advice tailored to their individual needs from their doctors, and in my daughter's case, with her permission, it enables me to be a more informed member of her consultation team.

Finally, in my role as a father, I beg you to allow those suffering from MS, and their doctors, the freedom to decide whether or not to use Tysabri.

Thank you.

MR. CALFEE: I am John Calfee, an economist at the American Enterprise Institute in Washington, D.C., an independent research organization that receives contributions from many sources including pharmaceutical firms. My views

are my own and do not necessarily represent those of my employer or anyone else.

I wish to summarize the results of a telephone survey of a representative sample of patients who see neurologists for treatment of relapsing-remitting MS.

The survey was sponsored by Biogen Idec. I received compensation for designing and launching the survey, but have not been compensated for analyzing the results, for writing the paper I submitted for the record, or for appearing at these hearings. Biogen Idec did not see my paper, did not review it until after it had been submitted to FDA.

Survey participants were recruited by neurologists who appeared on the American Medical Association's master list, which includes non-AMA members. The survey was conducted by Roper Public Affairs.

Briefly, here is what we found:

Respondents suffered substantial disability. Fifty-nine percent said fatigue was a

major problem, 10 percent use a wheelchair half or more of the time, one-fourth always or nearly always use a cane, crutch, or other support, and two-thirds require support at least occasionally.

Only 20 percent had not suffered relapses in the previous year. Half had suffered one or more relapses, and a quarter had suffered three or more.

Ninety-seven percent of patients were currently on drug therapy. Half had switched drugs, one-third had switched at least twice. Ninety-five percent or more thought it was very important to have new drugs that reduce the frequency of relapse and retard progression in disability.

We specifically asked about balancing risks and benefits, but we did so without referring to Tysabri. Approximately 55 percent said they would definitely or probably use a drug that significantly reduces frequency of relapse or retards progression in disability even if the drug involves a 1 in 1,000 chance of a fatal side

effect. One-third said they would definitely or probably use such a drug with a 1 in 500 chance of a fatal side effect.

We also found that willingness to tolerate risk was largely unrelated to disability levels.

Several questions asked about the roles of patients, their neurologists, and the FDA. Seventy-two percent had seen their neurologist at least four times in the previous two years. Sixty-three percent said they talk about side effect more than half the time.

Seventy-nine percent said that they and their physician were equally involved in drug decisions. Fifty-four percent agreed that the FDA should tightly control drugs with safety concerns, but 71 percent said that once the FDA has provided a warning, patients should be free to decide with their physician whether to use such drugs.

Finally, almost all patients said they would be willing to visit their neurologist more often in order to use risky drugs.

Thank you.

MR. TRIEDMAN: Thank you for the opportunity to comment on Tysabri. My name is Steven Triedman. I am from Providence, Rhode Island, and my wife and I flew down today specifically for this hearing.

We have a relapsing-remitting course of MS. I have the physical effects, and she gets to deal with everything else.

MS is an insidious disease that affects not only we, the patients, but our families, our friends, and everybody else. I have no ties to any drug companies although I am a very good customer.

I participated in the Sentinel study and was on both Tysabri and Avonex for over two years, and I continued after that. I lived a normal life to the point that if I didn't tell someone that I had MS, they didn't know. I have had MS for 11 years this month. I didn't relapse and I didn't have any adverse effects.

Since I have been off Tysabri, it has been a difficult year. I have had numerous relapses and have switched drugs as we try and deal with each

step, and I have also had steroids on a regular basis.

I am a graphic designer, so my work, it has been difficult at times because of my motor skills and some cognitive issues. This is a disease that for 10 years, we have been hearing about drugs, we haven't seen any new drugs besides the ABC drugs, so this, to us, is a breakthrough drug, and for someone with MS, four years is an eternity. It could be four years, it could be six years until we see another new drug.

I have a lot of experience with MS, as well as access to exceptional information professional resources. When I was diagnosed with MS, my uncle was a recently retired, very prominent neurologist, and I have numerous friends, doctors, and relatives in the field, and I receive superlative care I think from my MS team in Boston. In fact, selfishly, when I saw my doctor here, I said to my wife, "I think he came for me."

They are very proactive in the research. They believe in this drug, so I believe in this

drug. In addition, I chair the board of the MS Society and serve as representative on the national board, so I have been to the meetings, I have seen all of the drug things. I have not seen anything nor heard anything like Tysabri.

I was on the drug for more than two years. I will continue on the drug if I can get it, and I would like, and I wish the committee would recommend, that it be approved, because I think people that have MS need that opportunity.

It's a personal decision whether you go on the drug or not, but for those that have been on the drug, and it has been successful, it's a decision I think they would make.

Thank you very much.

DR. MOSADDEGH: We are looking for our last public hearing speaker, George Grafas, if he's in the audience. Mr. George Grafas.

DR. KIEBURTZ: While we are waiting, if he appears. I just wanted to thank all the open public hearing speakers for their frank and heartfelt comments. I don't want anyone to think

that by limiting time, we somehow limit the importance of your comments.

The committee is very grateful to everyone who made so much effort to come here and to speak. It helps us inform our deliberations of tomorrow. I apologize to those who couldn't finish their comments in the time frame allotted.

We have some time that remains on the agenda, especially while we are waiting for our last speaker. So, if the committee at this time has questions they want to address to the sponsor or to the FDA, that were left over from the morning, we can take some time to do that.

Except for the one last speaker, we will not entertain any other comments in terms of an open public hearing, and we will not begin deliberations today, as I alluded to at the beginning of the day.

Does anyone on the committee have a question that they would like to address to either the sponsor or the FDA at this point? Dr. Couch.

Questions from the Committee

DR. COUCH: Is the panel going to receive the most updated form of the RiskMAP study? There were some comments made about the slides were slightly inaccurate, there were some additional data. Are we going to get the very latest version of that by tomorrow morning?

DR. WALTON: The RiskMAP has been in discussions between the company and the agency, and what you heard were some of the intended changes, but there was not a completely coherent rewritten form of it. So, I think that we have given you the information about the initial plan and the key questions that we hope for you to be able to comment on.

DR. KIEBURTZ: It will be our job to, in the absence of a concrete document, present what we think our opinions are. Dr. Temple.

DR. TEMPLE: I actually just wondered whether there was a copy of the latest version of the checklist, which, unless I missed it, I couldn't find anywhere. Dr. Wysowski referred to having it, so she must have seen it, but I am sure

that would be at least of some help to the committee.

DR. BOZIC: I can present it in slide format.

DR. TEMPLE: Well, let me ask the committee, do you want to see it now or do you want to see that tomorrow?

DR. KIEBURTZ: You can see it tomorrow. I see a consensus nodding.

DR. KATZ: Is it possible to get hard copies for the committee just to look at this evening?

DR. BOZIC: Yes, we can, yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I would like to go back to the pathological examination of Patient 1. I would like to ask Biogen to comment on some of the questions that are being raised. I initially asked the question this morning and I would like to know if there was an independent examination of the pathology from the first patient.

DR. PANZARA: Well, Biogen Idec was not

involved in that autopsy in any way. It was actually done by Dr. DeMasters. The full description of the autopsy findings were presented in the New England Journal of Medicine, and the level of description in there is our understanding of the pathology.

DR. McARTHUR: It would seem to me absolutely critical since we are talking about decisions based on three cases of PML, only two of which were in patients with multiple sclerosis, and only one of which had autopsy confirmation, that we need to know as much as possible about the pathological findings.

I am frankly surprised with your answer.

DR. PANZARA: Again, part of the process following the diagnosis in that patient was that the autopsy was performed at the University of Colorado where the patient was seen. Biogen Idec was not actually permitted access to that information until after the publication of the articles in the New England Journal of Medicine.

Since then, the autopsy material has been

provided to Dr. Gene Major at NIH, who has performed, to my knowledge, some testing on it, and has confirmed the presence of JC virus by in-situ hybridization, so that the diagnosis in Gene Major's opinion confirms the diagnosis of PML.

DR. McARTHUR: That's not the question. The question is whether the patient had multiple sclerosis, since our entire, or at least a lot of our discussion today is on whether that case, that patient had multiple sclerosis. I am not disputing the fact that the patient had PML. I am raising the question as to whether the patient had multiple sclerosis.

DR. PANZARA: It is our understanding of the pathology report that they could not find an MS plaque in the autopsy of the brain. We do not know to what level the spinal cord was evaluated for the presence of MS plaques.

I should say that, as you saw the MRI during the open hearing, the PML developed in the region of the T2-hyperintense lesions that were seen on that MRI. Thus, the autopsy, as presented

in the New England Journal, states that they could not find it, but they conceded that the PML could have occurred in the region of MS lesions, and thus, could have obscured it.

DR. McARTHUR: Not to be argumentative, but we saw four or five tiny white matter hyperintensities. The PML lesion was almost a panhemispheric lesion, so I think it's impossible to say where that lesion initially began.

DR. PANZARA: No, I agree with you on that point. I just mean to suggest that that was a panhemispheric lesion that developed for PML, and that if there were MS lesions there, they could have been obscured by the PML lesion itself. That is again from the pathology report and from the pathologists at Colorado, who have indicated that fact to us.

DR. McARTHUR: So, the obvious next step is to examine optic nerve and spinal cord in that case.

DR. PANZARA: Again, my understanding is of the autopsy that was performed, they did not

find lesions in the--again, this is from the New England Journal of Medicine--in the optic nerve or the spinal cord, but we don't know what level of analysis was done in terms of number of sections, et cetera, in the spinal cord.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: We are going to be talking tomorrow about I guess the risk minimization plan and the early patient identification. But assuming that the system as was described is completely effective, what data are there that early detection alters PML would alter the disease course?

We are putting a lot on detecting these cases early and stopping the infusion. How do we know that that is going to alter the disease course in any way?

DR. PANZARA: The best data that exists is currently in the HIV experience, but it is not exactly analogous. The other experience is in transplantation, and the series in transplantation have been small.

There are typically case series of 25, 10

to 25 patients, and then a long list of case reports. That data suggests that when the immunosuppressant therapies are discontinued, there can be an improval in survival.

Again, the types of agents used there, obviously not natalizumab, but agents such as azathioprine, cyclosporine, in those circumstances, based on the case series that have been done, about a third of patients survive, and those that did survive, it was nearly uniformly they had a decrease in their immunosuppression.

That is really the only literature that exists in this area.

DR. KIEBURTZ: Dr. Ricaurte?

DR. RICAURTE: I was just going to take up on the point that Dr. McArthur raised. Regardless of what the outcome is, the issue seems to be did the patient have or not MS, and was she appropriately enrolled in the study, so the question I have is what will be done in the future, or was there something that should have been done in the past to guard against that, or do things

have to be changed in order to preclude an error, if it was an error, in the future.

Just comment on the issue of enrollment and ensuring that appropriate patients are selected.

DR. PANZARA: You are referring to the risk management program, or in clinical trials, in what area specifically is your question regarding?

DR. RICAURTE: Well, we don't know what the outcome of this is. In the most liberal form, I suppose it would be suppose it is approved to go on the market, how do we, as a committee, gain assurance that the drug will be appropriately used in patients, appropriate patients.

DR. PANZARA: I am going to turn that over to Dr. Sandrock.

DR. SANDROCK: We rely on our sites to make the diagnosis. With our advisory committee and with the FDA, we write protocols. The protocol required that the patients had relapsing MS for the McDonald criteria.

We also require that patients have cranial

MRIs consistent with MS, and we rely on our investigators, and we go out and we make sure that the investigators are qualified, and we rely on our investigators to make the diagnosis and enroll patients according to the protocol.

That patient had, in her history, had an episode of acute visual loss with documented loss in visual acuity in one eye. She had an episode of myelopathy with spasticity in the lowest extremities. She met clinical criteria for multiple sclerosis, and she met the protocol requirements.

DR. RICAURTE: Although they were vague, the history, as I read it, because she also had a long history of migraine.

DR. SANDROCK: Yes, she did.

DR. KIEBURTZ: Let me take a little prerogative.

I think it is inevitable that individuals are misdiagnosed with neurologic diseases. We will have to factor in, in our decision-making, which, of course, won't happen until tomorrow, that there

will be some finite level of misdiagnosis. It is human and unavoidable.

I think that is something we will have to talk about, how to minimize the chance of that happening. I am not asserting whether it happened in this circumstance or not.

MS. SITCOV: I was just going to ask, would you concede that it is possible that she was misdiagnosed and that she was inappropriately put in the study?

DR. SANDROCK: Ma'am, I did not see the patient, and I don't like to second guess my colleagues, who actually saw the patient, examined the patient, found neurologic findings that were objective, and MS is a clinical diagnosis. It is not made by MRI scans. It is made by qualified neurologists. In this case, this was a board-certified neurologist who saw the patient, took the history, did the examination, and I don't like to second guess my colleagues.

MS. SITCOV: Well, could you ask the neurologist who diagnosed the patient? I don't

mean call him up right now, but at some point, find out the reasons for his diagnosis?

DR. SANDROCK: If you are asking me to do so, I will.

MS. SITCOV: Thank you.

DR. KIEBURTZ: Other questions for the sponsor or the FDA at this point?

[No response.]

DR. KIEBURTZ: This meeting is adjourned until 8 o'clock tomorrow morning.

[Whereupon, the proceedings were adjourned at 4:00 p.m., to resume at 8:00 a.m., Wednesday, March 8, 2006.]

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