DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

Volume II

Wednesday, March 8, 2006

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

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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: Good morning. I think we will get started.

Just a few reminders to the committee, as well as the observers. The open public hearing is over, so the committee members essentially are going to discuss among themselves, that is, the voting and non-voting members of the committee, discuss among themselves the questions that have been proposed to us.

Please, everyone bear in mind that we can specifically ask questions both to the sponsor and to the FDA about additional analyses. In fact, we have some information and follow-up on questions that were posed to both yesterday, so we will get to that shortly.

Just general format, remember it's a discussion, but it is a structured discussion, and I think it will facilitate things if people do not jump in. Let me recognize you, so that we can go in somewhat of an orderly fashion.

If you feel your point will be diminished by waiting, try to look even more urgent towards me or something, but otherwise, try to go in a structured fashion and, for better or worse, I am the one who gets to structure it, so if you don't like it, you can let me know on the break.

Regarding the questions, just bear in mind that in the preamble there, FDA also encourages the Advisory Committee to discuss any other issues that the members believe are relevant to the current submission.

If you do not believe the current questions adequately cover the issues we need to be covering, I would like to know about that earlier rather than later, and I would propose that you tell me that, and then also, to help sharpen your thinking, put in a question, similar to these questions, so if you think there is an issue that hasn't been addressed by the question, write out another question and then just give it to me.

With that preamble, before we commence properly, we need to once again introduce ourselves

and have the reading of the Conflict of Interest Statement.

So, why don't we go clockwise again, please.

DR. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office of New Drugs in the Center for Drug Evaluation and Research at FDA.

DR. TEMPLE: I am Bob Temple. I am Director of the Office of Drug Evaluation I.

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

DR. WALTON: Marc Walton. I am the Deputy Director of the Division of Neurology Products.

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 at the FDA>

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 a committee member. I am Professor of Biostatistics at Harvard University.

DR. COUCH: I am James Couch. I am a committee member. I am Professor and Chair of Neurology, University of Oklahoma Medical School.

DR. MOSADDEGH: I am Sohail Mosaddegh. I am the Acting Executive Secretary for the PCNS Advisory Committee.

DR. KIEBURTZ: I am Karl Kieburtz. I am Professor of Neurology at the University of Rochester and chairing this 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 almost 31 years.

DR. JUNG: I am Lily Jung. I am a neurologist with the Swedish Neuroscience Institute and Clinical Associate Professor at the University of Washington. I am the Consumer Representative on this committee.

DR. SACCO: Ralph Sacco. I am a member of the committee, Professor of Neurology and Epidemiology at Columbia University.

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

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

DR. DeKOSKY: Steven DeKosky, Professor and Chair of the Department of Neurology at the University of Pittsburgh.

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

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

DR. PORTER: Roger Porter, Adjunct Professor of Neurology, University of Pennsylvania, Adjunct Professor of Pharmacology at USUHS. I am the non-voting pharma member.

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 updates from the committee members on the Conflict of Interest

Statement?

[No response.]

Committee Discussion

DR. KIEBURTZ: I just want to sort of housekeepingwise deal with three things that were brought up yesterday. One is receiving copies of the checklists. Each of the members of the committee should have gotten that. If you don't, let us know and we will distribute it. We won't discuss that right now, but I just want to make sure you have it.

Then, there were two other questions. I believe Dr. Goldstein brought up both of them. One was about integrating or summing across infections. Folks from Biogen Idec, there was a slide that was proposed to look at that, I think it's 16-91.

DR. PANZARA: Thank you, Mr. Chairman. It is Slide 16-91.

[Slide.]

This is a summary slide of the data we did share with you yesterday except that now it's all, as requested, compiled into a single slide. This

is the placebo-controlled experience in the middle portion, but on the far right side of the slide, in the shaded portion, is the cumulative experience. It includes all open label, as well as placebo-controlled.

Focusing on the top line was the overall infection rate. Again, it was 74 percent in each group, and the cumulative exposure, there was additional exposure, the incidence is 65.6 percent, herpes infections 6.1 versus 7.2. Again I shared that with you yesterday, the cumulative is 6.1.

Now, the way this is set up is you have the overall infections, the herpes and the serious infections are a subset of that overall infection, and those rates are given. Again, serious infections were balanced and remained a similar rate in the extended experience.

Then, underneath serious infections, you have the subsets of serious herpes infections and opportunistic infections, and then under opportunistic infections, you have the subset of patients who developed PML.

So, that is how the data is rolled up into our overall serious and overall infection rates, and I call your attention to the bottom of the slide where we have done the same for malignancies at 1.3 percent on placebo versus 0.7 percent on natalizumab, with a cumulative incidence of 0.7 percent, and the deaths. Those are the same deaths that I outlined for you in detail yesterday.

DR. KIEBURTZ: Thank you.

Another question was on the prevalence, the numbers, the treatment discontinuations in various randomized studies of interventions for MS. I can't remember who actually asked that question. I am sure the record will tell us. But Dr. Walton has prepared some information to give us sort of the scope of that.

DR. WALTON: We have a slide also. Sohail has the table that could be passed out for the committee, but Dr. Goldstein had asked for what the treatment discontinuations were in various prior experience.

[Slide.]

That slide and table that is going around gives some of our prior experience over the course of more than the past 10 years in studies from a variety of different sponsors in multiple sclerosis.

Obviously, longer studies tended to have somewhat larger treatment discontinuations, just as kept occurring during the course of this study.

The lower part of the table, there are both the treatment discontinuations that were designated as being related to an adverse event and also those that were designated as listed just patient decision or patient choice, which may be relevant to the question that Dr. Goldstein was asking, which was I think trying to infer what treatment discontinuation in clinical practice might be, so patient choice might fall into that, as well.

The bottom box listed two natalizumab studies that we heard about here yesterday.

DR. KIEBURTZ: Thank you. So, I think that sort of cleans up some of the housekeeping

from yesterday.

Does anyone think that they are going to be drafting an additional question to the questions that were already proposed by the FDA? Just so I know. You don't have to tell what it is.

DR. GOLDSTEIN: We may be able to integrate it in part of the other discussion, but it gets to the issue of what patients and physicians should be told about not only what we know, but what we don't know as part of that informed consent process. We may be able to integrate that into part of the other discussions.

DR. KIEBURTZ: Let's see how that goes.

Dr. McArthur?

DR. McARTHUR: Do you want to know what the question is now, or just that I am composing it?

DR. KIEBURTZ: Just that you are composing it. It sounds like you are. Just so I can plan, just because we have quite a list of questions before us.

Before we address the questions, are there

any additional clarifications from the sponsor or the FDA that anyone wishes to ask at this point? Dr. McArthur or Ms. Sitcov, either way.

MS. SITCOV: Perhaps this question is better asked of the FDA. When Dr. Richert spoke yesterday, one of the things that struck me is that the current drugs that have been available for MS don't really have a fatality rate connected to them, or morbidity, I guess, is how it would be termed, but the 1 in 1,000 figure that exists now for this drug, how, when you compare drugs for other autoimmune diseases, such as rheumatoid arthritis, or Crohn's disease, or lupus, where does 1 in 1,000 come out in comparison with those kinds of drugs, because for the current MS drugs, we don't see those kinds of numbers.

DR. WALTON: I would say for some of the more recent products for things like rheumatoid arthritis, which have been the TNF antagonist products, those do have serious side effect risks associated with them.

Probably amongst the most prominent are

two categories. One is infectious risk and one is concerns about malignancy. On the malignancy side, it is very difficult to figure out what the drug associated risk is, because there is a strong impression that malignancies are higher in the rheumatoid arthritis population than in the general population, but it is very difficult to figure out exactly what that background rate is because most of the rheumatoid arthritis patients are on other forms of immunosuppressive drugs, so distinguishing between the true background rate and their drug associated rate for the other drugs is confusing.

So, consequently, the data we have on malignancy rates in people being treated with the TNF antagonists becomes difficult to interpret. We do believe that there is some drug associated increased risk, and those products have warnings related to that, but we don't have a good quantitative number for that.

With regards to infectious disease risks, again, we have some good numbers that I do not recall offhand, that are certainly higher than 1 in

1,000 for bacterial type infections, and those are in the label, and those were things that we saw in controlled clinical studies and can have a good estimate for.

Of course, for those, for bacterial infections, we have antibiotics that can treat those if picked up early, so a good surveillance of patients can help ameliorate those risks for the sake of prompt treatment.

There are less common infections like tuberculosis that we have seen with those products. Again, we have an approach that we have confidence decreases those risks - the testing for TB prior to initiating the TNF blockers, and again surveillance to institute treatment, to be suspicious for the development of TB and institute treatment.

They are a little bit different in terms of the nature of the risk.

DR. KIEBURTZ: Let me just make sure. I don't want to start edging in to discussing the questions yet. This is getting clarifications of material that was presented yesterday. That is

what we are doing right now.

Dr. McArthur.

DR. McARTHUR: My question is for the sponsor, and it relates to the issue of certainty of diagnosis and identifying patients with multiple sclerosis who might be most likely to respond to the drug in question.

So, has an analysis been done or are you able to present an analysis of treatment response in terms of relapse frequency or changes in MRI images for patients who entered the trials 1801, 1802, with contrast-enhancing lesions? So, is there a subgroup analysis of just that patients?

DR. SANDROCK: We have done that, stratified patients based on the presence or absence of enhancing lesions at baseline. Could I have the slide that shows that, the relapse rate ratio, please? Yes. Could I have Slide 422.

[Slide.]

This is the annualized rate ratio where the vertical line is a ratio of 1 and points to the left of 1, indicate a treatment effect in favor of

natalizumab.

Patients with zero enhancing lesions and at least 1 enhancing lesion are shown here. The confidence intervals do overlap in both groups. You see a substantial treatment effect. Even the patients with less than 1, or even patients without lesions have a rate ratio that looks like it's a little left of 0.5, indicating a greater than 50 percent decrease in the frequency of relapses.

Does that answer your question?

DR. McARTHUR: Thank you. Just remind us, if you can, what proportion of patients at baseline had contrast-enhancing lesions?

DR. SANDROCK: It's about 49 percent, as I recall, in this trial.

DR. KIEBURTZ: Dr. Sandrock, while you are up there, can I ask you a couple of other questions.

The actual cumulative probability of relapse by two years in 1801?

DR. SANDROCK: Yes. It's from my core presentation, the risk of relapse, the Kaplan-Meier

plots.

DR. KIEBURTZ: The numbers are called out at Year 1.

DR. SANDROCK: The reason for that is that that was a prespecified secondary endpoint, the proportion of relapse-free patients. It was not a prespecified endpoint at either time. I restricted my talk to all the prespecified primary and secondary endpoints.

Could I have Slides 24, please.

[Slide.]

I don't know if the statisticians could give us the actual numbers, but extrapolating from the curve, it looks like about 60 percent of patients had a relapse in the placebo group compared to about 30 percent in the natalizumab group, something like that.

DR. KIEBURTZ: So, for the context of our future discussion, let's use those as round numbers, 30 and 60 percent of two years risk of relapse in 1801.

DR. SANDROCK: It looks like it's about

right.

DR. KIEBURTZ: That's fine. Can I ask you another question? The rate ratios are hazard ratios for relapse and for progression of disability by EDSS stage. You showed us that yesterday, the subgroup analysis.

Could you just show us those again for both endpoints?

DR. SANDROCK: Sure. Could we have I guess it would be display 2-9 and 2-10 from the briefing document.

DR. KIEBURTZ: To the other committee members who have questions, I realize I have jumped the agenda, but I figured since Dr. Sandrock was there, I would just--

[Slide.]

DR. SANDROCK: So, this is display 2-9 in your brief document. The third segment are the EDSS scores at baseline - zero to 1, 2 to 2.5, 3 to 3.5, and greater than or equal to 4, and the relapse rate ratios are shown there.

DR. KIEBURTZ: Could I just clarify, the numbers in parentheses following the greater than stage 4, 37 and 79, so there were maybe 120 subjects in the trial who had an EDSS score of 4 or higher.

DR. SANDROCK: Yes, that's exactly right.

DR. KIEBURTZ: Thank you.

DR. SANDROCK: The next slide 247 shows the hazard ratio.

[Slide.]

This is the hazard ratio based on the cumulative probability of progressing by two steps on the EDSS scale, again, the same divisions on EDSS, and you can see the hazard ratios there.

DR. KIEBURTZ: Thank you.

Go ahead, Dr. McArthur.

DR. McARTHUR: Would that particular slide, which is 217, it looks like individuals, you have a relatively small number of T2 lesions. There is no treatment benefit.

DR. SANDROCK: Well, it's a very small subgroup, 15 patients in the placebo group, 29 in

the natalizumab group. The confidence intervals go virtually across the entire screen.

On this relatively insensitive endpoint, the number of events must have been very small, so it would be hard to conclude one way or the other I would think.

DR. McARTHUR: I think that the point I am trying to make is again how do we identify which patients should or should not receive this agent.

DR. SANDROCK: I understand.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I had a point of clarification. I vaguely recall--and I wanted to check whether this was right--that there was an adverse event discussed yesterday in a child?

DR. SANDROCK: Yes.

DR. M. HUGHES: The question then is how much pediatric data do we have, and is pediatric use being considered as part of the RiskMAP.

DR. SANDROCK: The child you are referring to was a single patient IND. This was a little girl about 1 1/2 years old, who had a fulminant

inflammatory disease of the white matter, that was later biopsied and found to be consistent with multiple sclerosis.

She has been tried on interferon, high-dose interferon, cytotoxic agents, and she was declining, and we were asked to provide natalizumab on a compassionate use basis. We did so. She seemed to initially respond, and then she seemed to worsen again. The natalizumab was discontinued, and she eventually expired.

Other than that, we have not done a formal study of natalizumab in pediatric MS patients, and we are not seeking an indication for pediatric MS.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I have a question for the FDA, I am not sure which person. Not being an MS expert, it is important for me to understand, for MS patients, other potential therapies, and we have heard about a lot of them, and you have given us some numbers this morning on discontinuation rates.

There is one, though, that is mentioned, that does have some toxicity, and I just want to

understand a little bit more from the FDA's perspective something about I guess it's Novantrone or mitoxantrone that has the cardiac toxicity.

What is that about, the risk of toxicity, and does that have a specific labeling, and how that was dealt with? I know that's a complicated question. It just helps me to put into perspective other MS drugs that have been I assume approved with possible other kinds of toxicities other than infection.

DR. KATZ: Novantrone was approved for a different form of MS, for progressive forms of MS, and not relapsing-remitting, and it had been known, based on its prior use in the form of cancer, that it had a cumulative cardiac toxicity, cardiomyopathy basically, although it has recently been determined that cases of heart failure can occur even if there are one or several doses, and the original labeling said that you shouldn't get over, I think it was--I forget--140 or 120 mg/M-squared cumulative dose, and patients were supposed to have been followed.

After they achieved I think 100 initially, they were supposed to have cardiac evaluation, but that labeling has now been changed to require, essentially require cardiac monitoring prior to each dose.

When it was approved, it was approved with a requirement for the sponsor to follow a certain number of patients, several hundred patients, I think, to monitor to see actually what the incidence of this cardiomyopathy was in MS patients.

Then, it was also approved with a requirement for the sponsor to do a study to look at, in a real world setting, whether or not these studies were actually being done according to labeling. At least preliminary evidence from that study suggested that the protocol for the cardiac monitoring wasn't really being followed terribly well, although we didn't have very much data at this point, because it takes time for patients to get to that cumulative dose, but again the labeling has been changed to ask for cardiac monitoring

before each dose, because cardiomyopathy can occur with far less than 120 mg/M-squared.

DR. SACCO: I guess what I am trying to understand is it wasn't maybe a RiskMAP, but the sponsor proposed certain things that would be done, and from what you are implying, some things were done and some things weren't done.

I just wanted then to follow up with when there is toxicity in a drug, and there is proposed labeling as well as plans to follow up, how compliant, how accurate, how responsive are both the sponsor and the FDA in interpreting and acting on that follow-up data?

DR. KATZ: Well, I think it depends on the nature of the agreements. If I recall, in the Novantrone case, there wasn't a mandatory enrollment of the sort that the sponsor is proposing now here, so that not every patient who was prescribed Novantrone was enrolled into a registry, followed forward prospectively. It was handled quite differently.

You are asking how likely is such a

registry to be successful, is that the question?

DR. SACCO: Well, let's stick to just Novantrone, and you just implied that there were some cardiac echoes done, but you implied that the preliminary--in other words, I didn't have a sense from you that that was a robust interaction between the FDA and the sponsor in the monitoring of the cardiotoxicity with this drug, unless I misinterpreted what you said.

DR. KATZ: It was quite a robust interaction in terms of agreeing to what sorts of monitoring ought to be done, or what sort of labeling would be required. Clearly, we had a great deal of negotiations about the labeling.

DR. SACCO: Before, but then the follow-up.

DR. KATZ: Again, there were two studies, as I recall, required for Novantrone. One is for the sponsors to actually enroll, I think it was several hundred patients, and monitor, and another study was to just look at sort of the real world and what actually was happening.

We got periodic updates on both of these studies, so there was quite a--I would say, to use your word--robust interaction in terms of follow-up, but again, in terms of the total use of the product once it was approved for progressive MS, there was not the sort of required registration of every single patient before the drug was released, but, no, we got, and continue to get, periodic updates on both of these studies.

But again, at least initially, when the toxicity was considered to have been exclusively related to a cumulative effect, with very early exposure, there was very little data, because there was no requirement to do the testing until much later.

DR. KIEBURTZ: Let me just remind the committee--and then we are going to have Dr. Temple speak--that I really want to focus right now on clarifications of things that were presented yesterday, and we are getting ahead of ourselves, because a lot of these things we are talking about, we are going to come back to, and I really don't

want to do it twice today.

Dr. Temple.

DR. TEMPLE: I just want to note a complexity. Novantrone is an anticancer drug. It's available for the treatment of cancer. When you get a novel use, it's not so easy to put a special treatment regimen, because people can readily avoid it and just use the other drug. We have encountered that in other settings.

I guess the other thing I would say is we are becoming, and have been becoming, as is indicated in some guidance we have written, increasingly conscious of the need to look at the impact of the risk management programs that we have, and you saw some of that here.

A perfectly good question is what are you going to do now that you are discovering that people aren't doing that, and there are things you can do. You can give patient labeling. Most cancer drugs don't have patient labeling, but there could be a so-called "Med Guide" made available, and we need to think about all of those things, and

that is what we do.

But I would say there is an increased level of consciousness of the need to not just put something in place, but to see how it's going, and the guidance we put out makes that point.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: One of the questions that I had asked yesterday that must have fallen off your list was I asked for the numbers needed to treat data, and I asked for three things really.

It was numbers needed to treat to prevent one relapse over two years, to prevent progression of disability, and to prevent one of the major clinical endpoints, and I asked for it in two ways, one based on the control data from the 1801 trial, and then if you presumed a one-third response rate in the placebo group in that trial, since there was no head-to-head comparisons and we are told that there should be about a third response rate in the placebo group, what those numbers would work out to, and presumably also with the confidence intervals around those.

DR. KIEBURTZ: The sponsor may have an answer, but my back of the envelope number needed to treat two years, that is why the 30 versus 60 gives you a number needed to treat of about 3, and EDSS progression number needed to treat is about 8.

DR. GOLDSTEIN: From the numbers that we had from the FDA table on page 2 of their presentation is a slide, Slide 5. Just looking at the 1801 efficacy analysis, looking at the numbers of patients reaching a sustained disability progression, it actually works out to--if you go through all the math, it works out to a 1.2 percent absolute reduction that is not statistically significant assuming a one-third response rate in the controls, but I am not a statistician, you know, I did this on my calculator. That is why I want somebody who does know how to do these numbers to do them.

DR. KIEBURTZ: Dr. Sandrock.

DR. SANDROCK: Could I have Slide 16-79, please.

[Slide.]

Our statisticians did this calculation last night, and here are numbers. This is based on the 1801 monotherapy trial. Based on the annualized relapse rate, I put the actual annualized rates from the two treatment groups, the relative treatment effect, the absolute difference, and NNT is 1, so 1 patient is needed to be treated to prevent one relapse.

If you look at the proportion of patients relapsing, the NNT is 4, so 4 patients needed to be treated to prevent 1 patient from relapsing.

Based on the proportion progression, our calculations indicate 9 patients need to be treated to prevent 1 patient from progressing on the EDSS scale.

DR. GOLDSTEIN: And if you assume a response rate in the control group, because the control group here is placebo, but we are not comparing this to placebo anymore, we active treatments that work, that reduce the rates about a third.

DR. SANDROCK: So, we did that by

looking--could I have Slide 16-80, please.

[Slide.]

So, this now looks at the added benefit of natalizumab compared to patients who are only on Avonex from the 1802 trial. Again, the absolute numbers are listed here.

So, 2 patients needed to be treated in order to get a benefit of natalizumab compared to just being treated with interferon, 5 need to be treated to prevent 1 patient from relapsing compared to just treating with interferon, one of the current available therapies, and 17 need to be treated to prevent 1 patient from relapsing compared to just staying on the interferon.

DR. KIEBURTZ: I don't think we want to speculate too much about--these are the data from the two trials that are at hand, extrapolating outside of them would be difficult.

Dr. Porter.

DR. PORTER: You are going to discuss this checklist later in detail?

DR. KIEBURTZ: Yes.

DR. PORTER: I will pass then.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Again, this is a question for the company, and I suspect there is a rather simple answer for this, but the censoring data, let's just look in 1801. By week 108, was 9 percent in the placebo and a little over 7 percent in the Tysabri.

Then, when you talk about the total number of patients that were censored, it is listed as 73 and 83 percent. I suspect there is a very simple answer.

DR. SANDROCK: On the EDDS scale, two years is the bare minimum required to show enough evidence to show power. If patients haven't progressed by the end of the two years, they are censored. In every single MS trial that has ever been done, the vast majority of patients do not progress by two steps, sustained for three to six months.

So, in every other MS trial that has looked at disability progression, the majority of patients don't progress, and therefore, they are

censored by the Kaplan-Meier methodology.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Many of the anti-immune drugs that are currently available were mentioned yesterday - azathioprine, methotrexate, Cytoxan, CellCept, I don't remember cyclosporine being mentioned.

Do we know anything about, just in general, what is the malignancy rate and the serious infection rate for these drugs across the board, or can that information be made available sometime during the day, so that we could compare what we are talking about to these other drugs that were mentioned as possible alternatives to using Tysabri?

DR. WALTON: I think it would be very difficult for the sake that those products have not been approved for use in multiple sclerosis, so we don't have good studies, and data on them from other uses would include some very different ways of using the drugs, so I would be very reluctant to extrapolate those adverse event rates to use in

multiple sclerosis in whatever physicians are using them off label.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: From the practical standpoint, however,, since MS patients are using those drugs off label, it would be useful to be able to compare what few numbers we do have, accurate or not, compared to what is known about Tysabri, number one. Number two, going back to Dr. Sacco's question, what is the number, do we know that the number of AML that has been diagnosed with the use of mitoxantrone in the setting of MS treatment?

DR. KATZ: As far as leukemia, it is a couple of patients, I think, in MS. There are probably people here who can better speak to that, but there is one or two cases I think reported, but I don't recall exactly. I suppose we can try and get that information.

DR. JUNG: Based upon how many numbers treated.

DR. KIEBURTZ: Dr. Rudick, can you speak to that?

DR. RUDICK: I don't have the exact numbers in front of me, but at the European MS meeting, there was a report of some 18 cases or so from France with AML, who used mitoxantrone.

Anecdotally, I had a patient that just went in the hospital with acute leukemia from mitoxantrone, so I don't know that we have the numbers, but it is clearly more than one or two cases.

DR. KIEBURTZ: As usual, we want evidence where we don't necessarily have it, but anything we could accumulate by this afternoon, I suppose, about any evidence or reports regard AML might be of use.

Dr. Temple.

DR. TEMPLE: Just for something like mitoxantrone, the cardiac problems depend on how long you use it, but what it does is very familiar from daunorubicin and doxorubicin. It is part of cancer chemotherapy. It is unquestionably lethal if you keep going in the face of deteriorating cardiac function, so it is very hard to put a

comparable number on it, because it is dose related and all that.

DR. KIEBURTZ: I have a question for Dr. Bozic about yesterday's presentation. Slide 94, about the registry, the last bullet. I just want to make sure I understood that correctly.

So, it is proposed in the registry that all spontaneously reported events would be collected as part of the registry.

DR. BOZIC: That would be standard practice in safety surveillance that we collect all adverse events, so I wanted to make it explicit that, of course, in this mandatory registry, we would collect all adverse events and include those in the analyses.

DR. KIEBURTZ: And adverse events as defined in standard TCP, worsening of pre-existing conditions.

DR. BOZIC: So, any report that a physician would call in to us, or a patient would call in to us, either spontaneously or in the course of, for example, a contact that we make with

the physician.

Let me give you an example. Every six months we are going to be contacting physicians to tell us about whether any of their patients has had PML or another serious opportunistic infection, or whether the patient has died, or whether they discontinued Tysabri.

In the course of some of those contacts, we may get additional information on other adverse events. So, of course, I just wanted to make explicit that we will collect all adverse events.

DR. KIEBURTZ: Let me put a finer point on my question. So, the bullet before it says physicians are queried on every patient every six months.

DR. BOZIC: Yes.

DR. KIEBURTZ: So, they are going to be asked about these things.

DR. BOZIC: Yes.

DR. KIEBURTZ: Are they going to be asked to report at that time all adverse events?

DR. BOZIC: No. No, they won't be asked

to report all adverse events. The question will be specifically targeted around the occurrence of PML, any other serious opportunistic infection, any death, and any discontinuation, so it is a very targeted tracking system to evaluate further the events of high interest, the PML and the other opportunistic infections.

DR. KIEBURTZ: So, that bullet that says, "Collect all spontaneously reported adverse events," means if somebody calls you, you will keep track of it.

DR. BOZIC: Absolutely, and that is standard practice in post-marketing safety.

DR. KIEBURTZ: I got it. Slide 97, the frequency of evaluation in the proposed observational cohort study?

DR. BOZIC: Yes. In that study, we will be contacting physicians every six months to report all serious adverse events, as well as all concomitant immunomodulatory or immunosuppressant therapies, and any discontinuations, as well.

So, in that study, in addition to

collecting the PML, the serious opportunistic infections, and deaths and discontinuations, we will collect all other serious adverse events, as well.

DR. KIEBURTZ: You use the same verb there, thought, "collect," but in this, you are asking the physicians to make a--

DR. BOZIC: We are actively soliciting.

DR. KIEBURTZ: Actively looking for all SAs.

DR. BOZIC: Yes, exactly, much like in a clinical trial, for example.

DR. KIEBURTZ: Sorry to come back to this, but you said you will contact the physicians for this information. What is the proposed frequency with which the physicians will have an in-person evaluation of the patient in order to fulfill the obligations of the cohort study?

DR. BOZIC: So, because this is an observational study, the frequency of contact between the physician and the patient will be according to whatever the labeling says. Okay?

Now, part of the purpose of both this study and the Tysabri Registry is that this six-month contact with the doctor is intended to be a prompt for the physician to, you know, ascertain the status of the patient, because this is a study, it's a non-interventional study, so the frequencies of contact between the doctor and the patient would be according to whatever the labeling would say on that matter.

DR. KIEBURTZ: So, let me just restate that another way.

The cohort isn't proposing any more frequent contact than what is mandated by the label.

DR. BOZIC: Exactly.

DR. KIEBURTZ: Okay. Thank you.

Dr. Sejvar.

DR. SEJVAR: Just a quick question for the sponsor just for my clarification.

There really hasn't been a lot of pharmacokinetic and pharmacodynamic information presented to us, but had basically hematopoietic

factors been looked at long term, and are there plans to continue those assessments?

DR. SANDROCK: We did look at hematopoietic factors in the Phase III trial for two years. There is a transient slight decrease in the hemoglobin. It does seem to go back to normal.

In terms of, I don't know, when you said "hematopoietic," whether you meant immune cells, as well. Yes, we are planning to do an immune function study, vaccination study, for example.

DR. KIEBURTZ: Dr. Sacco, then, Dr. DeKosky.

DR. DeKOSKY: Back to I think Dr. Bozic regarding the risk management plan, on Slide 96, I guess, because I have asked the FDA a little bit, I ask the company a little bit, the last bullet, you say, "Ongoing assessment of benefit-risk," and I just want to get a better handle about what kind of ongoing assessment and what kind of possibly qualitative or quantitative rules you would use to make any alterations in decisions?

DR. BOZIC: I believe the question you are

asking is in the Tysabri Registry, we say that we will assess the benefit-risk profile of Tysabri in an ongoing fashion. What we mean by that is because we will have a complete denominator of all Tysabri-treated patients and complete ascertainment of every PML case, we can track the rate over time of the event, the PML event.

In addition, because we will know all relevant information about that case, we will know the outcome of the case, and we are going to carefully investigate all aspects of the case, looking for potential risk factors, for example, underlying comorbidities or concomitant therapies that might have contributed to the development of the case.

So, that is what I mean by an "ongoing assessment of benefit-risk." I just want to point out this is very, very different from the usual post-marketing setting of most drugs, where we generally don't know completely how many people have been exposed. We usually don't know completely how many cases have occurred due to

under-reporting. So, we have severe limitations typically in the post-marketing setting.

So, this registry is dramatically different from what usually happens when a drug gets introduced in the marketplace, because we will know all prescribers and every single patient and every single case.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: This may be a question for Dr. Sandrock as a follow-up to Dr. Sejvar's question.

The discontinuation of a drug to go into a trial with or into treatment with Tysabri was a two-week plan, I think, and it was based on the PK.

So, the PK, I presume is purely in terms of clearance of the medication or detectable levels of the medication, and my question was about other effects, not necessarily hematopoietic, but other systemic effects that probably would outlast the PK change and whether that is accounted for in those two weeks, as well, or whether there is reason to wait longer.

DR. SANDROCK: Actually, it is based on the PK and the pharmacodynamic effect, so we can measure biological responses to interferon by looking at interferon-inducible genes or their gene products, and some of those inducible responses can persist for approximately one week, so that is why we recommended the two weeks.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. Sandrock, sorry to have you jump up and down, but could you go back over the thinking about the collection of serum specimens? In some of the cases that were presented yesterday, serum JCV-PCR did become positive before the onset of PML symptoms.

I realize that you don't have all of the sensitivity, specificity, performance characteristics pinned down, but why not attempt to collect serial serum samples as part of the RiskMAP program?

DR. SANDROCK: I may ask Dr. Panzara to supplement my answer, but the bottom line is that we have extensive data from our safety evaluation.

We felt that the sensitivity and the positive predictive value are so low that we could not recommend widespread use.

We chose instead to study this in our re-dosing trial to understand more about how often you get positive. Since we don't understand the meaningfulness of a positive result, since people who weren't even on Tysabri got positive responses, and we have seen it in HIV and other places where people become positive, and they don't get PML, we wondered how disruptive this would be in the practice to have a positive results, what is the meaningfulness of that.

So, if Dr. Clifford or Dr. Panzara would like to come up and comment further, because we did develop these plans based on expertise from people like Dr. Clifford.

DR. KIEBURTZ: So, the speaker is Dr. David Clifford, who was introduced yesterday in the sponsor's presentation.

DR. CLIFFORD: Right. I am obviously a member of the Independent Adjudication Committee

that was trying to look at the experience of the population exposed to natalizumab and the relation of that exposure to possible markers for PML or the risk of PML.

Our main obligation was really to seek out cases that we could definitely identify as PML cases, and as we reported last week in the New England Journal, there were no cases with really quite an extensive effort to identify them both through many CSF analyses and MR analysis, and careful review of the clinical evaluations of the patients.

We know that this JC virus is present in normal people, in a majority probably of normal adults, and that, in fact, there is replication and shedding of this virus certainly in the urine of most normal adults at as much as 30 percent of the time.

We are also aware that it is present in the serum, the plasma specimens when carefully measured. Frankly, we decided ahead of time that this was a measure that we couldn't factor into

diagnosis of PML at all based on the experience of many cases followed over time with a high risk of PML, who have circulating plasma JC and never develop the disease.

Frankly, I was quite surprised that there were so few cases of circulating JC virus in the population surveyed, and the fact that with the commercial survey that we were able to do, the large, more than 2,000 samples, that a majority of those had circulating virus in those never exposed to natalizumab, made us believe that the signal was, at this point, quite a weak signal, and that we scientifically could not interpret it.

It would require a very large study to probe that more deeply, to have a scientific basis to say that this was a risk factor for future development of PML.

I think it remains a fascinating problem, and I do hope that I can work with the company and probing further any other ways that we could identify risk from that circulating virus, or their rearrangements or other things that could predict

it, but at this point, really, I think the interpretation of that is so difficult that we really wouldn't know what to tell a patient in whom we found positive circulating JC DNA.

DR. McARTHUR: Just as a follow-up, I accept what you say, but I guess my question or point was why not collect a serum specimen from individuals who would go on to receive Tysabri even if you are not using those results individually in those patients to decide anything, because I think I agree with you, you can't tell anybody anything sensible at this stage, but if there were a crop of PML cases down the road, those banked specimens--

DR. CLIFFORD: Samples banks would be a very rational thing to be able to look at to identify risk patterns if they exist.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Since we are talking about blood, something else came to mind that I want to get clarification on.

We heard yesterday about hypersensitivity reactions, some of them being serious, some of them

not, but up to possibly 10 percent. In the risk management plan and in some of this blood collection, I didn't see much mention of how that falls in, whether you collect blood for checking for antibodies and whether antibody positivity affects continued use of the medication.

Maybe I missed it, but if somebody can just clarify that.

DR. KIEBURTZ: Can I change that question around a little for you? Do you currently plan to be screening for neutralizing antibodies as part of the registry or the cohort?

DR. SANDROCK: I just wanted to clarify one thing, the rate of hypersensitivity reactions. Could I have the slide on hypersensitivity reactions, please, Slide 8-12, please.

[Slide.]

Actually, the incidence of hypersensitivity reactions in the 1801 monotherapy trial was 4 percent. So, there were 25 reactions, 25 patients with 27 hypersensitivity reactions, so a couple of patients had them twice.

Fifteen reactions occurred on the second infusion, and the incidence of serious hypersensitivity reactions was 1.3 percent.

So, this is the rate in the monotherapy situation. In the combination trial, it was lower, but we think this is the rate that is applicable since we believe Tysabri should be used an monotherapy.

DR. PANZARA: The only thing I would add to that is that the rate of 0.8 percent you saw yesterday was the placebo-controlled experience, so was the overall experience, hence, the 1.3 versus the 0.8, and it was actually very similar to the anaphylactic, anaphylactoid rate that you see on the bottom of the slide.

I would also like to say that there will be a commercial test available for the testing of the neutralizing antibodies, and it is recommended that anybody in which there is a suspicion of diminished efficacy or, as was described yesterday by FDA, the occurrence of certain adverse events, such as flushing and other things that would make

physicians suspicious that person may have neutralizing antibodies, we would recommend testing, and if the test is positive, the patient should not receive natalizumab.

DR. KIEBURTZ: Thank you. That answers my question.

Well, hopefully, stretching helps before running, because that's what we did for the last hour, so I would like to turn our attention to the questions, and thank you to the sponsor for being responsive to our questions.

Response to FDA Questions and Committee Discussion

DR. KIEBURTZ: The first two questions are has Biogen demonstrated efficacy on the reduced frequency of relapses through two years and fulfilled the commitment made under the Accelerate Approval conditions to verify the sustained clinical benefit.

Is there anyone who feels that the answer to this is no?

[No response.]

DR. KIEBURTZ: So, everyone unanimously

agree that they have met that condition, they have fulfilled the commitment? Okay.

Question 2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?

Any discussion about that?

DR. RICAURTE: I have a question in that regard. This is to the Agency.

There was a comment made about--this has to do with progression to disability--that between the screening exam and the enrollment, there had been variability in terms of the score obtained on the EDSS and how that complicated matters.

I guess the question is: How did that variability between screening and enrollment compare relative to the treatment of that? I am just trying to get a sense of how much is natural variability, how much is the treatment, how does that compare, and why, just to expand on the comments that were made in the written statements here on the Agency's analysis.

DR. WALTON: Okay, let's see. Some

answers and not exactly necessarily in the way that you have asked them.

The screening and the official baseline exam, as I understand, were done by the treatment and the evaluating physicians, they were done by different physicians, so that is a portion of the variability.

Another portion of it is we know from all of the multiple sclerosis studies that we have done, that there is a variability from time to time, from evaluation to evaluation, even with the same patient and the same physician in the EDSS.

That variability is a portion of the assessment that went into the determination that we have to have a full point, a full 1 point EDSS change to, and sustained over some number of months in order to be able to confidently regarded as a meaningful, reliably assessed change.

So, that variability is something we see in every study. In terms of the impact, if one uses the screening exam instead of the baseline, you have some patients who shifted down between the

two, and therefore are a new progression that were not previously deemed a progression in a few patients that shifted up, and they lose their designation as a progresser.

It does make a little bit of difference in the exact numbers, you know, for each group, the exact percentage who are deemed progressers. It is a little bit larger fraction of exactly which patients get deemed progressers, but the net effect is that the treatment effect remains, and the precise, the point estimate shifts slightly one way or the other in each arm, but there still remains a clear-cut treatment effect between the groups.

Have I answered?

DR. RICAURTE: Yes. The second thing would be just I don't use this scale, I am not familiar with it, but just to get a sense of clinically, what does this mean, a change in 1 point, 1.5 points. I am looking at the scale, but it is kind of hard to get a sense.

So, relative to the variability that one can see depending on the examiner, depending on

time, how robust is this treatment effect, and what does it translate into clinically?

DR. WALTON: I think I will break your question into two parts. One is how robust is the treatment effect. Our analyses convince us that the treatment effect is robust in the sense of various ways of looking at it, some of which have been shared with you in these documents, and other ways that we have tried to tease apart what is occurring, that are just too arcane to try and fill into the briefing document. We do believe that the treatment effect is robust to analysis.

The other part of your question, though, is I think what is the meaning of this change, and for that, the EDSS scale is not a linear scale in the sense of every interval along it has the same meaning to the patient. At the very lowest end of it, a 1-point change is really translated more as a reliably determined change in clinical signs that one can reliably and reproducibly determine on the patient. That is at the very lowest end of it.

As you move up, it really does become a

disability or impairment scale that will take into account upper limb function, real impairments that are meaningful, perceptible to the patients in upper limb function, as well as lower limb function, as well as a bladder function.

As you get into sort of the middle range and higher, the scale really shifts into some significant amounts of impairment in ambulatory ability and becomes very big changes in that, but experience has seen that for this scale, it needs to be that large a change in steps in order to be confident that it is reliably a real change in the patient's condition, and not part of their day-to-day, week-to-week variability of function related to a constant disease state.

Does that help?

DR. KIEBURTZ: I would just throw in there, I am not sure, we could probably spend the better part of today and tomorrow arguing about a clinical equivalent of EDSS scale, and not to close it off, but I think the general consensus is that this definition of disability progression is

acceptable, if not universally acknowledged.

So, back to Question 2. Does anyone feel that Biogen has failed to demonstrate efficacy on reduced accumulation of physical disability as defined in the protocol?

[No response.]

DR. KIEBURTZ: Then, we are all in unanimous agreement that they have. I believe there is 12 voting members, so I would say, we didn't take a formal vote, but it's unanimous.

DR. KATZ: We don't need a formal vote on this question.

DR. KIEBURTZ: Thank you.

DR. WALTON: There is one question for which we do want a formal vote, but the others you need not impose that.

DR. KIEBURTZ: Just for the context, just bear in mind, Dr. Sandrock put up a slide with numbers needed to treat, so rather than 60-30, the percentages of people who had a relapse by two years was 54 percent and 28 percent, so roughly speaking, about half the people in placebo did not

have a relapse, and about 75 percent in the treatment group did not have a relapse.

Roughly, a quarter of the people in placebo had disability progression, I will a third, and half of that did in the treated group. So, these are minority events. Most people didn't have the events. Most people in these studies did not have a relapse and did not have disability progression.

The frequency of relapse is about twice that of disability progression, but still I guess 54 percent is technically a majority, but just to frame up the events.

On to No. 3. Outside of PML, are there safety-related issues associated with the use that you consider to be important considerations in making a risk-benefit assessment including non-infectious disease risks and non-PML infectious disease risks?

So, non-infectious disease risks, those would include the things we have heard about, malignancies, hypersensitivity reactions, and so

forth. There are important other safety-related issues that we should be thinking about.

Dr. Koski.

DR. KOSKI: Well, I think when you look at the numbers of patients relatively in the placebo arm and the Tysabri arm, I don't think that it comes out to be very prominent, at least in these two groups, over the period of time that we looked at, but still think it's a consideration when we are talking about patients that are likely, if this drug is approved, to be on it for really long periods of time, much beyond the two-year period.

So, I think over time, cumulatively, they may be an issue, any anytime you have increased risk of herpes, eventually, you know, I would anticipate that we might see like B-cell lymphomas in the CNS.

DR. KIEBURTZ: So, are you speaking to (b), the non-PML infectious disease risk?

DR. KOSKI: Right.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I guess I would go back to

just the hypersensitivity risk. I mean I think there is some, and I think, to me, it is something that is possibly preventable given the antibody detection.

So, under (a), I guess the question is whether hypersensitivity would fit there or not. There were some that were anaphylactoid, and we saw some of the numbers, but is that important? To me, it is.

DR. KIEBURTZ: I will just voice my opinion on this. I think the development of neutralizing antibodies is probably an important event for two things. One, it certainly seems to be a signal for risk of a hypersensitivity reaction, and also seems to be a strong signal of a population that has decreased benefit.

So, when we start considering risk-benefit ratios, it may be favorable in the non-antibody-positive population, but I think we have seen evidence to make us wonder whether it remains favorable in the antibody-positive population. I believe what we just heard from

sponsor is they would promote, they would suggest or have proposed clinically-based testing for antibodies based on the occurrence of side effects, and not recommending any further treatment in those who are found to be persistently antibody-positive, if I heard that correctly. I see nods, so I think I summarized it accurately.

So, I would say to the Agency I think that is a concern.

Dr. Koski.

DR. KOSKI: I would just point that, you know, currently, in treatment of MS with the interferon products, there is a known rate of positive antibodies that actually evolve most frequently after about a 6-month period.

Currently, there are I think evolving recommendations in the field to handle this, because it is realized that when you have these neutralizing antibodies in a specific or consistent fashion, that the drug is not as effective, and at that point, you either change to one of the other drugs that has less of an incidence of antibody, or

to something like glatiramer.

DR. KIEBURTZ: Unless I have misunderstood things, one slight difference here is it looks like--and maybe Dr. McDermott could, or Hughes--I think the development of antibodies was sort of paradoxically quite early on, because it is associated with hypersensitivity reactions, which occurred early on also, so a little bit different than others is that this seems to be a relatively early phenomenon.

DR. A. HUGHES: One of the difficulties--and the sponsor may be able to talk about this a little bit more--but antibody formation was assessed every 12 weeks, and I believe the median time for anti-natalizumab and antibody formation was 12 weeks, but we are not exactly sure in that interval when the formation is occurring. I do think it is quite early.

DR. KIEBURTZ: Any other questions on Question 3?

Dr. Sejvar.

DR. SEJVAR: I am sorry, I just wanted to

clarify with the sponsor, the apparent decrease in response to the product would also prompt looking at the antibody, as well, right?

DR. SANDROCK: Yes.

DR. KIEBURTZ: I think maybe we can incorporate our recommendations on testing, timing, and triggers when we talk about the risk management plan.

Dr. Jung.

DR. JUNG: Do we have any information about the severity of the anaphylactic reactions which occur? I believe previously, when the drug was marketed, that the feeling was that the anaphylactic or anaphylactoid reactions were relatively mild and treatable with just the use of Benadryl.

DR. PANZARA: So, in the clinical trial setting, in the slide I showed you earlier, we have a total of five patients in monotherapy study who had serious systemic hypersensitivity reactions.

We pre-defined these as any event that was urticaria with associated systemic symptoms, mostly

respiratory symptoms. Out of those five patients, there was no cardiopulmonary compromise in any of those patients. Actually, all of them were treated with Benadryl and corticosteroids. One of them received epinephrine, but not in the setting of a blood pressure abnormality. All maintained oxygenation throughout. All recovered fully.

In the later stage, open-label study, there was one case of anaphylactic shock where the patient did have a lowered blood pressure. Other than that, that is the total numbers we have.

DR. KIEBURTZ: Thank you, Dr. Panzara.

Dr. Couch.

DR. COUCH: Just one comment that is self-evident, but I think should be on the record, and that is, we are dealing with a disease that is very chronic and may have a survival of between 20 and 30 years, even 40 years, so we are trying to extrapolate from 2- to maybe 3-year experience, to something that we have no idea of what it was going to be like in the future.

The 10 years, maybe 15 years of experience

with the interferons has certainly shown that the field changes, and we really just cannot predict what is going to happen 10 or 15 years from now.

DR. KIEBURTZ: I think the data we have largely is confined to 2 and 3 years of follow-up with large numbers of people, and we do not know whether there will be accumulating risk or declining risk with further follow-up, but we are going to make our recommendations based on the observations we have, but your point is well taken.

So, let me summarize. I forgot I am supposed to summarize for the record what we decided on 1, 2, and 3.

So, 1 is that Biogen has demonstrated the efficacy on reduced relapse rate and have fulfilled their commitment for the Accelerate Approval of showing a sustained benefit at 2 years.

No. 2 is that they have demonstrated efficacy on the primary 2-year endpoint, which is reduced accumulation of physical disability.

No. 3 is that our safety issues of concern revolve around the unknown likelihood of non-PML

infectious disease causes, which potentially have a signal in this period of observation, particularly herpetic and serious infections, and secondly, the development of neutralizing antibodies and their possible association with hypersensitivity reactions and decreased efficacy are the safety concerns outside of PML.

Dr. Katz.

DR. KATZ: I think what we meant in this question is whether or not the committee felt that there was anything besides PML that we have seen in the data so far that would preclude approval.

So, I think people should sort of think about it in those terms, and if you think you have the answer to that question, fine, I think we do.

DR. KIEBURTZ: Does anyone feel there is any safety issues aside from PML that would preclude reintroduction to the market? Dr. McArthur.

DR. McARTHUR: I think Dr. Sacco's point is a good one. If regular screening for neutralizing antibodies is incorporated into a

safety plan, that would reduce hypersensitivity reactions or could reduce hypersensitivity reactions, and could reduce exposure to non-responders.

DR. KIEBURTZ: So, that is manageable, not a doesn't preclude.

Dr. DeKosky?

DR. DeKOSKY: Dr. Hughes, I thought I saw a 6 percent rate--I couldn't find it when I looked back in my notes--on the number of subjects with neutralizing antibodies, that showed up at the first 12-week assessment essentially.

Was there an increasing prevalence of antibody as they tracked through their two years of exposure, or if you are going to make them, do you make them early, so that this is or is not a potentially increased risk for long-term administration of the drug?

DR. A. HUGHES: Generally, if you are going to make them, you make them early. I think that 90 percent of patients who became antibody-positive did so in that initial 12-week

interval. Yes, it was a 6 percent persistently antibody-positive incidence, and 4 percent transient positivity. I think we know a lot less about what that means.

DR. DeKOSKY: There was no evidence that they tracked consistently with a percent or two over the two years of the study in increasing numbers.

DR. A. HUGHES: No, there was no evidence of that. I should, though, note again that there were some serious hypersensitivity reactions that occurred further out than would be expected. There was one associated with the 13th infusion, but most did occur in association with the second infusion, as would be expected.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. Hughes? Sorry.

DR. A. HUGHES: I think Dr. Walton wanted me to clarify that not all hypersensitivity reactions were associated with anti-natalizumab antibodies, but all anaphylactic reactions were.

DR. DeKOSKY: My issue had actually more

to do with the risk over time and abatement of clinical response, not so much necessarily the hypersensitivity reaction in terms of approval beyond what we know about what happens with the biological effects of the drug. Thank you.

DR. A. HUGHES: It doesn't seem to be cumulative based on what we know.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Dr. Hughes, the first measurement was at 12 weeks, so we really don't know about early antibody formation and whether one could detect that neutralizing antibody signal at 3 weeks, 4 weeks, 6 weeks, allowing for an early detection of people at higher risk. There seems to be a 10-fold higher risk of hypersensitivity reactions in neutralizing antibody-positive patients.

DR. A. HUGHES: That's right, the first assessment, that's exactly right.

DR. KIEBURTZ: Question 4 is essentially does the committee believe that the risk of PML is limited to patients exposed to a second

immunosuppressive agent, that is, do you think the risk is entirely mitigated by giving the drug as monotherapy. That's how I read that question.

Is there anyone who would say yes to that?

[No response.]

DR. KIEBURTZ: We unanimously answer this one no, that is, the committee believes that there is a treatment-associated risk of PML even when given as monotherapy. None of the observed cases, I mean I think we all understand that none of the observed cases happened in that situation, and it is possible that the co-administration of secondary immunosuppressive agents increases the risk, and it is, in fact, possible that it may only exist in those individuals, but we don't know that yet.

That would be my comment.

Dr. Koski.

DR. KOSKI: I would just go back and point out that the one case in the patient with Crohn's disease was largely on monotherapy. I know that, you know, it was pointed out that we did not have a lymphocyte, a total lymphocyte count on that

particular patient, but he had been off concomitant immunosuppressive therapy for eight months.

DR. KIEBURTZ: Any further discussion on this question? Dr. Hughes.

DR. M. HUGHES: Just a comment for other studies that might be relevant here. It would be interesting to look at the extent of immunosuppression across subjects on monotherapy compared with those on combination therapy.

DR. KIEBURTZ: Do you have a proposed measure of immunosuppression in mind?

DR. M. HUGHES: Not especially, no.

DR. KIEBURTZ: A point well taken. I didn't know if you had an operational plan.

Dr. Sejvar.

DR. SEJVAR: I mean looking specifically at CD counts would be I think very helpful.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: In terms of I think maybe screening patients, one could do some skin testing for common antigens, and I think that is something that we usually use for patients who are going to

undergo immunosuppression, because we really want to already know whether they are in such a condition.

DR. KIEBURTZ: I think these are good points. I am sure we are going to come back to this topic when we define who might be appropriate patients for this treatment.

I would like to move on to Question 5.

I believe this question is--I will ask if I am framing this properly--I believe what we are being asked is do we feel there a study or studies which must be conducted prior to allow remarketing of the agent, that is, do we feel there is something that must be done before we can vote on Question 7.

Dr. Porter.

DR. PORTER: I would just point out that remarketing is not really remarketing in the ordinary sense where the drug is just put into the pharmacy shelves. I mean this is remarketing under a very, very controlled circumstance, so remarketing here has a special meaning.

DR. KIEBURTZ: A point well taken.

Dr. Goldstein.

DR. GOLDSTEIN: Question 5 may be out of order, because I think maybe what we should do is come back to that once we have sort of gone through some of the other questions. I think the way you answer that question depends upon for whom, under what circumstances, and we may need to have that discussion first.

DR. KIEBURTZ: I see your point, but I would say this. I think to frame it like the adverse experience question is if you know right now that you don't think we should return the drug--allow the possibility to return to marketing for anyone until certain studies are done, then, we should know about that now.

Presumably, if you feel that it's not the case, that is only so if we clearly define in whom, for how long, et cetera, and under what circumstances.

Dr. Walton.

DR. WALTON: I think that is exactly

right. The intent of the question was do we have such insufficient information that it's impossible for you to discuss the way the questions, or are you prepared to discuss them.

DR. KIEBURTZ: Are we discussed the later questions? Is anyone opposed?

[No response.]

DR. KIEBURTZ: I will take that as we feel that there are sufficient data to move forward. Of course, all of us think that there will be more data that need to be generated to help refine these questions. That is part of the point of the registry, and that is part of the point of the cohort, and there may be other studies we would suggest in our discussion although that isn't a specific question that has been posed to us.

So, we are willing to move on.

So, the technical answer to Question 5, are there additional data that you recommend to obtain prior to determining whether to return to the marketplace, the answer is no with the caveat that we are going to specify clearly under what

circumstances we think it should be potentially reintroduced.

Is that sufficient discussion? Okay. Well, that's 5 of 11 questions, if anyone is keeping count.

Question 6. There are multiple parts to this question. I think we are getting down to the nub of some of the issues. If we return to commercial distribution, are there specific subsets of relapsing MS populations for whom you would consider use reasonable or, on the contrary, inappropriate?

Then, we have examples, and I don't think we should feel constrained by these particular examples. These were just examples, people who have tried other therapies, people with a certain level of disability needs to be required or have to be below a certain level of disability, whether they have to have tried other treatments, whether they have to have failed other treatments, whether they had to have intolerable side effects from other treatments, whether it should be given with

other treatments.

Now, we have heard from the sponsor, I believe, so (e) is kind of moot in the sense that I believe the proposal is for it to be administered only as monotherapy, and we could consider whether we feel differently, so it is not entirely moot, but we should bear in mind that the sponsor is not proposing at this time that it be co-administered with any other available MS therapy.

There may be other ways of categorizing or characterizing patients who we think are most appropriate for treatment.

Dr. Walton.

DR. WALTON: In spite of the fact that monotherapy is the proposal, I think it would remain useful just to understand whether or not the committee concurs with that or not.

DR. KIEBURTZ: Yes.

DR. TEMPLE: And it has implications for the patient agreement, for example. At present, the patient agreement doesn't say I am not taking anything else, maybe it could.

DR. KIEBURTZ: Understand.

Dr. Koski.

DR. KOSKI: This is actually a question that I am relatively conflicted about, and the reason is as follows. You know, what we are beginning to realize is that the earlier the treatment that you get, the more you prevent disability and presumably the brain atrophy which is the long-term manifestation of the primary progressive or the secondary progressive phase.

So, on the other hand, if you have a patient that is very mild, there is a percentage of them that actually--you know, that you really do not see progress. I will see that that is the minor percentage. On the other hand, if you have a patient who is having a series of attacks, two a year, and has clearly evidence of enhancing lesions on MRI, I think that that is the type of patient that you most likely want to put on monotherapy relatively early in their clinical course.

Additionally, I think the other things that we also talked about is people who were not

able to tolerate some of the ABC drugs and were continuing to have attacks and the same types of enhancing lesions. Again, this is the type of person that you really want to have on it.

DR. KIEBURTZ: I think we can think about defining populations in several ways. One is there are particular characteristics of their disease, that is, do they have relapsing-remitting MS. Another aspect is do they have a certain level of disability, and then there is a separate question about how their drugs have been managed beforehand.

I mean there are several kind of conceptual ways of categorizing people, and I think we should consider many of them, and you discussed two of them.

Dr. DeKosky.

DR. DeKOSKY: While we are on this topic, one of the things that I wanted to clarify was the role of steroid infusion during the course of being on the medication. If I remember correctly, the proposal was that high-dose methylprednisolone in the course of a relapse during therapy would be

allowed, and the question of how to manage that, whether it is considered a second kind of immunotherapy, how many times one might do that through the course of this, and how we would track it is an issue that I think relates to this discussion.

DR. KIEBURTZ: Okay. Dr. Porter.

DR. PORTER: I have been holding back on this question, which I asked yesterday, but I think now that we are talking about treatment, we have to know how they are going to great, and I think that is an integral part of deciding whether or not they will treat in those areas.

What I am referring to actually the last part of the little questionnaire. For example, are you currently experiencing any continuously worsening symptoms that have persisted over several days - eyesight, balance, or strength?

If the patient answers yes, they cannot receive Tysabri. Now, I think we need to walk through this, what this means logically, because this has a huge impact on what kind of therapy the

patient is going to get, because the patient will appear in the doctor's office with an acute exacerbation of MS relatively frequently.

Now, they gave us figures that it won't happen that often, but if you listen to the audience, it happens pretty frequently especially in this population.

Now, the assumption here is that this might not be MS. I mean that is the assumption because we are not going to give Tysabri. The assumption is this has a chance of being PML, which who can say it is not. We discussed this yesterday and there is a huge overlap of symptoms.

So, I think we need clarity on how we are going to treat patients, are we only going to treat patients with Tysabri between exacerbations, and if a patient does have an exacerbation, are we going to treat them as if they might PML, or are we going to watch them to see if PML looks like it develops, or are we going to wait to see if this exacerbation begins to look more like an MS event, and then treat with Tysabri.

I think this issue here is very muddy, and I would like to hear the sponsor address it.

DR. KIEBURTZ: I hear your point. I think part of that discussion needs to happen later, that is, how do we actually--

DR. PORTER: My argument is that if you are making decisions about who is going to be treated, you have to know how the treatment is going to be administered, but then I will yield to the Chair at this point.

DR. KIEBURTZ: I would say the base case of what we should be thinking about, that it is going to be administered monthly, and not in the setting of an acute exacerbation. So, it can't be administered when there is an acute exacerbation.

DR. PORTER: Does that mean that every acute exacerbation will then be looked at as a possible PML event?

DR. KIEBURTZ: That's a separate question. That is what I want to talk about later.

DR. PORTER: Okay.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I would like to condense these questions into my own thoughts especially as somebody who treats many patients with multiple sclerosis, the data that was have suggests that patients with a disability up to an EDSS of 5, we have data on that. We don't have data beyond that, but I think the reality is that there is no trend suggesting there is a safety issue in treating patients who have exacerbating or relapsing disease and higher levels of disability should not receive this agent.

The second point as to who should receive this agent, individuals absolutely, definitely have to have confirmed multiple sclerosis, and I think the only criteria that we have that are objectifiable are MRI criteria.

The third, I would suggest that individuals should try other agents first. There is obviously a decade's worth of experience with other agents. We know the safety profile of those agents well. We don't yet know the safety profile of Tysabri in longer term use.

So, those would be my three caveats - not to restrict to a specific level of disability, not to treat individuals who have unsubstantiated disease, and to require use of an alternative agent first.

DR. KIEBURTZ: Thank you.

Let me go in order. Dr. Jung.

DR. JUNG: I would like to address a couple of comments made by my colleagues, first of all, regarding Dr. Porter's comments. I think that similar to what we see in the use of Novantrone with MS, that you will not see family practitioners or even general neurologists without a large collection of MS patients using Novantrone.

I think that most of the neurologists who currently do use Novantrone are those with a substantial population of MS patients who feel comfortable using that, so I think that the concern that Tysabri would be used relative willy-nilly would be fairly unlikely.

Number two, addressing Dr. McArthur's comments, I respectfully disagree. I think that we

have talked frequently in MS about time is brain, and so you really do need to individualize the treatment of the patients, and if you have someone who is clearly going downhill quickly, that waiting for that person to fail one of the current therapies, given the discrepancy in terms of the efficacy of Tysabri compared to the current therapies on the market would be harmful to the patients.

We have also talked yesterday about the unmet needs of MS patients, and although those of us with large populations of MS patients know that we talk when patients are diagnosed about the four therapies that are on the market, there are substantial numbers of patients--and I don't remember the exact numbers--that we know are not being treated even though there are therapies available, and you have to look at the individual patient in terms of needle phobia. The idea of doing self-injections has really turned a lot of patients away from doing the current disease-modifying therapies.

I know that when I have talked to patients about the idea of getting an I.V. infusion once a month, where they are not the ones who are injecting themselves, that there is that attractiveness to that.

I think obviously, we need to be very careful when we are doing informed consent to talk about the risk of PML as we know in that setting compared to what we know about the relative safety of the current commercially available disease-modifying therapies, but I think that that unmet need needs to be addressed.

We know that there is a substantial number of MS patients out there who are not being treated.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think we need to keep in mind that what we are proposing, as Dr. Porter alluded to, is something between a release of a drug and a long-term clinical study, that we are really looking at something that is going to collect data, a mechanism of collecting data over a longer period of time in a situation that we don't

know what is likely to happen in 5 or 10 years.

There are a number of different situations here - has the patient had pretreatment with one of the usual drugs, has the patient had pretreatment with something else, have they had a couple of courses of a blast of prednisone followed by perhaps some other anti-immune drug, et cetera. There are a lot of different situations.

The other point that has come out very strongly recently, and alluded to earlier, of course, is that the earlier you treat, perhaps the better you are able to prevent long-term disability.

I am wonder if we might not have, since the proposal is to be dealing with a limited number of skilled physicians working out of infusion centers that are going to be known to and working with the company, have a series of gradations of patients, groups that are going to agree to take the medication early after a clearly definite diagnosis is made, the people that are going take it later, people that want to try it early, people

that don't want to try it early, but have tried it after many other things.

I think there is a lot of different areas that need to be explored. I don't think we know what the effect on chronic progressive MS is and yet yesterday we heard a number of testimonies saying that this drug worked at least temporarily to chronic progressive MS.

I am not sure how to answer the question.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Actually, I wanted to go back to--I don't know if it was a debate or not--between Drs. McArthur and Jung and see where they disagree.

Dr. McArthur, were you basically saying that nobody without some disability is a candidate? Is that a proper interpretation of what you said?

DR. McARTHUR: That nobody without disability?

DR. TEMPLE: You should at least have some disability before, not just an episode or not just the diagnosis, but some degree of disability, was that your criteria?

DR. McARTHUR: Let me clarify what I said. I was actually addressing the other end of the EDSS spectrum, and just to go back to what Dr. Jung was saying, I totally agree with her, and I think the concept of neuroprotection, preventing neural degeneration before it happens, I totally agree with that.

I don't think we have yet any hard evidence as to exactly when that should occur, whether it needs to occur in Year 1 of multiple sclerosis diagnosis, or Year 5, or Year 15, bearing in mind that this is a lifetime process.

DR. TEMPLE: But just to be clear, one could, because of the risk, say fine, we understand getting neuroprotection in early is good, but because of this risk, we don't want anybody who hasn't manifested some degree of impairment, residual impairment treated yet. I am not advocating that. I am just saying one could say that.

One could also say that's part of what a patient and the physician ought to decide together,

how much they want to try to do that. You could also say, well, you should have sure that interferon alone won't do the job.

I mean there is a million different things one could impose, and I guess I should add one could, quote "impose" them with varying degrees of stringency. One could say it is recommended for use in this, one could say it is contraindicated in other people.

These is a wide range of ways to incorporate those views once you decide what the views are. Obviously, this is very important to us.

DR. McARTHUR: Right. So, to answer your question, I don't have any firm ideas of conclusions about at the lower end of the disability scale, because frankly, I think at that end of the scale, the available clinical metrics that we have are pretty imprecise.

I also think it's relatively imprecise to decide whether a patient clinically is having an exacerbation, a new lesion of inflammatory damage

within the central nervous system as opposed to all of the other things that can produce neurological symptoms.

I do think, however, that objectifiable MRI evidence of disease activity, contrast enhancement, there are very few people who would argue with that as being a marker or a metric of ongoing disease activity, and that is why I asked the questions as to whether there was a differential response.

There are only a relatively few number of individuals in the 1801 study who did not have contrast-enhancing lesions. It looked to me, even though the numbers were small, that the treatment effect in that small group was much less favorable for individuals with contrast-enhancing lesions.

DR. TEMPLE: That part seems less controversial. The controversial past is, is there some degree of badness that should be a pre-condition, and if so, do you suggest it, do you require it, do you make someone sign something about it, but we will get to all that.

DR. McARTHUR: No, I would not set a minimum level of clinical disability for this drug. I think we all see patients who have no disability, but terrible looking scans, and I think those patients should be treated aggressively with whatever one wants to treat them.

DR. KIEBURTZ: I want to move it around, so that we hear from other people.

Dr. Goldstein.

DR. GOLDSTEIN: First, just a point of clarification. We were talking about disability and impairment as if it's the same thing, and there is a difference between impairment and disability.

Impairment is something that I find when I examine a patient. It may be an arm drift, it may be a little problem with coordination, but it doesn't affect activities of daily living or daily life in any way.

Disability is something that impacts on daily life. It is people that can't do their laundry, can't go upstairs, can't take care of their kids, it's that kind of thing. So, when we

are talking about impairment and disability here, we are talking about two different things.

The point that I want to try to make is that, you know, we are going to be talking about a lot of imponderables--well, they are ponderable, but things without answers--because we don't have the data. We can ponder all we want.

I think what we need to try to crystalize is what we really know and what we don't know, and the reason that I think that's so important to do is that if we come down saying that this is something that is worthy of being reintroduced, the people out there need to know, and the physicians need to know, what to have, what the basis is of this risk-benefit discussion.

We don't have good data on people who fail therapy and then switch to a new therapy. That data does not exist as far as I can tell from reading through this.

The data from the 1802 study is not relevant to that because they weren't treated with monotherapy, and we already know from at least the

way the sponsor is proposing this, that monotherapy is not something that they--I mean dual therapy is not something that they are going to proceed, so we don't know that.

We don't have data on people with secondary progressive MS. That data is not here. We don't have data for people with primary progressive MS. Those data are not here. So, as we are talking about, you know, how to frame this and how to frame risk-benefit, I think it needs to be done in a more authoritative way than just having patients and physicians randomly searching the Internet for the next miracle drug and getting misinterpretations of the available data. I think as we frame this, we need to frame it in that setting.

The other point again that I have made several times, I think, is that there are no direct head-to-head comparisons between this drug and the other available immunomodulatory agents, that the data that we are comparing here is data from trials that were done a decade ago to things that were

done relatively more recently, and we are assuming that this difference that we are seeing means that this may somehow be more efficacious than what other drugs are available.

We found time after time after time after time when we try to do that, we are just plain dead wrong, we are just plain dead wrong when we do head-to-head comparisons. So, that needs to also come through that we don't know that that is the case.

I think then people out there and physicians can try to make informed decisions based upon not only what we know, but what we don't know, and as we frame this, who should get what, under what circumstances, I think that needs to really come through very quickly, that we are making guesstimates here.

DR. KIEBURTZ: Let me just take one step back and say that the only reason that we are here, the only reason there is an advisory committee is because there is an absence of data, and I don't think it is going to help us too greatly to

continue to characterize what we don't know.

The reason we are asked to come here is to give our opinion in the absence of data. So, we need to crystalize, each of us in our own minds, what we would suggest, so that these guys can hear it. We are not decisionmakers, we are advisers. They need to hear what we would advise, and if they think we sound like a bunch of loonies, they will ignore us.

If we sound reasonable, they will take our advice, and I am not being critical of you, Dr. Goldstein. I think you are doing a good job of setting up what the issues are, but I also want to drive towards people coming up with their opinion on this, and I think Dr. McArthur has made a good start of that, which is given the risks, we have to be very clear on the diagnosis, we have to be definite on the diagnosis, more than so than we would be with other agents, and we have to be sure that people have definite MS.

He is suggesting that there be MR confirmation of that and that the people have

relapsing as opposed to a progressive MS, so those kind of concrete recommendations, particularly if people disagree with what has been said before, I would like to hear that.

Ms. Sitcov.

MS. SITCOV: Yes, I agree with Dr. McArthur that there must be a concrete diagnosis of MS, but I also just wanted to second something that Dr. Jung said, and that is, I am a Patient Representative and I am here representing patients, and there is a very big needle phobia, and there is a huge unmet need.

I have been injecting intramuscularly for six years, and I close my eyes when I do it, and I get lucky and I hit the right spot, but there is just a very large unmet need, and I have peers who have flat-out said to me--they are not on anything, they have relapsing-remitting, and if this drug becomes available, they will get monthly infusions.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Thank you for letter me speak before I burst. I want to address a couple of

comments. First of all, I think part of what we are struggling with is the heterogeneity of the disease which I think is obvious, but we need to be very careful when we say that you need specific MRI confirmation of MS.

As we know, there is a small percentage of patients with MS who clearly have negative MRs, positive spinal fluid, and so given the conflict that is out there amongst MS neurologists about how to specifically diagnose, we need to be clear about that. Having said that, I understand that we need to be very clear.

The other point I wanted to address was the comment that Dr. McArthur made about requiring MR evidence of active disease. As we know, MR is exquisitely sensitive and one of the things that we need to be careful about is that we don't go over to the other side, which is do we treat the MRI scan and not the patient.

We know that there is frequent changes on MR that are seen when the patient is clinically stable, and so we need to find a comfortable

balance between that in terms of clinical presentation versus MR.

The other point is going back to the comment about failing current disease-modifying therapy. We traditionally tell patients that to see the biologic effects of one of the disease-modifying therapies, that they need to wait six months before we can address whether one of the drugs that they are taking currently is a failure, and again recognizing that time is brain, we need to be clear that we can't use that absolute necessarily on all of the patients.

I think those were my main comments.

DR. KIEBURTZ: Next, is Dr. Sacco, but I am just going to throw in my points since I put myself on the list of things.

I just want to concur with Dr. McArthur that I think being absolutely certain about the diagnosis in an uncertain world is necessary, and although there are possibilities of people having MS with less levels of evidence, just like there are in other illnesses, I think whatever diagnostic

criteria represent the most stringent should be employed here because of the risk of treatment, and the drug as best we know only helps relapsing-remitting multiple sclerosis. That is the only evidence we have. It may help in other things, but we don't have evidence of that, so we have to be very clear that that is who comes in and give practical ways of defining who that is.

I am not expert enough in that to say precisely, but I think that needs to be operationalized in a coherent way.

I think the other thing is based on subgroup analysis it is very hard to predict a clinical subgroup which is going to fare better than others or worse than others aside from the issue of neutralizing antibodies.

That aside, I don't see any demographic clinical or pretreatment characteristics which identify a group of people who are more likely to benefit than others, and we have precious little data above an EDSS of 4, however, a total of somewhere about 120 patients of 4 or higher, so

that starts to define an upper boundary around which we have data, at least the data we are looking at here.

I have to agree with Dr. McArthur, I can't see a lower bound to that. People that are enrolled and eligible all seem to benefit. I have to disagree with him in that I am not certain that there should be a requirement for prior use and failure of other drugs, whether due to lack of efficacy of side effects.

I agree there is a subgroup of people who are non-progressers, who may be exposing themselves to unnecessary risk, but at the point in time that decision has to be made, it is impossible to know who will be these fast and slow progressers as best as I know at this point in time.

As long as those decisions are made with as much information as possible, and that's conducted in a way to minimize risks, I, for one, can't support a criteria of having used and failed other drugs.

Dr. Sacco is next.

DR. SACCO: I also agree with all the comments you made about selecting the right group, and I think Dr. McArthur's points about the MS group is key.

I think the other things we need to be thinking about is when a clinical trial is done, it is set up with inclusion/exclusion criteria, and there are some here that it is worth going back to and reflecting one, because then when a drug gets released, it sometimes gets used beyond that inclusion/exclusion criteria.

One of them was an EDSS has to be less than 5. You couldn't get into this trial if your EDSS was greater than 5. So, I think making sure that we operationalize and make as clear as possible that the inclusion criteria, from the evidence we have in these trials, will be important, and adding to that regarding the diagnosis of MS, because what I am concerned about after hearing yesterday, is that this is perceived as a wonder drug, and it begins to get used in populations that maybe the original trial didn't

include.

That is why I think we are struggling because of the fear of risk from the data we have in the trials that we have in front of us, so making as clear as possible, I think in our inclusion/exclusion criteria, and going back to looking at them I think would be key.

DR. KIEBURTZ: Dr. Koski and then Dr. Temple.

DR. KOSKI: Thank you. You know, one the problems actually is the fact that when a patient is getting towards an EDSS of 4 and 5, very frequently they are beginning to enter into this secondary progressive phase.

So, this has been one of the issues obviously with interferon treatment over the years, because that was also approved primarily for relapsing-remitting, but I will tell you that over time, you know, increasing numbers of patients with the secondary progressive phases actually are on that drug or on those drugs.

So, I think, unfortunately, it's part of

the disease, and I will bet that it will happen, but we can try and limit it by saying that patients under 4 or patients under 5 EDSS, you know, should be the ones that should be considered for the drug.

DR. KIEBURTZ: Dr. Temple and Dr. Katz.

DR. TEMPLE: One encounters this kind of problem all the time. You put people in your trials that you hope you can show improvement in. As they get sicker, you are not sure you can do that.

We don't necessarily always say a drug if only for the people who have been studied. That is a question that arises all the time, and I just want to point out the distinction between telling people who the studies were done in, which is one thing, and literally saying if you are over 4, don't do this.

First of all, I doubt anybody would pay any attention to that, but leaving that aside. Those are two different things. It is a little--I mean I have never treated anybody, but it's a little hard to swallow the idea that as you get

into the places where you are really worried, you stop using the drug that looks like it works rather well. It just seems unlikely to prevail.

On the other hand, telling people where the data came from, even including the patients, to tell them, you know, that is another thing to consider.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I really want to make the same point, but just to emphasize, remember this is presumably, if it is remarketed, it will be done under a very strict registry with forms that the physician will have to sign, which says my patient has disease X.

I mean here, to speak to Dr. Temple's point, we can describe who the studies were done in, but are we really contemplating having the physician sign a form which says my patient has relapsing-remitting MS with an EDSS of 4 or less, is that what we are talking about, because here we are contemplating fairly strict control over who gets it, or at least having people sign forms that

allegedly are truthful.

So, I am wondering are we asking for that sort of documentation in this case, in other words, restricting it specifically to patient who were studied and having the physician affirm on the form that his or her patient meets all of the criteria, the inclusion criteria, is that what we want?

DR. KIEBURTZ: We will see what people say.

Dr. McArthur.

DR. McARTHUR: I already expressed my opinion. I don't think there should be an upper limit restricting the use of this agent for all of the reasons that Dr. Temple just said.

I did want to clarify why I believe that this agent should probably not be used or considered as a first line drug, and just echoing off of some of Dr. Jung's comments, I mean first we have a lot of experience with the available drugs.

We heard eloquently yesterday that many, many patients do not tolerate them well. Many patients have flu-like reactions, et cetera. On

the flip side, we didn't hear yesterday from the many patients who do tolerate some of these drugs very well for long periods of time.

I think we should not fail to recognize that a monthly infusion of a drug is a complicated process. I am not convinced that the risk management process that is being proposed is going to do anything but make it a nightmare.

For example, I think the last question on the checklist, "Are you current experiencing any continuously worsening symptoms," et cetera, et cetera, I would guarantee that most patients will say yes to that, if they are answering truthfully, and if that's the case, that is going to trigger yet another check with a neurologist or yet another MRI before administration of the drug.

So, this is not going to be an easy process for patients to receive. It is not going to be an easy, one-stop shot monthly infusion, and that is why I believe, in addition to the safety issues, which I do think are tremendously important, the logistics of administering this drug

should restrict it to, if you will, a second line agent.

DR. KIEBURTZ: Dr. Walton.

DR. WALTON: Yes. Adding on to the aspects that Dr. Katz asked to please ensure to be addressed, another part of what I am hearing, and some differing viewpoints that I would like to encourage the committee to clearly address, is the idea of restricting this to use as a second line drug or not, and that will be an important piece of advice for us to consider.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: I just want to add my comment that I did not believe that the drug should be restricted to people specifically within the lines of the trial, that is, I would not, especially given the fact that it was those with the higher levels of disease activity who appeared to have a better response, at least within the limits of the two-year trial. I don't see a reason to limit it just to people who were in the trial, and would use it for EDSS's who were higher.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: My original comment really had to do with the fact, to just reaffirm, that this really is a spectrum of disease, and one of the problems, of course, is when you really enter into the progressive phase. That is the natural history of what happens with significantly involved MS patients.

I think that then it makes it very difficult to determine on terms of these risk issues, you know, what is going on with the patient, and, indeed, as Justin says, you know, you are going to end up doing probably a larger number of MRIs most likely, and some patients will really object to this more frequent analysis of their spinal fluid.

I think that these things are manageable, you know, particularly in the context of MS centers, but these are all going to be major issues, and I agree to some extent that we may not want to limit the use of the drug to an EDSS of 4 or 5, but I think clearly these patients have to

have relapses and remissions, so that we have a characterized population, but that might be on the background of progression.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I guess just to go back, and I guess I would like to concur with Dr. McArthur about the concept of using it as a second line agent simply because, you know, given the fact that people with severe debilitating disease may want to take this risk, I still think that we are very unclear about what exactly the risk is.

Until additional data are available, I think it would be reasonable. We are not limiting the access completely, but we are being a bit more prudent until further data are in.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I agree that I think the diagnosis is most important. I don't agree with the idea of restricting it to second line therapy. In my mind, we will probably get to this later, but the observational study that is being proposed, I am not sure that a huge amount of useful

information will come from that.

In a sense, I would prefer to see those resources, dedicated controlled studies in some of these populations that we are talking about in concert with a broader RiskMAP program.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Just to follow up on the other comment and agree with, I think the people who are entering into a chronic progressive phase or look like they are beginning to have more frequent relapse are going to be the people that are most likely to be really wanting to have this therapy.

We don't know whether, at that point, you would be able to prevent the development of chronic progressive therapy, so I am just seconding Dr. McArthur's comments that let's don't put an upper limit on it.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Again, just when people comment, it would be useful to know whether or not people think it should--obviously, we are talking about who it should be restricted to or not--but

specific elements of the restriction that people have in mind, it would be very important for us to hear what everybody thinks in terms of must it be limited by severity, must it be limited by as second line, and must it be limited to relapsing-remitting even if it's associated with disability, or does the committee rule out the possibility that it could be used in patients with primary progressive or other forms that weren't studied.

So, relapsing-remitting, disease severity, and second line, it would be useful if people could address those three criteria.

DR. KIEBURTZ: Do you mind--after a little more discussion, I may actually go around on each of those questions?

DR. KATZ: Yes, I think it would be actually useful to go around.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I want to clarify that I am not advocating we treat anyone with an unclear diagnosis of MS, so recognizing that there are

criteria out there that we need to make sure that the patients who qualify for the drug truly do have MS.

I do not agree that this should be used only as a second line therapy for the record.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Two points. One is, or a question actually, can we recommend, getting back to Question 5, can we recommend that a clinical trial be done as part of this approval process that we are at now?

In other words, again, what we don't have to answer, you know, we are battling should it be first line, should it be second line, can we recommend that a prospective randomized trial be done comparing this drug with another established immunomodulatory agent and determine that, get the data for that, at the same time that we recommend restrictions in certain circumstances based upon what we know now? Is that a possible recommendation?

DR. KIEBURTZ: We can make whatever

recommendations we want.

DR. GOLDSTEIN: Is that a reasonable recommendation from a regulatory standpoint?

DR. KIEBURTZ: Let me just point that we already said that we don't recommend anything to make it contingent.

Go ahead.

DR. KATZ: Certainly, there are times when we ask sponsors to do studies after approval, so-called Phase IV commitments, which they agree to, and they are required to complete. So, you can certainly recommend that the sponsor, that we require such a Phase IV study of a particular design, to answer a particular question.

But right, the critical question for us, as Karl said, which is do they need to do that now before we contemplate reintroducing it.

DR. WALTON: Also, a recommendation like that would be useful for us to understand the objective of the study. Much of the deliberation here is related to the uncertainty of the risk of natalizumab, so for any study that you might

recommend, a better understanding of what the primary objective you see from that study and how it might be applied to our oversight over the use of natalizumab would be valuable to us.

DR. GOLDSTEIN: I think I understand. You know, it is getting back to Question 5, was there a study that I thought needed to be done before this was potentially reintroduced in any population, and we answered that question.

Now, what I am saying is that given the things that we don't know, is there a critical question that needs to be answered to try to address these issues that we are debating, that we don't have the data for.

The question I was asking, is that possible from a regulatory standpoint, and the answer was yes.

DR. WALTON: Yes, it is, and you should also understand that we recognize that we only have the data that we have now.

DR. GOLDSTEIN: I understand.

DR. WALTON: That recommendations that we

receive from you at the present time are recommendations for what we should do at the present time, and that as additional data come over the course of the next few years, that changes may well be appropriate one way or another in whatever is recommended or put in place at the present time.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I wanted to go back to the issue--first, I will put on the record that I am not saying this should be second line, because I think it would be available for first line--but I want to go back to this issue of evidence-based recommendations, what is written in your package insert, and what societies will write in their evidence-based guidelines.

I still believe that based on the group in the trial, that is the group that is most likely and should be treated with the drug. So, when Dr. Temple say, you know, well, people may do other things, I agree, but lawyers and other people will read what is written in package inserts, as well as what is written in guidelines.

I think that is where we can at least try to inform both the public, as well as the practitioners, who is the best group to be treated.

The issue is the uncertainty of risk, as well as the uncertainty of benefit, to me, in people with the progressive MS, the group with EDSS above 4 or 5 are progressive. So, I still think that is important, and that needs to be somehow reflected when we think about choosing the MS group for this drug.

DR. KIEBURTZ: I think it should be clear, and you can have relapsing or remitting features with an EDSS of higher than that, you start to get accumulating disability that is progressive underlying it, people still have a relapsing-remitting feature.

I think that gets to your point of if they have that feature, but their EDSS is higher, does that somehow exclude them just because their accumulated disability is higher.

No one has spoken to how they think this should be used in combination with Avonex,

Betaseron, Copaxone, Rebif, and Novantrone. Is that because nobody wants to do that, or is that because you just haven't gotten there yet?

Dr. McArthur.

DR. McARTHUR: We are all terrified. Seriously, i can't believe anybody would recommend that at this point.

DR. KIEBURTZ: I just wanted to get that on the record.

Ms. Sitcov.

MS. SITCOV: I would also be very frightened of using Tysabri with a five-day course of Solu-Medrol.

DR. KIEBURTZ: I think we definitely need to come back to the timing and the co-administration and the management of relapse. We will come back to that. We have to face that at some point. I know Dr. Porter is intimately interested in that.

Do you have something else you want to say, Dr. Porter?

DR. PORTER: Yes, I just wanted to say

that--and this will surprise you coming from the Industry Representative--that I think that this has to be a second line drug. In the classic administration of medications, we always give drugs first that are safe and effective. This one is less safe at the present time given the data that we have, the limited data.

So, I think we would be, from the standpoint of the point Dr. McArthur made, which is we didn't hear about a lot of people who do well on all these other anti-immunologic drugs, and many of them do, number one, and number two, the medical-legal implications of giving this drug as a first drug before trying something else, I think propels us for sure into saying at the moment, maybe later this won't be true, but at the moment this should not be the first drug that is given to the patient with the disease.

DR. KIEBURTZ: So, can I go through a little exercise here now, which is I am going to ask everybody to answer a Yes or No question, and there is going to be a series of them, and I am

just going to go right around counterclockwise starting with Dr. Porter and ending with Dr. Hughes.

Bear with me. Just say Yes or No, and don't explain yourself.

Would you permit use as a first line agent?

DR. PORTER: Non-voting No.

DR. KOSKI: Yes, I would.

DR. GOLDSTEIN: Not now.

DR. DeKOSKY: I would.

DR. KIEBURTZ: I should say your name.

Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: I vote yes.

So, there you go. No consensus. Sohail will tell us what the numbers were, I presume. I think the point there is you are not going to get a--there is a division of opinion, which I think reflects the reasonableness.

DR. KATZ: Do you actually have a tally somewhere? I realize it's split. I would just like to know what the exact numbers are.

DR. KIEBURTZ: Did you include Roger?

DR. MOSADDEGH: I did, yes.

DR. KIEBURTZ: He's non-voting.

DR. KATZ: Dr. Porter is a non-voting member, but we did ask him, just to get an idea. Give us the tally with and without Dr. Porter. We will figure it out.

DR. KIEBURTZ: Dr. Porter voted No.

DR. MOSADDEGH: 6-6.

DR. KIEBURTZ: 6-6 excluding Dr. Porter, and Dr. Porter voted No.

You missed a vote.

DR. KIEBURTZ: One more time. We missed a vote.

Perhaps more slowly. Would you allow first line use? Dr. Porter.

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Yes.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Still Yes.

DR. KIEBURTZ: This is a chance to change your vote.

Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: Dr. Kieburtz. Yes.

7 Yes, 5 No. The non-voting is a No.

The second question. Would you impose any limits of functional disability specifically any cutoff scores on the EDSS for eligibility to use the drug?

DR. PORTER: Are you talking the up side or the down side or both?

DR. KIEBURTZ: Either.

Two votes. Would you impose any upper

limit on EDSS severity?

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No, but I would want to make it very clear that there were relapses and remissions. I mean I think that has to be--

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: No.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: Dr. Kieburtz. No.

One Yes in the voting group, and the non-voting was No.

The same question, different. Would you impose any lower--not saying what it is--but would you want to impose any lower limit of disability scale score on the EDSS?

DR. PORTER: Non-voting Yes.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Abstain.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: No.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: I vote No as well.

The tally on that is 10 No, 1 Yes, 1 Abstain, and a Yes from the non-voting member.

One more question. We are making progress.

Do you think MS patients without relapsing-remitting features, that is, with primary progressive MS or solely progressive MS without any more relapsing-remitting features should be allowed to take the intervention at initiation?

DR. PORTER: You mean at this time?

DR. KIEBURTZ: At this time.

DR. PORTER: Non-voting No.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: No.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: No.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: No.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: No.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: No.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: No.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: No.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: No.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: No.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: No.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: No.

DR. KIEBURTZ: I vote No, as well.

I think it's unanimous on a No for including individuals who do not have relapsing-remitting features.

Are we getting to things that are helpful for you guys?

DR. McARTHUR: I just think you should clarify that question. It is not so much relapsing-remitting as relapsing, and relapsing progressive, I think would still be encompassed with certainly my recommendations.

DR. KIEBURTZ: Features that include exacerbations.

DR. McARTHUR: Take out the word "remitting."

DR. KIEBURTZ: Would anyone change their vote if we say "relapsing"? I think I am using some different vocabulary, but I don't think anyone changes their vote. I think they can have a

progressive illness, but they still have to have relapsing features.

No one endorses the idea at this point of approval with co-administration of any of the other agents currently approved for the use of MS. The committee was unanimous on that, too.

DR. KATZ: I am sorry. It's unanimous that people believe it should not be co-administered with other?

DR. KIEBURTZ: --approved agents.

DR. KATZ: All other approved agents.

DR. KIEBURTZ: Avonex, Betaseron, Copaxone, Rebif, and Novantrone.

DR. McARTHUR: Chronic administration, because we are still going to have to deal with the issue of methylprednisolone.

DR. KIEBURTZ: Yes. The management of acute exacerbations we have not touched on, but chronic co-administration.

DR. KATZ: And that is because even though we can't say with confidence that the risk is any different with concomitant MS therapy, we are more

nervous that it is, or there is no evidence that those other drugs add anything to the effectiveness of Tysabri? I am just interested in what the rationale is.

DR. KIEBURTZ: I will give you my rationale, and then I will let Dr. McArthur. I think we don't know yet, and it will allow us to get a clear understanding of what the risk is with the agent alone.

There may be circumstances and, in fact, trials where you would allow co-administration, but I would not support marketing, because we don't know yet, and we need a larger sample to get a sense of what the actual risk is.

DR. KATZ: We don't know yet, but we are nervous or you are nervous that the risk is greater?

DR. KIEBURTZ: That is my concern, that there is an enhanced risk with the co-administration of an immune modulator and immunosuppressive agent. Secondarily, 1802 suggests that there is--

DR. KATZ: Well, 1802, I think suggest that adding Avonex to Tysabri doesn't really give you very much more.

DR. KIEBURTZ: Adding Tysabri to Avonex, yes.

DR. KATZ: Right, adding Avonex to Tysabri doesn't really give you much more than Tysabri alone. That is a hint, it's not proof, and we don't know anything about what happens when you add any of the other approved MS agents.

DR. KIEBURTZ: Right.

DR. KATZ: I am not advocating a position. I just want to flesh out the committee's thinking.

DR. KIEBURTZ: I understand. So, did that help what I said, and you understand my thinking?

DR. KATZ: Yes.

DR. McARTHUR: My opinion would really just be based on safety issues, but I don't think it is adequate to just list these five agents. I think we need to specify other immunosuppressive agents. They may not be approved for us in multiple sclerosis, but they are being used, and in

my view, there is the potential for enhanced risk with the co-administration of those agents.

DR. WALTON: We take that point very much. These were listed only because they were the approved agents and might come most prominently to mind.

DR. KIEBURTZ: I think we have had enough discussion on Question No. 6 for the moment.

I think we will take a break for 15 minutes and come back and address Question 7.

[Break.]

DR. KIEBURTZ: Question 7. Considering the currently available data, please discuss whether natalizumab should be returned to the marketplace for at least some patients--and we discussed that without conclusion exactly whom, but with some guidance, I think the Agency can consider--taking into account the preceding discussion of specific populations. After discussion, please vote on this question.

DR. Walton.

DR. WALTON: You may want to decide how

much discussion you still need, because after all, the previous question had very extensive discussion.

DR. KIEBURTZ: I am not sure we need any discussion, unless I see someone putting their hand up.

So, having done that, and having a full complement, why don't we take a vote on this and we will start with Dr. Porter, who I would like to know even though I know it doesn't count.

So, should we return Tysabri to the marketplace for at least a defined set of patients?

DR. PORTER: Non-voting Yes.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: Yes.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Yes.

DR. KIEBURTZ: Dr Sejvar.

DR. SEJVAR: Yes.

DR. COUCH: Dr. Ricaurte.

DR. RICAURTE: Yes.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Yes.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Yes.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes.

DR. KIEBURTZ: Dr. McArthur?

DR. McARTHUR: Yes.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Yes.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: Yes.

DR. KIEBURTZ: It's unanimous, 12 to zero, we vote in favor of returning it to the marketplace.

Well, we are halfway there.

So, we have talked about in whom, and I think discussion should now continue on a similar vein, with not necessarily reaching consensus on the how.

Question 8 spans three pages, and it talks

about the essential or nonessential features of an acceptable risk management (minimization) plan. In this discussion, consider the risk management plan proposed by the sponsor and comment on the appropriateness of specific aspects of the proposed plan. Please include in your discussion potential restrictions to patient availability, such as, and then there is Items (a) through (h) with subparts to each of those (a) through (h), somewhere between one and five subparts.

The first question is would we only want patient mandatory registration that is distribution to patients enrolled in the registry. That is what the sponsor proposes, but can we have discussion on that, whether people think that is a good idea or not, or should it be available outside of such a registry.

Dr. Koski.

DR. KOSKI: I would say that it should be absolutely mandatory.

DR. KIEBURTZ: Any disagreement on that? Dr. Katz.

DR. KATZ: You could just sort of ask for a consensus. We don't need a lot of discussion I think if everybody agrees.

DR. KIEBURTZ: I think the general feeling is that there should be a mandatory registry in keeping with the sponsor's proposal.

The second part of that is what information should be collected on all patients in the registry, and what you have heard, and I think we heard reiterated this morning, is that the physicians will be contacted by the sponsor every six months for them to relay information about deaths, PML, discontinuations, but then there is other things here - other infections, serious adverse events, concomitant immunomodulator use.

What do you think should be transmitted from the physician to the sponsor at this every six month, what is the minimal essential information?

Dr. Hughes.

DR. M. HUGHES: I guess my feeling here is that mortality, in-depth information about the causes of mortality is probably the most important

information for understanding the risks of this drug in clinical practice.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think that if we look at the experience with the NIH stroke scale, which other people at the table can comment about more than myself, it would not be unreasonable to require that the patient have an EDSS recorded on each monthly visit. That would be relatively easy.

Perhaps elements of the multiple sclerosis functional component that they have mentioned, can the patient walk 25 yards, et cetera, et cetera. I think several easy things, these could be done by the staff t the infusion center whether it's a nurse, a physical therapist, a PT aide, whatever, but I think having this kind of information in addition to the mortality, infections, adverse events would be very useful and would provide us with an ongoing database by which you could begin to establish whether this drug is effective over a longer period of time.

DR. KIEBURTZ: Are you referring to the

cohort study or the registry?

DR. COUCH: I am referring to patients who would be in the RiskMAP Registry, every patient.

DR. KIEBURTZ: So, the current notion is that physicians provide information every six months, and you are suggesting every month?

DR. COUCH: I am suggesting that as part of the recordkeeping, when the patient returns, you can do an EDSS very quickly, at least from the impairment/disability standpoint.

You could carry out at least one or two components of the multiple sclerosis functional component, can they walk 25 yards, can they do a few things like that, and then go ahead with the infusion, but this could be done by a trained staff at the infusion center.

This is perhaps not that much different than in the ongoing stroke studies where nurses, technicians, what have you, provide NIH stroke scale data on patients that come in for the JCAHO stroke certification.

DR. KIEBURTZ: Just so I make sure I

understand, so that information would then be held at the site?

DR. COUCH: I believe this information could be recorded and then at the six-month interval transmitted.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I share Dr. Couch's belief that more information is likely to be better, but I am not sure logistically how most infusion centers would be able to do this. I know our own infusion center, I would not feel comfortable that our nursing staff who are very good at what they do, they are not trained to do neurological exams, they are not trained to do EDSS, and I think the variability would really make the data less than useful.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I think the other thing would come up, I mean our own MS center would probably be able to do that. The difference is, however, interpreting that data on a month-to-month basis, because there is variability that occurs, and the

other thing is that, you know, after an exacerbation, you have some persistence of symptoms that, to some extent, resolve.

So, unless you have that all in a linear fashion, I think it would be very difficult to sort of put it together in a cohort type of analysis.

DR. COUCH: I think that would be the advantage of having the linear information to document exacerbations, remissions. I am not suggesting that we are going to look for a linear progression, but we are going to look for what is going on during the time the patients are getting the infusion.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I guess I would just like to respectfully suggest that the question about efficacy and the question about safety are maybe two slightly different things, and the purpose of the registry, I think should focus on the safety question and kind of focus on that.

DR. KIEBURTZ: Let me just remind people about Slide 94, which is the proposed registry at

least by the sponsor. What the sponsor proposed is any known PML event is reported I think immediately to the sponsor, but then the physicians will be queried every six months for PML, other serious opportunistic infections, death of any cause, and discontinuation.

Those are the only bits of information that would be mandatorily collected on a six-month basis. I believe that is the current suggestion.

What Dr. Couch, if I understand it correctly, is suggesting is that that be augmented by that information being collected monthly along with EDSS and some aspects of the MS functional capacity scale.

Dr. Goldstein.

DR. GOLDSTEIN: I tend to agree that the issue of safety is a slightly different issue than trying to track this information. It may be better to try to track this in the cohort study.

The other point is the list of things to be reported includes concomitant immunomodulators, and it was my understanding from what we discussed

previously, that these folks should not be on concomitant immunomodulators, so I don't know what the purpose is of reporting that. It should be zero.

DR. KIEBURTZ: These questions were written before we voted.

DR. GOLDSTEIN: I understand. So, I think that could come out, but the thing that I would probably put in there is use of I.V. methylprednisolone, because that might be a surrogate indicator for exacerbation, and it is a concomitant medication that may prove important to know about depending upon some of the other risk. So, I would just make that switch.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I think we need to add serious adverse events, because I believe that was not on the RiskMAP.

DR. KIEBURTZ: As currently defined, serious adverse events would not be collected in the context of the registry every six months, but would be in the context of the proposed

observational cohort, which would be a subset of people.

DR. JUNG: I believe it should be part of the registry, as well.

DR. KIEBURTZ: Other comments?

Dr. Sacco.

DR. SACCO: I think it is important just to clarify the purpose like we have been talking about. We will have the opportunity I think to talk about the cohort where we may be able to get more of the other information that Dr. Couch is mentioning, EDSS score, other risk factors, a larger sample. So, clarifying the purpose, the registry, to me, it sounds like is giving us some safety, but also giving us this connection regarding who the drug should be dispensed to. That is part of the registry, as well.

DR. KIEBURTZ: I think the intent of the registry, as I understand it, is to be able to track this issue almost singularly of PML.

Dr. Temple.

DR. TEMPLE: Just the thought that you may

not want to abandon asking about other immunosuppressives, even though it wouldn't be intended that they be used, because things happen that, you know, you didn't intend. So, someone else, some other neurologist might put them on it and ignore the rules. So, I guess I wouldn't drop that too quickly.

The only other thing I guess I want to say is that hoping that a registry will produce useful effectiveness information is something of a fantasy. They don't really do that.

DR. KIEBURTZ: Dr. Dal Pan.

DR. DAL PAN: Yes. One of the other things we were thinking about with regard to the registry was complete dosing information, so that when we look at whatever adverse events come out, we have some sort of accurate denominator against which to look at the numerator.

DR. KIEBURTZ: And by "complete dosing," you refer not only to doses given in the context of the registry, but any information about prior usage that occurred in trials and in the previous

marketing experience?

DR. DAL PAN: We would be interested in all that, yes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: Is the intent here that--maybe I am moving ahead to the distribution system--but the registry forms and whatever is decided should be in those forms be received by this central distribution center before drug is dispensed?

DR. KIEBURTZ: I believe the proposed registry, as we saw yesterday, the forms have to be completed before shipment. No?

DR. KATZ: The initial form has to be completed, the acknowledgment form or whatever we are calling it, before the initial shipment of drug, but there is currently in the proposed plan no requirement that there be sort of a real-time--and this is something actually we ask about in one of our questions--there is no requirement that there be some information received back at the distribution center every month before

the next month's shipment is released.

That is a question we had about whether or not that might be more appropriate for various reasons that you can talk about, but that is a question we have. It's not the case in the current proposal.

DR. McARTHUR: So, it seems to me, then, an ongoing cross-check between the receipt of safety information centrally and the dispensing of drugs is critical. No patient is going to enter Tysabri treatment with PML. That is an incredibly unlikely event. It is also pretty unlikely that they will develop PML during the course of Tysabri treatment, but that is the event that we are looking for.

So, in my opinion, we have to link drug dispensing to receipt of patient safety information on a continuing basis not only for as long as the patient is receiving it, but I think for a prolonged period of time after they have received Tysabri.

DR. KATZ: Well, again, that is a critical

element or potential element of the plan that we would very much like to hear what the committee thinks. There are those of us who agree with you and those of us who don't necessarily.

So, we really want to hear a discussion on that specific point, and again I believe it is a specific sub-question a little bit later on, so you can talk about it now or whenever.

DR. KIEBURTZ: We can talk about it now.

Dr. Porter.

DR. PORTER: Good. I think that there is no doubt that you want to have the safety information at hand before you dispense the drug, but I don't think that what you want to do is have an incredibly bureaucratic pass back to the drug company to make sure that they look at the safety data and say, oh, yeah, we agree with, Doc, it's okay to give the drug.

So, I think that it's reasonable to have a safety check, but I think it can be done at the front line with the physician.

DR. KIEBURTZ: Dr. Dal Pan.

DR. DAL PAN: With regard to Dr. McArthur's point, I just want to mention that Question (c)(4), because it's exactly about Question 8(c)(4), should there be a periodic reauthorization of Tysabri administration, if so, how often? For example, prior to each infusion, every six months, or whatever other recommendation you come up with.

So, that issue is important for us to hear you discuss.

DR. KIEBURTZ: If I understand it correctly, after the initiation procedures, and the registration of the person, depending on how we suggest distribution, it is possible that the person will not be seen by a neurologist for another year, another two years.

There is no mandated reassessment, reevaluation, examination. It is just every six months the physician will be called or contacted by the sponsor and asked do you know anything about PML, other opportunistic infections, deaths, or discontinuations, but that doesn't require that the

physician actually have examined the patient as it stands, as I read it.

Dr. McArthur.

DR. McARTHUR: I think it's an excellent point, and I think it would again, in my opinion, be less than standard of care to prescribe this drug and not follow the patient on a continuing basis or continuing regular basis.

I also, with respect to Dr. Porter, I think placing this just in the hands of busy neurologists, we are notoriously not very good at reporting things on a voluntary basis. I think the FDA can attest to that in terms of their post-marketing experience.

That is why mandating some sort of no form, no drug experience is I guess what I am proposing.

DR. PORTER: Well, I agree with you. In fact, what I was saying is don't make it so tight that every time a dose has to be administered, that there has to be a link back to the drug company, because that will drive everybody crazy. But a

process of reporting the data back to the company, I was sort of expecting.

Apparently, that is not part of the plan? I thought that was part of the plan, that the data that the doctor was going to be collecting on this patient would be, as part of the registry, would be sent back to the company.

DR. KIEBURTZ: Could you clarify that issue for us about the proposal?

DR. BOZIC: We are mandating that the doctor provide us with these data every six months - the PML, the deaths, the discontinuations, and what we have decided is that if we don't get these data from the doctor, then, we are going to directly contact the patient to obtain the data, and if still after that we don't get the data, we will de-enroll that patient, and if the doctor continuously has a pattern of not giving us the data, that doctor will be de-enrolled.

So, we have a mechanism to obtain that safety data, and that is our proposal.

DR. McARTHUR: So, how complicated would

it be, Dr. Bozic, how complicated would it be to mandate that, again no form, no drug on a six-monthly basis? You are going to do a lot of detective work. The doctor doesn't send the form back, now you are going to call the patient, the patient is out of town, et cetera.

Why not just make it mandatory every six months if you are on this drug, your doctor needs to provide this form before the drug is released?

DR. BOZIC: I think that what we are proposing is a system that has a great deal of controls in it already. I can walk through all the controls because I think it does bear repeating since I only presented it once yesterday.

So, can I have the slide from my core presentation, please.

[Slide.]

Before the patient and physician start Tysabri, they discuss the risks and benefits. They will read and sign the patient/physician acknowledgment that we circulated today, and then they will send it in to Biogen Idec.

We are going to verify that that document has been signed and that the patient fulfills the criteria, in other words, they have relapsing MS, and then what we are going to do is we are going to sign the patient authorization to that patient, and then we will match them to a registered infusion center.

So, that gives the authorization to that registered infusion center to begin dosing the patient. How does that center become authorized? They have received training by our field personnel on the risks and benefits of Tysabri and the risk management requirements.

The requirements that they have to fulfill are they have to dose only patients in Tysabri Registry, they have to provide a Med Guide to the patient before every dose, they have to complete the checklist before every dose, and they have to document all this in the Tysabri infusion log.

They also receive training on the importance of reporting adverse events to us including PML, and they have to agree to submit to

periodic audits, to verify that they are compliant with this.

So, once an infusion center becomes registered, now they are known to our centralized distribution system, and they can begin receiving Tysabri shipments. So, they can have a small amount of inventory on site, and then once all that happens, the patient can begin receiving Tysabri treatments.

The other mechanisms in the system to facilitate close monitoring of the patient, close clinical monitoring of the patient are, number one, the checklist. The purpose of the checklist is many fold, so one purpose is to make sure that there are no concomitant therapies being used, so we reinforce that.

We reinforce the risk. We make sure the patient has read the Medication Guide, is aware of the contents of the Medication Guide before each dose, and also there is a neurological screening questionnaire to make sure the patient doesn't have any new neurological symptoms that need to be

investigated, and if those are detected, the dose gets suspended and the neurologist gets called in.

So, we have a mechanism to call in the neurologist for cause if there are new neurological symptoms. The other mechanism that we have to facilitate close follow-up with the neurologist is in the Tysabri Registry where we ask for safety information on that patient every six months.

So, that is meant to be a prompt to the physician to, at a minimum, be aware of what the patient's status is. They may choose to have the patient in the office to evaluate that, they may do it by phone. We leave that kind of flexibility in the system there.

So, what I am saying is this is a highly controlled, closed, mandatory system with a lot or regimentation in it already. What you might be proposing, I mean sort of this vial-by-vial sort of distribution model that I believe is coming up in one of the questions, the issue with that is that is very different to how infusion centers operate.

Most infusion centers have a small amount

of inventory on site, and what that allows them to do is to permit scheduling of the patients in some logical fashion. As you saw yesterday, a lot of patients have a lot of difficulty traveling and coming to their visits.

So, you can imagine if a patient shows up for their appointment, for their infusion, and the vial isn't there, that is going to cause a lot of disturbance to that patient, or similarly, if the patient shows up, the vial is there, but the patient hasn't been authorized, these kind of logistical issues are very important in the management and the timing of these infusion centers.

We did a survey also of infusion centers, and we found out that many hospital-based and MS centers, in fact, simply don't want to participate in a model where they would have no inventory on site, because of all these burdensome issues for their patients.

DR. KIEBURTZ: Currently, I just want to reiterate the point you made, that the six-month

safety evaluation, which is mandatory, and if the physician doesn't do it and the patient doesn't do it, they get disenrolled.

DR. BOZIC: Yes.

DR. KIEBURTZ: The physician can do that in any way he or she feels is appropriate, there is no guidance on that. In fact, they don't even have to contact the patient.

DR. BOZIC: We leave it at the discretion of the physician. I think it would be very hard, as a physician, to give an answer on the status of your patient unless you have actually contacted them.

DR. KIEBURTZ: I think we could make a recommendation to make that clear, that, for example, you can only fill out the six-month evaluation based on an in-person evaluation. I want the committee to know that's the kind of guidance I believe the Agency is looking for.

Dr. Katz.

DR. KATZ: A couple of things. There is at least two issues that are important for us to

hear the committee's views on. One is how often should the patient be seen by the physician. You have just said maybe every six months, and we need to talk about that, whether you want to do that at all. So, that is one thing. That is how often they should be seen by the doctor.

The other is are the elements of the registry, as currently proposed, are they being followed the way they are supposed to be followed. For example, there is supposed to be a checklist administered before each dose.

One question is how do we know that is happening if we think that is an important thing to be done, how do we ensure that in real time that is actually happening. Right now the sponsor is proposing every six months to sort of assess how well the system is working on a number of fronts.

Let me propose a very intensively monitored, restrictive system. It would be useful for us to know whether or not the committee thinks that it is too restrictive or not.

Along the lines of what Dr. McArthur is

saying and along sort of the clozapine-like, you know, no blood, no drug, no forms sent back to the company or the distribution center, no next vial sent, you just heard why, from a logistical point of view, that might be very difficult to do. You will have to think about whether you agree with that.

But in the most restrictive scenario that I would paint, in order to ensure that the dictates of the registry are being followed, let's say the checklist is being actually administered every month, the company or the distribution center would have to get back a copy of that checklist filled out to ensure that it is being followed appropriately and therefore the drug can be released.

So, that is one sort of scenario, no drug unless you get the forms, as Dr. McArthur put it, on a monthly basis. That would be probably the most restrictive.

One other advantage of at least getting the forms back every month, if not making drug

release contingent on that, but one of the advantages of the distribution center getting the forms back every month is that if a form doesn't come back, the distribution center or the company can call the doctor in real time and say how come no form, how come we didn't get last month's form.

It could be because they forgot to send it in or it could be because the patient discontinued or something happened to the patient. It would be a signal that some follow-up is necessary. So, one scenario would be form sent back or something sent back every month to the distribution center and follow-up to the doctor or the infusion center if a particular month's form isn't returned.

This doesn't require that the drug be released on monthly basis. You could release the drug every six months, let's say, but still require that the form come back every month, and if the form doesn't come back every month, then follow-up, as opposed to waiting for six months, because we want to get this information in real time. If a patient has PML, you don't want to wait six months

to hear about it or something else bad.

So, that's one proposal. It could be electronic, of course, the details to be worked out. So, the question about should a form be sent back every month independent of how often the drug should be sent, it is very useful for us to know what the committee thinks about that kind of system.

DR. KIEBURTZ: Let me make sure I understand. So, imagine a system in which six months' worth of drug is shipped and available at the infusion site, but monthly, in advance of each of those infusions, there needs to be forms.

If those forms are not received electronically, fax, however, by the central distribution center, even though drug is at the infusion center, there would be some feedback to the infusion center you are not supposed to administer to that patient because you haven't given us the information. Is that it?

DR. KATZ: Something like that or just a query why didn't we get the form back, and that

would alert the company in real time with a month's lag that something might have happened to the patient requiring further follow-up. Yes, that's the idea.

DR. KIEBURTZ: Just to expand on that a little and perhaps a conclusion to it, if you then had to have a physician-patient interaction on the six-month basis, the way you get your next six months is that that happened, there is documents that that happened, and the prior six checklist forms also have to be on record, otherwise, you can't get your next six months, so that least you wouldn't have redistribution.

Even if forms aren't coming, it may be hard to stop those infusions, but the maximum you could do is an additional five without forms, because then it would stop based on the next evaluation.

DR. KATZ: Right, and making each monthly dosage, the release of that dose contingent upon getting the forms would be the most restrictive because the physician could not possibly administer

even the next dose because they wouldn't have it.

DR. KIEBURTZ: We have heard some issues about impracticality around that.

Dr. Dal Pan.

DR. DAL PAN: I just wanted to reframe the issue the way Dr. Wysowski framed it yesterday.

So, there is three things that we want to hear about, that are separate but related, and may not be so separate. One is what actually allow the patient to get each dose. Two is should there be periodic reassessments by the physician, and three, periodic reauthorizations, and you can imagine a system where you bundle all that into one or where you separate them. So, that is what we are interested in hearing about.

The second issue is with regard to every six months Biogen Idec contacting the physician about PML and other serious adverse events, opportunistic infections, and our concern was that from the surveillance point of view, that should probably be more frequent. Of course, we would like to hear what the committee has to say about

that, as well.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Just along the same line, I would like to ask Dr. McArthur and Dr. Jung what their feeling is on what the routine follow-up should be for a stable MS patient, how often should that patient be seen in the regular world.

I am assuming that if the patient does have additional symptoms and it looks like they are having a relapse, they are going to come in anyway, but if you have got a stable patient, what would be your recommendation for the length of time between follow-ups?

DR. KIEBURTZ: I am going to let Dr. McArthur speak to that and whatever else he wanted to speak to, and then Dr. Jung.

DR. McARTHUR: I think the issue is not their stability, but we are treating them with an active drug and a drug that potentially has side effects. It looks like the incidence is extremely low fortunately. So, I think initially, in a new entry of this agent into the market, six months

would be a reasonable compromise.

It is not practical for them to see a neurologist every month or two months, and this is probably not necessary, but every six months would seem like a reasonable compromise. If nothing happens in terms of safety issues over the next couple of years, then, we could probably liberalize that.

I would just like to go back to the whole forms issue. You know, this is not rocket science. I mean the forms should be web based. There is no reason to be shuffling paper around the country. The forms should be held centrally in a HIPAA-approved manner.

That means that Biogen Idec and the FDA, and whoever else needs to monitor these things, knows that the forms are being completed relative to the patients who have been registered into the study. I mean to rely on things being faxed around the country is just ludicrous, frankly. It should all be web based.

How you do it in terms of releasing the

drug, whether you have a small inventory for each site with an authorization code, these are all just details that can be worked out, but there needs to be a mandate that that safety information gets back before there is continuing use of the drug.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I believe that given what we have seen with the studies, that with the hypersensitivity reactions and some of the problems that can occur early on in treatment, that probably when you first initiate treatment, seeing the patient within the first three months would probably be appropriate, and then if they are stable, then, going to a six-month period is pretty appropriate.

I am concerned about the idea that from just the logistical standpoint, even for a web-based system, which I think is a great idea, that given the nature of the patients that we are taking care of, to expect them to be able to smoothly receive an infusion once a month based upon feedback from their physician on a monthly

basis is impossible.

You are talking about patients who are traveling in from perhaps rural areas to an MS center for infusion, and the idea that if their doctor happened to not have filled out a particular form within that week, and having the patient turned back is just unacceptable I think.

So, I think monitoring is important, but on a month-to-month basis trying to keep track of that is not manageable.

DR. KIEBURTZ: Let me just clarify. I think what we are talking about on a month-to-month, is that the immunosuppression checklist and the PML checklist is completed prior to infusion, and that is what is sent, so that not a physician assessment, just those checklists although we are going about the content of those, that those are gone through prior to infusion and are recorded.

The physician assessment--and I think you make a reasonable suggestion--it would have to happen before the first dose, at three months, six

months, and every six months thereafter seems like a reasonable schedule, getting back to Dal Pan's question.

But I just wanted to clarify the difference between a physician assessment the pre-infusion checklists, I think we are just talking about receiving the pre-infusion checklists.

MS. SITCOV: Just in terms of the pre-infusion checklist, as a potential consumer in this, I very much care about the safety, but it seems so burdensome to really carry out, because so many of us with MS, in the course of a week can have symptoms that might show up and them remit, and then show up again and then remit, and it doesn't mean that I am having a flare-up, but if I have got to report all of these, and a nurse who is trained at this is perhaps assuming or might be trained to look at any symptom or any change, when am I ever going to get the drug?

I speak of me in the singular. I mean that really generically. It just strikes me as

very burdensome. I wonder if there is just another way.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I would like to actually respond to certain aspects of that question and then one other thing.

First of all, fluctuating symptoms are an aspect of MS, and I think anybody who takes care of MS patients realizes that. The difference is you are trying to look for a progressive type of symptom that has extended over a period of time beyond when the patient has last been seen.

So, I don't think that that type of thing would necessarily, you know, this fluctuating type of symptom would interrupt therapy at that time.

The other thing I wanted to comment on is somebody brought up the issue about a physician, the "neurologist," quote, unquote, that is caring for the patient should perhaps see the patient if there has been an infusion-related reaction.

You know, most of those are going to happen very rapidly, you know, around the time that

you actually get the infusion. Again, I can't speak for all infusion centers. I know with our own infusion center, we actually do have a physician on site. That physician would see that patient for the infusion-related reaction and respond appropriately.

So, it may not be the same person, but usually, that is right at the time the treatment is going forward.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: We are now getting into I think questions of the substance of the questionnaire or the checklist, and we have questions specifically. One of them is up there.

I would just like to know whether or not there is more or less general, before we get to those substantive questions, whether or not there is more or less general consensus that, for example, the requirement that the form be sent back to the sponsor on a monthly basis is something that we should impose.

That is the last suggestion that was on

the table, but I don't know if there is general agreement that that is something that should be part of this.

DR. KIEBURTZ: I agree. Before we get to the substance of the checklist, both about PML risk and immunosuppressant risk, let's talk about the format in which it would be filled out.

Dr. Hughes, Porter, then Temple.

DR. M. HUGHES: My question is on another issue, so I will pass for the moment.

DR. PORTER: My view is very simple, and that is, I have no objection to the concept of having these monthly forms coming back and having it sort of a mandatory process, but I think the forms should be at the infusion center, and if the patient arrives and there is no form filled out, there should be a nurse available to fill out the form, so that they could do it on site, right there on site.

DR. KIEBURTZ: That's the intention.

DR. PORTER: And then the patient isn't penalized for coming 100 miles to get their

infusion because somebody didn't do it, or didn't do the last one, whatever.

DR. KIEBURTZ: That is where the forms would be. They couldn't be completed in advance or anywhere else but at the time of the infusion.

DR. PORTER: As long as the patient isn't penalized, because the patient is the one that is left holding the bag in these processes, as has been pointed out already.

DR. KIEBURTZ: If it's an authorized infusion center, there should be no difficulty in having the forms and filling them out. That would be who would be an authorized infusion center that they have them and can fill them out.

DR. PORTER: Exactly.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: That is what I was addressing. What I hear people saying about this is that you would learn early whether the forms are not being filled out, but that would not affect the infusion on the day they failed to fill it out. It would remind them that there is something they had

been check, so during the next month, they would call up, ask what is going on, and so on. So, it would really affect that infusion.

DR. KIEBURTZ: No, I mean there is going to be the risk of infusing someone who has symptoms of PML at the time they are infused, because someone may not use the checklist as appropriate.

DR. TEMPLE: But you would know that within a short amount of time.

DR. KIEBURTZ: You would know how many infusions are happening without forms being filled out based on how many don't come back, but it won't prevent that from happening if people flaunt what they are supposed to do.

Dr. Koski.

DR. KOSKI: No, Dr. Temple's comment was mine.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Again, presumably, this would be a web-based system, so that the reporting would be automatic, you fill out the form and the form is reported, so that what you are doing is

looking for a longer term compliance of every six months you review and you say we shipped for this number of patients, and we only have this number of forms, if you are a bad actor and if you don't fix this, we are stopping.

Now, the content, again, that is a different issue, and I think we will get to that later.

DR. KIEBURTZ: I would also just about one of the details here, which I would like to sort of cover (a) through (e) before we go on to (f), (g), and (h), and I think (d) and (e) are mooted actually. I think we are done with (d) and (e). We are only talking about giving this to MS patients who fulfill whatever the restrictions are that you conclude on.

Is that fair? Am I missing some discussion on (d) and (e), which is restriction to only MS patients, restriction to only MS patients deemed appropriate in Question 7? All right.

So, if, in fact, you had a distribution of 6 months' worth of vials, I think it would be

important that those vials be designated specifically for a patient, that the stock you have is not fungible, you can't move it around for a different subject, that it comes, it is for that person, and if they drop out or fail to meet criterion, it would be possible to retrieve those specific vials that were for that specific patient.

What do people think about that?

DR. PORTER: Actually, I think that is a little bit heavy on the bureaucratic side. I think that makes an extra burden on the infusion center and on the sponsor, and I don't think it's necessary.

I think you have got this process. If you have some vials available, it gives the infusion center flexibility, because something is going to happen. Something is going to happen where you need an infusion set for a patient who is right here right now, but you don't happen to have their name on it.

I think that what will happen is that you will end up with people coming to the center, and

they won't have one with their name on it, and this will keep them from getting infused, and it will be unnecessarily bureaucratic.

I don't think there is anything wrong with having, like you have in a pharmacy, a set of infusion packages that don't have people's name on it.

DR. KIEBURTZ: Other comments on that?

Dr. Goldstein.

DR. GOLDSTEIN: A question for the FDA. You have done similar things. I guess clozapine was one example. How does this work in reality? I mean we are very concerned obviously about putting unnecessary burdens on the patients and on the reporters. At the same time, we want to make sure that the data is being reported and reported accurately.

So, how have you managed these types of things in the past?

DR. KATZ: From the point of view of getting the next week's drug, and again, as Dr. Temple said yesterday, the actual frequency has

changed over time and changes with time, but the patient doesn't get their prescription filled until the pharmacy sees that they have had a blood count taken every week, well, again, every week in the beginning and then it's less frequently over time.

Again, there are provisions that if you meet certain criteria, you have had a case of agran, you are in the registry and you were prevented theoretically from ever getting that drug again, so I think it works pretty well as far as we know.

DR. GOLDSTEIN: And you are capable, and the FDA is capable of monitoring that and you feel that the data that you are getting is reliable and accurate and complete.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: Well, just to observe that the burdensome part in some ways, but not an unreasonable one I guess, I would say is the fact that there is a pre-infusion checklist.

Having it be web-based and going to somebody, so they can see if it is being filled out

doesn't really add to the burden all that much. That just says you are making sure it happens. It's as burdensome as it was before as long as people do it.

But we are very mindful of not making it impossible to use the drug, so you need to tell us whether you think some of these things are excessive or not. That is one of the things we are interested in.

DR. KIEBURTZ: Go ahead, Dr. Katz.

DR. KATZ: The major purpose of this requirement to have the forms be sent back on a monthly basis, if that is what you agree to, is not to second guess the decision made at the infusion center as to whether or not the drug ought to be infused at that particular time really.

It is really to see that the process that is in place is actually being followed. It is really a check on compliance, if you will.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I agree with Dr. Porter. I think the practicalities, if you follow the

clozapine model, the pharmacy has a big bottle of clozapine, it is not in an individual patient's name. They just dispense from that bottle.

If we followed that model here, the thing that we want to put in place and make sure that it is happening is the safety reporting on a continuing basis, and if that is left too much to the discretion of the infusion center without any consequences, meaning we have been checking your web-based forms or your paper-based forms, and they haven't been coming back regularly, we are not going to ship your next six months batch of Tysabri.

That is where I would go.

DR. KIEBURTZ: And if you have a pool, the unit of analysis moves from the patient to the center, and there are risks inherent in that, because if a center is not in compliance in general, you amplify the risk, because the noncompliance of a center can be amplified across dozens of patients if they are infusing it improperly by intent or mistake, whereas, if you

restrict the unit of analysis to the patient, the worst you can do is infuse in that person outside.

So, it is a different check and balance. We tend to think of what is the good, but we also have to consider what is the possible in this particular scenario, and there is a risk involved.

Dr. Katz.

DR. KATZ: I have another specific question. Let's say that the forms are required to be filled out monthly and received centrally with that frequency. If a particular form, let's say patients are getting drug for six months, and now on the seventh month, that form doesn't come back, would the committee require the sponsor to call in real time the infusion center and say how come we didn't get the form?

We are talking about going back every six months and sort of seeing how it is going, and maybe won't get the next six, you know, admonishing the infusion center you are not going to get your next six-month supply if you don't fill out the form.

So, I am wondering whether or not, because this is an idea we had floated, that if a particular monthly form on a particular patient doesn't come back, should the sponsor be required to follow up on that, because that could be the first sign that something has happened.

DR. KIEBURTZ: Dr. Porter and then Dr. Koski.

DR. PORTER: I actually think that is probably a compromise that is reasonable as long as it doesn't prohibit the patient who has traveled 150 miles to the infusion center to get their next infusion, but asking the company to follow up every 30 days is not so burdensome, because they should be tracking these anyhow.

I find that an acceptable compromise. What I am really worried about is trying to label the vials with the patient's name, because I think that will fall apart and make life very difficult and a lot of unhappy patients.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: At least it's my

understanding, the way I understood the distribution center, that it wasn't going to go to a pharmacy, that it was going directly to the infusion center.

So, I do think that some type of mandatory monitoring of return of those forms is very important on a regular monthly or bimonthly basis.

DR. KIEBURTZ: We haven't spoken to this, but some level of compliance or rigor in which a center is applying these things might lead to--we talked about deactivating a patient and deactivating a physician, but we didn't talk about deactivating a center.

The amplifying effect of a center problem could go across multiple physicians and hundreds of patients, so I don't believe the sponsor spoke to the criteria for deactivating center, an infusion center.

DR. BOZIC: Our proposal is the infusion centers are attesting that they are going to be doing the checklists, they are documenting that they are doing them, and we are going to be

auditing them.

If a center is noncompliant, they will be deactivated. So, I wanted to make that explicit, as well.

The other thing I wanted to say about this business of vials coming on with a patient's name on it, most hospital pharmacies simply don't purchase drug in that way. They purchase it in small quantities, in this case for natalizumab, but they don't have the patient's name on them, and again it speaks to that notion of having a little bit of scheduling flexibility.

Then, the pharmacy would receive the drug in the hospital, and they would put the patient's name on it and issue it to the infusion center. So again, I just think there is a big burden on shipping on an individual patient basis with the patient's name on it, and I think Dr. McArthur spoke to that, as well.

The last business here is discontinuations due to follow-up, the discontinuations and following up on them. You saw discontinuations in

clinical trials, but those are not reflective of what happens in the real world, and we know from many data that on current ABCR therapy, patients can discontinue at an annual rate of 20 percent, and they most discontinue for all sorts of reasons.

So, we were to follow up, you know, within a month of someone not bringing in a checklist, that could lead to lot of phone calls both to the infusion center and to the physician. Most of those phone calls will end up finding out that the discontinuation was, in fact, not related due to PML, because PML is a very rare event.

So, I guess what I am suggesting is that that is an enormous amount of burden on the infusion center and the physician, when, I think what we are proposing is extremely focused and targeted, and very targeted on the problem at hand.

We have heard from focus groups, from physicians, that if they have a case of PML, they are going to report it to us, and I think that speaks to the nature of the event, the level of concern, the seriousness of the event, and then we

have this additional layer of tracking where we are asking the doctor every six months, on every patient, under penalty of de-enrollment to provide us with those data.

So, you know, we carefully considered all these options, and we believe we found the right balance of, you know, patient protection and also burden and feasibility, and we really tried very hard to find that right balance.

DR. KIEBURTZ: One thing we haven't discussed, but would help address one of your concerns is if when someone discontinues, that that actively be reported rather than retrospectively grabbing that on a six-month look.

That would help issues. It is one of the actually hardest things to know is when someone actually went off treatment, and it would be important for surveillance and understanding the actual cumulative exposure, and that can only be addressed by knowing an end date for treatment.

We are not going to discuss this a whole lot more.

Dr. Goldstein.

DR. GOLDSTEIN: So, what you propose then is to put that as to one of the things that is reported as part of the regularly reported registry information, that if somebody goes off therapy, that that is reported as one of those monthly reports, is that right?

So, it would be information on it, other serious adverse events and/or discontinuing therapy would then be added to those monthly reports, and presumably, there would be some way of saying the reason.

DR. KIEBURTZ: Currently, there is no monthly reports.

DR. GOLDSTEIN: With the infusions.

DR. KIEBURTZ: Checklists.

DR. GOLDSTEIN: Right, with the infusions.

Dr. Jung.

DR. JUNG: We mentioned de-enrollment of centers and of physicians. We haven't really addressed, and I don't think is in the questions, how does one get re-enrolled if one gets

de-enrolled.

We don't want there to be a nominal slap on the wrist if a center is consistently not being compliant, yet, we also need to recognize that we may need to allow some centers to come back and show that they have had improvement.

So, is there a plan that has been thought out about that?

DR. BOZIC: If this becomes the proposal, the accepted proposal, we will work with the FDA on the nature and more details around the plan.

DR. KIEBURTZ: So, let's recap and go back to (a).

So, there is a patient registry, what information would be in that. This is the sponsor contacting the prescribing physician, every six months is the current frequency, to find out about deaths, PML, other serious opportunistic infections, and treatment discontinuations, and we have proposed to add to that other serious adverse events.

There are other things that are in (a)

that we have not talked about including. Use of intravenous steroids is another thing that would be worth tracking on a six-month basis.

Skipping over (b), because we haven't really talked about (b) very much, what the cohort study might be. Regarding restrictions on the distribution system, I don't want to go through each of these things, but have you heard enough discussion about the issues what might be pertinent, or do you want to hear some more specific member-by-member comments on how restrictive this might be?

DR. KATZ: The one thing I think I heard, maybe I wanted to hear it, was that the form should be sent back monthly to the sponsor, and that if, I guess over some period of time, from a given center, the forms are not returned, there is some interaction.

We just heard the sponsor say that following up a particular patient whose last month's form has not been received, following up on a patient-by-patient basis in that way is

potentially problematic. I don't think I know what the committee thinks about whether or not there should be specific follow-up for a specific patient if the previous month's form has not been received back. I don't get a sense of where the committee is on that.

DR. KIEBURTZ: Just to get to that question, for a given patient, should the infusion center and/or the prescribing physician be contacted to be made aware that the required forms that were to be completed prior to infusion were not received on the most recent infusion?

Is that something that should be fed back to the centers and the prescribing physicians?

Dr. Porter.

DR. PORTER: I think what you are saying is reasonable as long as the patient who has arrived on the site isn't penalized.

DR. KIEBURTZ: The infusion is done, they are gone. This is a retrospective. You infused this patient, and we didn't get the forms that you were supposed to fill out beforehand. There is the

implicit threat that if that carries on for long, then, you are going to be deactivated.

The question of how long does that go on for, or how much follow-up, I don't know that we need to get into that.

DR. KATZ: I am actually more interested in not so much the admonition or the threat, but finding out whether or not the patient was lost to follow-up and something bad happened.

DR. TEMPLE: How do they know specifically that an infusion was, in fact, given?

DR. KATZ: How does who know?

DR. TEMPLE: How does the company know?

DR. KATZ: Well, they won't know unless they get the form back.

DR. TEMPLE: No, what I am saying is they don't get a form. How do they know that an infusion was given, but no form came?

DR. KATZ: They don't know what. All they know is that the form didn't come back. The way you follow up, a patient is supposed to get treatment more or less every month. So, if a

patient has been getting it for X number of months, and then the next month's form is not received, there is a number of possibilities.

They decided not to take the drug anymore, that is one possibility. The other possibility is that the patient is lost, didn't come back, you know, is truly lost to follow-up, and you like to find out what happened to that patient.

DR. TEMPLE: So, what they will notice is that somebody who has been getting infusions now is missing a form for a period of time. I guess my gut says sometimes a month might be too short to know. Maybe they were out of the country for a month, and you might have to wait another month.

DR. KATZ: But you could find that out. You would call up the infusion center.

DR. TEMPLE: So, you would have a sort of expected time of arrival.

DR. KIEBURTZ: Once someone has been approved and they are registered, one would anticipate that forms would be coming on a regular basis with some periodicity because either that

should happen, the person has discontinued, died, lost to follow-up, or they forgot to do it.

I think not getting a form should trigger a clarification, what happened here.

DR. TEMPLE: So, as part of the registry, it seems to me they will need to set up some kind of trigger that says if it doesn't show up by blank, I have got a question.

DR. KIEBURTZ: Right.

Dr. McArthur.

DR. McARTHUR: I guess I am missing something here. If my electric company can send me a bill once a month, and if I fail to pay, send me reminder notices, we should be able to have a system that a patient is scheduled for a 10:00 a.m. appointment in the infusion center, they arrive, the pre-infusion checklist is completed.

The patient has the infusion. The presence or absence of infusion reactions are documented, and those data are completed on line during that visit, at the end of that visit, within a 24-hour period into this web-based system.

That gives you, not only the pre-infusion checklist. It tells you that the infusion was done, and it tells you whether there are any reactions to the drug.

What is the problem?

DR. TEMPLE: There is no objection, but you don't know, if you are the company, that the infusion was, in fact, given if they don't report to you. You can only know that you expect an infusion to be given, because one was given two months before.

DR. McARTHUR: Right. So, that would trigger a telephone call to the infusion center to find out if the patient has developed PML.

DR. TEMPLE: I am just saying they are going to have to have an expected date for each patient.

DR. KIEBURTZ: I don't think anyone can disagree with that. I think we did hear some pushback from the sponsor about being concerned about having to initiate the dunning letter to continue the analogy from the electric company.

Dr. Goldstein.

DR. GOLDSTEIN: I was just going to make a similar kind of comment, that this kind of system can largely be automated, and it's an automatic thing. You know, the report goes in, and it's an automatic feedback if the report is missing, and then you get at the end of a certain period of time, a summary report they were missing X number of reports.

Then, you could follow up for the individual patient, but also the surveillance of a center, as well, so it is sort of a double level look of control, but all of this can be completely automated. You know, there is no papers flying around here.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: Just the point of practicality. Perhaps as we are designing this form, the ability to mark a couple of things would be helpful and may allow the sponsor not to make a lot of phone calls.

First of all, patients go on vacation, and so if we know that there will be an anticipated

halt to the infusion for a period of time, maybe that can be put in there, so that it doesn't trigger a call.

Number two, the ability to transfer physicians. We know that sometimes patients move from one doctor to the next, so the ability to easily move that patient as opposed to the physician in terms of monitoring might be a reasonable thing to consider.

DR. KIEBURTZ: If you were to follow Dr. McArthur's model, if it's completed at the end of an infusion, if you could indicate the next anticipated infusion date, that would then reset the clock as to when you would next expect a form.

I think we have had enough discussion about those things. We have not discussed two things which I want to do before we break for lunch.

One is there is in addition to the registry, which I remind you is mandatory and for everyone, the proposal to have a more expanded cohort, which would be a subset of people followed

for some period of time with more intensive evaluations in the mandatory registry.

We have already heard from Dr. Hughes some thoughts about that. Maybe you want to reiterate those.

DR. M. HUGHES: I can reiterate some. To me, the registry is really collecting information about exposure and PML, PML mortality, and it would probably provide very useful information on that simply because PML is so rare in untreated patients.

When we go to the cohort study, I am less clear what the real objective is for this study. If it is really to look at SAEs, other infections, and so on, then, I think it is striking to recall that in the two randomized trials that we have looked at so far, the differences in the rates of those events are potentially relatively small, and that's in a controlled setting.

So, it is difficult for me to see that the observational study is going to provide a lot of useful information on those sorts of events in the

absence of having a control group.

I mentioned earlier the idea that maybe instead of the observational study, there should be randomized trials which seek to move into answering some other questions of interest. The alternative is to have a nonrandomized control group in this particular study in which you would collect the same sorts of information about infections, and so forth.

So, I think to me, the observational study as it is currently designed, I don't think it is going to provide particularly useful information in the absence of a control group.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I totally agree with that position. If you design a study, you have to know what question it is you are trying to answer, and I am not entirely clear what question is being answered by this observational study.

On the other hand, as we polled the committee for an earlier question, we were split evenly as to whether the drug should be first line

therapy or not, and there is clearly a major uncertainty about that, and I think that is a major clinical question for physicians caring for patients with this disease, as well as for the patients, as well.

So, rather than investing time and energy for an unclear question, for an unclear reason, I would much rather the effort be put into answering a question that is of direct clinical relevance of importance, which is my view would be that head-to-head comparison as first line therapy.

Then, we will have the data as opposed to debating the data.

DR. KIEBURTZ: Would you like to clarify what the aims of the observational cohort are for us briefly?

DR. BOZIC: Actually, let's just go through my core slide.

[Slide.]

The primary goal of the observational cohort study was to evaluate the safety of Tysabri in the clinical practice setting and over the long

term. We understand the safety of common events, such as all SAEs, I think very well based on the clinical trial data, and we understand those quite well through the end of the two-year period, because that is where most of our data are.

So, what we don't know as well is what will be the safety in the clinical practice setting. So, that is the number one goal of the study.

The other goal of the study is what is the safety overall beyond two years of dosing, and so that is why the study is five years in length.

We can't address the safety in the clinical practice by doing clinical trials, and that is why we are proposing this study. Then, the long-term nature of it, five years again, you only get that in an observational cohort study of this kind.

The second issue that came up was the control group. There are a variety of ways of looking at these data and we are proposing looking at an external control group, a variety of

different ones.

So, for example, we could go back to the clinical trial data and compare back to the clinical trial data, and ask the question, you know, if malignancies are occurring at a certain percentage rate in the clinical trials, now, at what rate are they occurring in the clinical practice setting and over the long term.

So, I think that is one question that we could answer with this study. We could also go back to other databases, like the SEER database, and ask are the rates of events for malignancies over the long term with natalizumab what we would expect based on SEER. So, there are a number of valuable things we could learn from this study.

I think in terms of getting an internal control group, like a disease-based registry, you know, part of the issue with that is, number one, there is a practicality issue that, in general, it can be very difficult to enroll disease registries, because if you think about it, Tysabri-treated patients will be quite motivated to enter in this

type of study, whereas, patients on other therapies may see less of a reason to participate in this type of study, so there is a practical reason here.

The other reason is that having an internal control group, like in a disease registry, doesn't completely eliminate bias by any means, because the practice patterns for Tysabri may be quite different than they are for the ABCR drugs, and that, in and of itself, may influence the type of safety events that you are observing.

So, an internal control group will simply not eliminate the bias, and that is why we are proposing an open-label design for that.

Finally, let me just go through the next slide, which is the sample size calculation slide, please.

[Slide.]

So, I just wanted to share your thoughts on how we sized this study. We sized this study to look at small increases in rare adverse events, and these could be any types of adverse events, but they are rare events that might not have been

picked up in trials, but which sometimes might be picked up in clinical practice when you treat more patients.

So, what I wanted to show you was that this study is really fully powered to address really very small differences that might occur between the clinical trial setting and in the clinical practice setting.

So, what I have shown you here are the events in clinical trials and the rates of those events as a function of, for example, the serious infections occurred at 1.4 per 100 person years in clinical trials.

This study is fully powered to detect a 1.5 times increase in that rate, which I think is a very conservative viewpoint. Similarly, even for serious opportunistic infections, which I know we are collecting in the overall registry, this study is, in fact, fully powered to look at those.

Those events occurred at 0.07 per 100 person years. I am counting the two PML cases and the Cryptosporidium in the MS placebo-controlled

experience as the rate. That study is fully powered to look at even very small changes in that rate, let alone all serious adverse events, which occurred at an incidence of 7.5 percent annually.

So, what I am saying is this study is very well powered to detect small increases in rare adverse events, and that is why we would advocate for collecting all serious adverse events in this study, but not in the Tysabri Registry, because this study is fully powered to address common serious adverse events.

The last thing I wanted to address was in the Tysabri Registry, I know the committee has made a proposal to collect all serious adverse events on patients. Again, the incidence of serious adverse events in the clinical trial setting is 7.5 percent per year, and what we are talking about collecting are hospitalizations for MS relapses, hospitalization for UTIs, hospitalizations for common bacterial pneumonias.

Our recommendation would be that we can really gain a very good understanding of those

types of events from a 5,000-patient five-year study, and we don't need to do it in the Tysabri Registry.

DR. KIEBURTZ: Thank you.

Dr. McArthur.

DR. McARTHUR: So, you say fully powered. Do you have actually the power estimates?

DR. BOZIC: What this is, is a probability estimate, because you are comparing between a background rate and looking at your ability to detect a 1.5 times increase in that rate, so it's a 95 percent probability estimate.

DR. KIEBURTZ: I would be interested, I mean I think your inferential abilities regarding what the cause of that increased rate would be rather limited in having an historical group that may have a lot of different characteristics than the treated group, so I am not sure. You could detect a difference, but it would be difficult to know what to ascribe it to.

Dr. Hughes.

DR. M. HUGHES: I guess I would like to

make much the same comment. You are sort of arguing against yourself about using the placebo period of these trials when you think that the rationale for having this study is there may be different rates in clinical practice, there may be different rates over the long term.

DR. BOZIC: But my point is that an internal control group will actually not be that helpful, because you may, in fact, have different patients being treated with Tysabri than patients treated with ABCR.

You know, doctors may choose to use Tysabri in a different way and in different types of patients regardless of the indication statement, and that may influence the safety profile. So, you will still have that difficulty in interpreting the data.

DR. M. HUGHES: I guess at the end of the day, I don't know if this observational study adds a whole lot to the information that is needed to evaluate the drug.

DR. KIEBURTZ: Thank you. I think it

would be a reasonable thing to ask the committee another set of Yes/No questions, or one Yes/No question, which is the following:

Do you think it's crucial for the sponsor to commit to such a cohort study given that we have asked that the serious AEs be incorporated in to the registry?

DR. PORTER: And that you are going to have monthly monitoring.

DR. KIEBURTZ: Go ahead, Dr. Sacco.

DR. SACCO: I think the only thing that is missing in the registry are certain other baseline variables that others have raised before, so when you want to start teasing apart potential factors, risk factors for serious outcomes, the registry may not have the baseline information you need.

So, if we want to have the registry answer that question, then, I think the registry has to be expanded a little bit with certain baseline information to look at either by EDSS, by just other variables that could be predictive of adverse risk.

That is my concern about trying to have the registry do that.

I was going to say for the cohort study, depending on the outcome of interest, I agree for PML, if it's 1 per 1,000 and we have five of them, it is going to be hard to tease out risk factors, but for certain other outcomes, maybe that have a cumulative risk that is a little greater, maybe we will, depending on what baseline characteristics they collect, be able to tease out groups that seem to have a little greater risk depending on the proportionate outcome.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I assume that these baseline factors might be incorporated into that initial enrollment form, and then we would have that data, and you could do those types of analyses.

DR. KIEBURTZ: Remember there is no clinical demographic baseline features. I believe the only thing that is proposed, Dr. Sandrock, the only thing that is currently proposed at entry is

an MRI, is that correct?

DR. BOZIC: The data collection in the observational cohort study in terms of the demographics of the patient?

DR. KIEBURTZ: No, that is a separate question.

DR. BOZIC: In the registry, it will be just patient name and age and diagnosis.

DR. KIEBURTZ: But wasn't there to be a baseline MRI before initiation of treatment?

DR. BOZIC: Right, we are asking the doctors to give us--well, we are asking that they do the baseline MRI, we are not collecting that information, because that information will be really not very I mean I think relevant to us in terms of just finding the incidence.

DR. KIEBURTZ: You answered my question, thank you.

So, that is the only bit of information unless there is a cohort study, which would gather more information by EDSS and other clinical--whatever else. The registry won't have

that information.

Dr. Koski.

DR. KOSKI: I actually would like to propose that we talk about some evaluations that should be done or what we think ought to be done on patients prior to being placed on Tysabri. I don't think that is discussed in any of the questions. I sort of took a fast look.

In other words, if something in addition to an MRI ought to be done or recommended.

DR. KIEBURTZ: So, (h) is sort of what other potential ongoing monitoring, and I suppose we could add to that baseline monitoring.

DR. KOSKI: Right, I am talking about baseline.

DR. KIEBURTZ: Go ahead.

DR. KOSKI: I mean the thing is that to my way of thinking, I think definitely, you know, an MRI would be absolutely mandatory for a lot of the reasons that we talked about earlier in terms of disease activity.

In addition, I would honestly also feel

that in addition to somebody sort of saying, well, I don't think I am immunosuppressed, I think that things like maybe total lymphocyte counts, perhaps skin testing, as I mentioned earlier, ought to also be considered, and then in addition, and I know that there will be some resistance to this, I think that there ought to be a baseline CSF examination with perhaps some PCR data done.

I know that a lot of that in the beginning, you know, presumably is going to be totally negative, but I think it would be helpful in terms of the subsequent evaluations of patients, those that do have a problem.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: I don't want to interrupt that discussion. I will ask my question later.

DR. KIEBURTZ: Dr. Porter.

DR. PORTER: Well, as an old-time neurologist who did a lot of LPs when you had very little else to do, and you didn't have MRI scans. I like LPs, but I actually, in today's world, they are considered an invasive test, and I would have

to know--let me finish--I would have to know for sure that I was really going to get an extremely valuable amount of information that would really direct me toward the process of what is happening with PML before I would be enthusiastic about LPs for patients before they could get what half of you think is a first line drug.

Now, we are doing LPs before the process. I did agree with second line drug. I am against the idea of doing LPs before the drug is given.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I would agree with Dr. Koski that a cerebral spinal fluid analysis prior to initiating Tysabri treatment would be critical. We don't know what we don't know, and we have already heard from the experts that we don't know adequately what occurs in the spinal fluid, and unless we collect that data, we are not going to ever find out.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: Using Tysabri is going to be an invasive procedure, and we want to be as sure as

possible, and I think making it as safe as possible, that we have the correct diagnosis is critical. There is a lot of MRI scans that are read as being compatible with multiple sclerosis, that don't turn out to be MS.

So, I would agree that doing the spinal tap with oligoclonal bands or whatever else we could do to try to make certain we have the diagnosis would be advisable.

Secondly, I agree with Dr. Jung that now we have we have another piece of the baseline for later comparison.

DR. JUNG: I didn't mean to say that we should be checking spinal fluid for oligoclonal bands. I meant to say for JC virus.

DR. KIEBURTZ: We previously talked about serum testing for JC virus and learned that it has a poor specificity and in addition to low sensitivity, at least in this situation and in other situations, and I am not sure that CSF improves upon that.

Dr. Clifford, do you want to comment on

that?

DR. CLIFFORD: Yes, I think that it is important for the committee to remember what has been done already.

I, too, love to do LPs, do several a week on a research basis, and I think LPs belong in research settings unless there is a clear indication.

In this case, I would remind you that we had CSF analysis on patients on natalizumab, or actually not on natalizumab, but within three months of the discontinuation of natalizumab, which we know that the biologic effect carries over after the last infusion, so we did a large number, 400 or so LPs on patients in this situation. We found no JC DNA with the most sensitive research assay that we could use.

So, I think that making it a practice to say you must do an LP so that we have this negative substantiated is really an extraordinary idea. I really think it is unrealistic. Further, MS patients, so there was a concern when we started

this business, is there some relation of 1 demyelinating disease with another, of JC with MS, and there was a somewhat confusing paper in the literature that suggested that might be the case.

We contended that wasn't the case, but we are not satisfied with that, and so got these 400 samples from the Karolinska of documented MS patients, looked with the most sensitive assay. These were negative, as well.

I think with 800 samples, carefully looked at including 400 on the drug, that this would be really unreasonable.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I would concur with Dr. Clifford. I think enough is being done with spinal fluid already, not to make this a mandate.

I urged before that there be some attempt to bank serum and although PCR may have limited sensitivity and specificity, we don't know what is going to come down the pipeline in terms of proteomics or other markers. If we don't have the banked specimens, we are never going to be able to

use them, so I would urge that we at least bank serum at baseline.

DR. KIEBURTZ: I think we have heard a couple different proposals regarding what clinical and laboratory assessments might be necessary before prescribing Tysabri, and this particular notion about having to have a JC PCR negative CSF before prescribing it, we have not discussed right now. I have got to say I am a little bit taken aback, I would have to agree with Dr. McArthur and Dr. Clifford that that seems like an excessively high bar to place on access to treatment.

Dr. Rudick.

DR. RUDICK: I just wanted to make a brief comment because it's hard for me to sit without making comments in general, but I have spent much of my career studying CSF in MS for its diagnostic and other value, and I do not agree that you need a CSF to make a diagnosis of multiple sclerosis.

I would recommend that the International Panel, which has worked for several years to establish diagnostic criteria for MS, be the

reference for the diagnosis of MS, and that the neurologists trained in this field be the adjudicators of whether a patient has MS, and I would note that a CSF is not required to diagnose a patient with relapsing-remitting MS by the international criteria.

As a matter of fact, it was required in the prior version for progressive MS, but that was just recently revised and published as no longer required. So, I think that if you required this for diagnosis, I think you would be very arbitrary in that requirement, and it would seem to me to be discriminatory against patients who needed to have Tysabri.

DR. KIEBURTZ: So, to clarify the two uses of CSF, one would be for diagnosis, which I don't think anyone is proposing at this moment, but two would be for some sort of risk reduction, that by establishing that the CSF is negative for JC PCR, that you reduce the risk.

If the best guess of the prevalence of JC PCR positivity in CSF in MS patients is somewhere

around, let's just be generous and say 1 in 1,000, the likelihood of a procedure-related complication, whether hemorrhage, infection, or persistent headache, must be an order of magnitude higher than that. So, I think we need to be careful about a procedure that may carry more risks itself than it would mitigate.

Dr. McArthur.

DR. McARTHUR: We don't have to estimate. We know from Clifford--

DR. KIEBURTZ: Zero out of 800.

DR. McARTHUR: We don't have to estimate. We know what it is, it's zero.

DR. KIEBURTZ: One is within the 95 percent confidence interval of zero, I think, unless we had 20,000.

Dr. Goldstein, Dr. Koski, and Dr. Hughes.

DR. GOLDSTEIN: Again getting back to the point of what is collected at baseline, with all of the caveats that we talked about in terms of the observational study, I don't know that it would necessarily provide an additional major burden to

obtain some baseline data that might help in interpreting these adverse events that we are talking about - age, baseline EDSS score, and whether the patient was on a prior immunosuppressive drug or not.

It is three simple check boxes that we then have the data, and then that again obviates all of the issues we were talking about with the observational study, and then we could again use those resources for other purposes.

DR. KIEBURTZ: Suggesting that as part of a baseline information when you are entering the registry.

DR. McARTHUR: That is exactly right.

Dr. Koski.

DR. KOSKI: Well, I would also just sort of say, I mean isn't it reasonable to have some sort of measures, actually laboratory measures of that, and I knew the CSF was going to be controversial. I just thought it needed to be brought up.

DR. KIEBURTZ: Dr. Hughes.

DR. M. HUGHES: I guess I would make a plea for keeping the registry relatively simple. I think it should be very much focused on the PML question, and if there are particular risk factors at baseline that could be measured easily in that context, I think that is valuable.

Maybe there is a rationale for the cohort study if you are really interested in understanding risk factors amongst treated subjects for rarish serious adverse events that may occur. I still don't believe it is particularly valuable in the comparative setting comparing with historical controls or understanding long-term adverse events in an uncontrolled setting.

DR. KIEBURTZ: I would tend to agree with that and think that although it is an opportunity to gather perhaps some more information about demographic and clinical characteristics of a subset of individuals who are in the treated group, but I continue to think there are going to be difficulties making inferences about changes in adverse event rates that are ascribable to the

intervention because the population will be different than other populations, but it doesn't mean it's not a good idea.

Dr. Sejvar.

DR. SEJVAR: As far as initial baseline work, again, I can think of various immune markers that would be useful to look at, but I would echo Dr. McArthur's suggestion of at least banked serum and blood.

DR. KIEBURTZ: To draw the distinction again, and it's implicit, but maybe it isn't explicit, so I will just say it. The registry is clinical practice. The cohort is clinical research. They are different things. You know, one is going to be what everybody has to do. The second is something that somebody will have to fill out an informed consent and elect to participate in, and questions that are addressable in one are different than the other.

I think Dr. Hughes made a good distinction, which is the registry's intent should not be compromised by additional questions, which

will be less well answered in that setting, and the registry's intent is primarily around this issue of PML and mortality and disability from it.

Dr. Porter.

DR. PORTER: Are we talking about banking samples for the 5,000 patient study, or are we talking about the registry?

DR. KIEBURTZ: Samples would be part of the cohort, not the registry, the research, not the care.

DR. PORTER: Could I ask, you are going to get 5,000 samples then. What are you going to do with them?

DR. KIEBURTZ: I would just say that this committee is not about designing clinical research studies.

DR. PORTER: Well, that is what we are doing, though.

DR. KIEBURTZ: No, we are not.

DR. PORTER: We are drawing blood. We are advocating drawing blood--

DR. KIEBURTZ: We are making advice about

potential future studies, but we are not designing it, approving it, or anything else like that.

DR. PORTER: My point is that unless we are absolutely certain we know what we are drawing these samples for, that I am not in favor of advocating it.

DR. KIEBURTZ: Dr. Temple.

DR. TEMPLE: I am generally in favor of banking samples because you can't predict the future. I think the last discussion got at what the company was trying to propose, that is, that the treatment part of it, the practice part of it should be kept relatively unencumbered and in order to do more intense looking at something, with all the difficulties that observational studies require, you would identify a group of people and a group of patients who are willing to be more aggressively studied.

So, I hear some tendency to try to include the stuff from the observational study back into the practice part of it, into the registry, and I think the intent was that you should try to keep

them separate, much as Dr. Hughes said, don't make it too complicated to be part of the registry, if you have other questions, study them in the observational study.

Now, the limitations of that study, I think you have all described, how much can you learn from an observational study of that kind, so that is a separate question, though.

DR. KIEBURTZ: You have heard a range of discussion about how much to put into practice including hedging into serious adverse events, which is both a clinical and research thing, and I think that may, based on the discussion, be over-encumbering that registry. It may not, and there may be additional reasons to want to do a cohort that would get at other things that the committee members have expressed interest in.

Ms. Sitcov.

MS. SITCOV: I just wanted to say that I agree with Dr. Hughes. I think that putting in too much is really just an over-encumbrance and a disincentive for the user of Tysabri.

DR. KIEBURTZ: It is 12:25. I am not going to pursue the question about doing a Yes/No vote on that, because I think we have had enough discussion that will be informative to the FDA.

We have not gotten to the checklist. We will not get to the checklist before lunch. I think that is going to be another discussion afterward, but I will consider the discussion on Item 8(a), (b), (c), (d), (e), and that's it, concluded. I don't want to revisit those unless absolutely necessary unless you feel that we have not had sufficient discussion. It sounds like we are doing okay.

I want to come back after lunch and talk about the checklists and then any additional monitoring. Just for the sake of the observers, we voted on Question 7. I don't necessarily anticipate there will be another question that we will vote on.

We may, we may not, but looking at the topics heading forward, there may not be any formal votes. I don't want you to think that I am

precluding them, but just so you can plan your day.

So, with that said, we will adjourn for lunch and reconvene at 1:30. Thank you.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

DR. KIEBURTZ: Just to recap after lunch where we are, we discussed 8(a), (b), (c), (e) and (f), not that there was much discussion on (e) and (f), because that was pre-staged by Question 6, and there was nothing that was voted on, but sort of the overall sensibility was that the proposed information, what the sponsor proposed to be in the registry was necessary.

There was a little bit of debate about whether that was sufficient, whether there should be more materials provided as part of the registry, which would be on a six-monthly basis, but there was no clear consensus on that. I think that is something, the discussion, we will leave up to the Agency and the sponsor to work out the details on that, and similarly, with the observational study, there would be some additional questions that the committee think are worth addressing, that would be appropriate in the context of a research study rather than mandatory as part of clinical care, and

that there should be some restrictions on distribution, but not on a one-to-one basis, and some mandatory monthly reporting back about the use of the checklists and that a feedback mechanism should expected checklists not be received, that that would be evaluated to find out why expected forms were not received, patient finished taking the drug or some other problem.

We also endorsed the idea that there should be some actual in-person evaluation, and in clinical care, that might be something on the basis of baseline three months, six months, and every six months after that, but again, that is not something we voted on. I think there was kind of a discussion around those items. Again, I presume that that is something that will further worked out in details between the sponsor and the Agency.

So, that is where we are. The things that we have not talked about is what those specific checklists would be that have to be completed at the time the patient arrives at the infusion center and is preparing to have the infusion, there should

be some evaluation to check on two things.

One, is there evidence that the individual is or has been immunosuppressed, which would increase the risk, or is there some evidence that the individual may now have signs or symptoms of PML.

I think we are essentially left with the notion that any exacerbation--and I don't mean to paraphrase the sponsor here--but I believe what we heard is that any exacerbation would be treated as if it could be a new case of PML and evaluated as such.

We haven't talked about what that evaluation would entail, but at least we know that that would entail an MRI scan and physical exam.

Let's go back to the checklist, what should be on the checklist, and we have proposals of both, I believe, in front of us about--it's one checklist--about what would be evidence of immunosuppression or risk for immunosuppression and what might be evidence of having signs or symptoms consistent with the development of PML.

So, I would like to entertain some discussion about the proposed checklist.

Dr. Jung.

DR. JUNG: I think as Ms. Sitcov had mentioned earlier, as is common for most MS patients, having waxing and waning of neurological symptoms is a part of the disease, so we need to be able to draw a line between at what point we get concerned.

So, I would propose that we consider changing the language for the last question in the patient checklist to persistent new symptoms or new symptoms that have persisted over perhaps a week or several weeks time as we know that the decline associated with PML is a more subacute, progressive set of symptoms as opposed to symptoms the last several days

DR. KIEBURTZ: There was some discussion or some speculation if there were a subset of symptoms that are characteristic of PML that could be differentiated from the signs or symptoms of an exacerbation of MS.

I think Dr. McArthur, you at least alluded to that that would be a very difficult task because virtually anything could be either.

DR. McARTHUR: I think virtually anything with the exception of optic neuritis could overlap.

DR. KIEBURTZ: Myelopathy perhaps.

DR. McARTHUR: Well, myopathy, but I think from a symptomatic standpoint, it is very difficult for just going on symptoms to distinguish no localization.

DR. KIEBURTZ: Dr. Sejvar.

DR. SEJVAR: I think maybe temporal profile might be somewhat more helpful, but even that is difficult to separate the overlap, I think.

DR. KIEBURTZ: You mean temporal profile in one sense that it's acuity?

DR. SEJVAR: Right.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: Just two points about this. One is I think this needs to go through the usual language correction for people's reading levels as we would normally do for any consent

document. This has a lot of very high level terms here that I think could be confusing or misconstrued or misunderstood, so I assume that is one thing that would happen.

I think the second point that I think comes out here somehow is that this is a surveillance system that has unknown insensitivity and specificity for picking up anything. We are sort of making this up as we go along based upon our best guess.

I think that that needs to come through also, at least in some framework, and that this is something also that is going to be reevaluated as time goes on.

DR. KIEBURTZ: So, just to reiterate that a little. I think that part of the Patient Medication Guide should indicate that by asking these questions, it doesn't reduce the risk of a person getting PML to zero, that somehow by completing this and going through this process, the risk is reduced to nothing.

We would hope that it's reduced, but I

think it is important to convey the sense that this is an attempt to reduce risk, but we don't know that yet.

Dr. Sacco.

DR. SACCO: I would agree, and I think we could probably sit here for a long time and try to figure out a questionnaire that could perhaps differentiate PML from MS, and it's going to be hard.

I think really from what I understand, if there is any neurological change, whether it's MS or for the PML, that is going to throw up a flag and then they are going to be evaluated further, probably with an MR, so I don't know if we need to really try to tease apart getting this question right for just PML.

DR. KIEBURTZ: And I would propose that. I think the nature of the questions here are is a checklist appropriate. I think everyone feels that we need some document like this. We have already talk about it, that it should be done monthly in advance of each infusion, and that it should be

conveyed to a central area where it would be expected, and its lack of arrival would prompt some action, where is it, what happened, trying to follow up about that.

We have not necessarily talked about who should administer it. I don't think this needs the involvement of a physician or a neurologist. It doesn't need a neurologist, doesn't need a physician.

I think one of the questions would be is it possible to have it be performed by infusion center staff, who are not that necessarily familiar with either MS or PML, and I think that is something that might be useful to talk about.

Dr. Katz.

DR. KATZ: I don't know if you are done with the discussion about how the questionnaire or the checklist should inquire about neurologic symptoms, but recognize that differentiating PML from MS may be very difficult, if not impossible, on a checklist, but it is important for us to know what the committee thinks about that, because if we

say something like any change in neurologic status, we have already heard that that would be extremely burdensome, people would never get their treatments. They would all be shipped off to the neurologist for further evaluation if the question is of that sort.

I know it is hard, but it would be useful for us to know a little bit more about what we think the checklist should say in that specific regard, because we don't want to make it so sensitive that no one ever gets their treatment without first being seen by the doctor.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: One of the other indicators at least of temporary immunosuppression is the appearance of herpes zoster, and would that be something that if the patient shows up with active herpes zoster, which is a pretty common occurrence, should the treatment be withheld at that particular time.

Dr. McArthur.

DR. McARTHUR: I don't think there were

any instances of zoster, or maybe one, in the 1801/1802 studies.

DR. KIEBURTZ: Is it an irrelevant clinical measure of immunosuppression, the occurrence of zoster, I guess, would you want to use it as a sentinel, but to get back to Dr. Katz's question, so we have some discussion about that.

One of the things that I have heard, I believe, is that the persistence of the change would be one thing that would trigger, and perhaps the nature of the change. I think I have heard some discussion about whether it is a change in symptoms or a change in signs, that is, if people have--I guess it is all symptoms until you have an exam.

Dr. Jung.

DR. JUNG: I would like to ask Dr. Clifford, do patients with PML typically respond to I.V. steroids? The reason for bringing this up is I can envision that we would be doing MRI scans on every single one of our patients getting Tysabri on a monthly basis.

Again, given the fact that patients do manifest new symptoms on a regular basis, and given the fact that if you look at the description of the patients that have been described with PML, they had a persistence of their symptoms over a course of time.

DR. CLIFFORD: Right. So, the first question is patients with PML did not normally respond to steroids even transiently. There often are confusions of this sort, and people are given steroids, and PML patients simply don't respond. The one exception to that is something that we are experiencing currently, and that is in the presence of a reconstituting immune system, there are what are called IRIS reactions or immune reconstitution reactions, which are a much more inflammatory form of the disease where part of the symptoms are due to the inflammation.

Those patients may have a partial response to steroids, but PML patients themselves, I think are really quite unresponsive to steroids in my experience.

DR. JUNG: So, would it be reasonable, then, to say that if patients come in with persistent new symptoms, you examine them, you think there may be a possibility that they may be having a clinical relapse of MS, treat them with the standard course of I.V. steroids. If they don't respond, then, move forward to pursuing the possibility of PML?

DR. CLIFFORD: I think that this is something that we have to train and work with clinicians to refine. I think that the company has set up an iterative process where we are going to have to learn how this works in this kind of practice, and I can envision the early part of it having quite a few iterations of people with symptoms coming in.

I think that somebody here was suggesting that some have new symptoms, persistent over at least a few days, and I think what would happen in practice is there to be a signal, and the whole point of this, I suggested this, I wasn't part of the writing or planning for this part of the

process at all, because I was entirely on the Adjudication Committee, but I was asked about what would be helpful, and I said, well, the most sensitive signal in my mind that can be done frequently is to ask for symptoms, because this is not a clinically silent disease for long, and therefore, people do come and tell you there is something different, and families and others, you know, they can't handle their silverware the same way they did, and that is definite, and they can tell you about that before you could possibly do recurrent blood tests, scans, and other things, and I think it is just important to take that seriously even in a patient with MS.

So, the intention here was to bring this to light and to have a clinician then evaluate them, and say, oh, yeah, well, this patient has had this four times in the last five years. Then, you know, they could follow it for another two weeks and see if it went away or give steroids.

If it is the first time they have ever had anything like that, then, I, as a clinician, would

do a scan, and if there were anything strange, I would think about a spinal tap, but I think people will have to learn how to do that.

I think it is important that clinicians, in an interactive process with the sponsor, who is trying to help them to apply this, be allowed to use a degree of clinical judgment, so that it doesn't get out of hand in terms of how sensibly it can be managed.

I think it can be done, but I think that there will be a different learning curve in different places, and folks will be terrified, they will be too casual. You know, I think people will have to work with them.

DR. KIEBURTZ: I will go to you, Dr. McArthur, next, but just to reiterate, the checklist is a screening procedure that would most likely happen at the level of the infusion center, which is going to be hopefully sensitive, but not necessarily terribly specific, but not so horrible that everyone is screening positive, horrible in the sense of its specificity, but that that would

then trigger an evaluation by a clinician who is familiar with the patient, may or may not be in person, probably wouldn't be in person initially, but maybe followed up in person and maybe followed up with more things.

I think we are not necessarily talking about what the post-screening activities are yet. I would like to focus still on what the content of the screen question is, but what happens after that in terms of the interaction between the clinician and the patient over the phone, in person, and what subsequent laboratory testing is decided before that person says no, it's okay, this does not appear to be evidence of PML.

That is another discussion, but right now I want to stay focused on the questionnaire.

Dr. McArthur.

DR. McARTHUR: This is another question for Dave Clifford. My read of these cases, and I did not see any of these cases, is that they presented in a somewhat different way than HIV-associated PML.

I mean typically, HIV-associated PML, we think of clear consciousness, motor deficits, visual deficits, cerebellar deficits, and then only later on is there more of an encephalopathic dementia type syndrome. It is relatively late, but these cases all presented with frontal lesions, panhemispheric lesions where encephalopathy and cognitive dysfunction was an early phenomenon, so could we try and focus the symptoms more on those?

I realize that if PML is associated with Tysabri, it, of course, may not be only associated with frontal lobe lesions, but could we use that somehow?

DR. CLIFFORD: I have counseled against that because I think that it is just not right to try to determine a pattern of disease on three cases, and so I really believe it's safer for us to think about the way white matter, subacute white matter diseases present.

I do think that the cases that have been seen in the setting of natalizumab treatment have been very recognizable as PML cases in the sense of

the tempo in the areas of involvement. I mean they went from a silent lesion to definite clinical symptoms one month late to severe disability by three months, and death by four or five months.

We are not dealing with a form of PML that is very different from what we see in badly immunocompromised patients, and I think it would be a mistake, and the way I led the screening of the entire exposed population was just to assume any definite focal progressive symptom had to be questioned, and I think that is the approach that I would counsel should be engaged by these questions, as well.

DR. KIEBURTZ: I think that characterization of new, focal, and enduring symptoms is a reasonable framework to think about this.

Dr. Sacco.

DR. SACCO: I was just going to emphasize that, as well. I would ask the question, if a patient was coming to an infusion center, and they had this questionnaire, and say it was a relapse,

which is possible, it does occur even though the drug reduces relapses.

I assume then they would not get the infusion, they would have to go to their clinician to decide the next step. So, whether it's a relapse or whether it's PML starting, the clinician gets brought in, and they are not given the infusion.

DR. KIEBURTZ: Correct. I mean the instructions are if it is yes to whatever this question is, the infusion is suspended, and the person is referred to their clinician.

DR. SACCO: So, I go back to saying that whether it's a relapse or it's PML starting, I think that's the appropriate plan for now, that we should be doing, getting clinicians involved in the decision-making process of what the next step is for that patient.

DR. KIEBURTZ: I believe that is what the proposal was.

Ms. Sitcov.

MS. SITCOV: This really illustrates my

lack of medical knowledge, this question, but if someone were to say to me is your immune system suppressed, you know, if they asked me did I have an organ transplant or do I have AIDS or leukemia or lymphoma, I would say no to all of those.

But are there other conditions, and there must be, for example, for about a nine-month period last year, I had C. diff, and does that make my immune system suppressed?

DR. KIEBURTZ: A point well taken. I think it has been alluded to that questions about, that's a qualitative judgment, do you have a suppressed immune system. I think that is what Dr. Goldstein was getting to before. That question is probably not a good one, but asking about specific conditions, HIV infection, AIDS, leukemia, lymphoma, organ transplant, and anything else. I think the Agency can work with the sponsor and what conditions maybe herpes, a recent herpes zoster is one of them, conditions that suggest a compromised immune system. A point well taken.

I think similarly having a sheet of what

would be considered an immunosuppressive or immunomodulating drug, have you taken any of these, do you remember taking any of these in the last month to look at, to say yes or no, and I think similarly recordings, we have already alluded to on the six-month basis, but I think this is not a bad point in time to be asking the subjects have you received intravenous methylprednisolone or other high-dose steroid treatments since your last infusion, yes or no, would be a reasonable thing to be checking here in this context.

Other comments or questions about this?

Dr. Goldstein.

DR. GOLDSTEIN: Just a general question. Are these forms going to be sent back or will the prescribing physician have access to these forms on each one of their patients? As I understand it, this goes to the central location. The sponsor looks at it, the FDA will look at it, but what about the doc on the ground, does he get these reports on a regular basis?

DR. KIEBURTZ: Currently, the proposal, as

I understand it, is the prescribing physician would be notified about the response to this checklist only if there was Yes to the new, focal, and persistent symptoms.

DR. GOLDSTEIN: Right, and as I read it, it's the patient's responsibility. They don't get the drug. It is the patient's responsibility to contact the physician about it. What I am saying is that maybe this should be another one of these automated things that these forms go to the prescribing physician on some regular basis also, because the patient may or may not decide to call the doctor that day.

DR. KIEBURTZ: I am not sure every prescribing physician would want every form that has No's on it, but some way of notifying the prescribing physician if there is a Yes to the question.

Dr. Katz.

DR. KATZ: Do we think it's the patient's responsibility to contact the physician if the infusion nurse gets a Yes answer? I guess I was

under the impression that the infusion center would take the responsibility to call the physician.

DR. GOLDSTEIN: Yes, and that is why I was raising the question. Around here I think it says the physician should be consulted, but it doesn't say who or under what circumstances.

DR. KIEBURTZ: I would just assume that the infusion center would take that responsibility.

DR. KATZ: The other thing is, just to correct something that you said, Dr. Goldstein, we here don't anticipate receiving these forms. Again, we would have to work out with the sponsor, you know, periodic reports from them to see how this whole system is working, but we don't anticipate getting the forms.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Two things I wanted to bring up for discussion. The first, in general, subjects who have MS come to clinic for treatment by themselves. What about levels of cognition impairment in people who have more severe disease, and whether or not they are able to provide this

sort of information, is that a concern, and how do we deal with it?

The second question, trying to put myself in a--having been a patient relatively recently, so I am having symptoms. I know, I have had the disease for several years, and I know when I am waxing and waning, and I know when I am getting a response, but I am also here to get this drug that is supposed to help keep me better.

Why would I tell you if I want to play the odds against relatively low, hopefully, likelihood of developing a fatal disorder, why would I tell you that I am having these if I know that it means I will not get my medication?

That is the piece I think we haven't discussed. Well, it sort of feeds in, in part, to the cognitive issue although I think it is different from the standpoint of impairment of cognition, but that is one of the things that I couldn't see my way to a clear response of the patient who would say I will pass up getting this medicine especially over the first couple of months

or years while people are so focused on this as a new option, and we probably should discuss that and whether there is a way to have less of a problem with people deciding they won't tell the physician or the nurse, because it means they won't get their drug, and they will figure that out fairly soon. In fact, they ought to be able to read that they won't get their drug, especially for people who know their disease.

DR. KIEBURTZ: So underreporting of these new symptoms or misreporting unintentionally due to some kind of cognitive impairment, we have not talked about and is likely to occur to a certain degree. I think the underreporting is really going to be--I don't know how to address that frankly, other than as long as people are informed of the risk and realize that they are putting themselves at potentially increased risk, but the misreporting due to cognitive impairment, this does presuppose, the checklist presupposes a certain ability to know these things, or come to the infusion with someone who does know them, if you don't come alone.

DR. DeKOSKY: In the perfect world, someone who had enough cognitive impairment, and maybe physical impairment along with it, since they currently bring someone with them who could answer the questions. My question was about the case in which these is someone who, as part of their impairment, doesn't recognize that they have a disability, simply cannot remember, or loses the insight to know that these are important questions to be able to answer.

DR. KIEBURTZ: It is a good concern to which we don't have a concrete solution right now.

Dr. Sacco.

DR. SACCO: Sometime in studies the way you have to approach this is the examiner or interviewer has to make some decision about how cognitively intact the person is to answer the questions, that the person is able to either provide consent or at least answer the questions appropriately, and maybe somehow we have to indicate that. If the infusion nurse, which isn't a physician, isn't doing any mental status, but if

there is some doubt in the ability to answer the questions appropriately, then, the whole system gets defaulted.

DR. KIEBURTZ: That is a possibility. The definitions of that will be tricky.

Dr. Goldstein.

DR. GOLDSTEIN: I think we are getting to the point that we raised earlier, that we don't know what the sensitivity and specificity is of the screening procedure. It is being instituted as the best idea of the best notion that we have right now, but that data, and the sponsor I believe said that, it will be looked at forwardly in an iterative process depending upon outcomes.

The other thing is that there is a check, and that is the physician evaluations at the three- and six-month periods. So, in addition to the subjective data that we are getting, that will be obtained from the questionnaire, there will be objective data from physician assessments also. That will help them also in designing this thing as it goes forward.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: Yes. This is in terms of reporting symptoms at the infusion center where there is the questionnaire administered by a nurse or whomever.

I know from knowing enough people with MS, myself included, that part of the way to successfully cope with the illness at times is the degree of denial, and you can't get away from that. That just has to be added to the equation.

Dr. DeKosky.

DR. DeKOSKY: In a way, I am sorry, I may have confounded the issue of the cognitive status of the person, which I think we just have to deal with, with the issue of what appears to be a relatively strong predilection to not tell you about symptoms if it means you are going to miss your drug.

While we may not be able to solve that, I think the question is whether or not we have way to check on it or some other way to put something else in place that would increase perhaps the

sensitivity to having this.

My specific concern is for people who know their disease.

DR. KIEBURTZ: One thing may be, which was just alluded to, that the exams that follow may pick up things that were not alluded to at the time of the questionnaire completion.

Dr. Couch.

DR. COUCH: One of the problems that MS patients run into may be a slow cognitive decline that continues over a period of time, and perhaps, although the Folstein Mini-Mental Status is not a particularly good instrument--and Dr. DeKosky is shaking his head over there--it has been shown to have a low sensitivity, but good specificity.

If we had that as one of the things that we are evaluating initially, then, perhaps yearly, you might be able to see that there is a cognitive decline, is not a cognitive decline. When the patient reaches a Mini-Mental Status of, pick a number, 25, 27, you then have to have information from other people.

DR. KIEBURTZ: That may be something that the sponsor would want to consider putting into the cohort study, which would help get at it, because people will be completing the checklists. Everyone will be getting the checklists. The cohort gives you the opportunity to look at the veracity of the checklist versus other instruments.

Dr. Koski.

DR. KOSKI: Again, I can only speak to our own infusion clinic, but basically, all of these biologicals, and this includes when Tysabri was being infused, were being administered by an RN.

In addition, we also had the policy that we have a physician on call for the infusion clinic, and the physician saw each patient before they actually received their infusion. It was a brief visit, but you got to know these patients, and I think that reasonable or very good infusion clinics are going to be able to handle this.

Over time, particularly when a patient is coming in on a monthly basis, you know how they are responding, you really do.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: A couple of issues. The cognitive dysfunction associated with MS is not easily picked up even by the most astute clinician, and certainly the Folstein Mini-Mental Status exam is useless when it comes to that.

The idea of trying to do neuropsych testing on every person before they get infused is obviously not possible. I think there are other ways which have nothing to do with the checklist itself, but perhaps going forward to how do we monitor our patients, perhaps with more regularly scheduled MRI scans that will give us some objective evidence of disease would be a better way to sort that out.

That would also deal with the potential for underreporting of symptoms for fear of having the infusion taken away.

DR. KIEBURTZ: So, it sort of edges us into (h) if you guys have heard enough discussion about (f) and (g). Thank you.

So, this regards JC testing in serum or

CSF, MRI, quantitative cognitive testing or some kind of screening instrument and full or brief physical examination or questionnaire. Let me just dissociate two things.

One would be a screen-positive individual would go into clinical assessment, and whatever that might be, we are not talking about that right now, what we are talking about is there some other routine evaluation that would be mandated as part of participation in the registry.

We have said we think it is reasonable to require a physician evaluation before it started, at three months, six months, and six months thereafter. We haven't specified what the contents of that evaluation are aside from what one would imagine is a history and physical exam.

The question is would we propose something more to be required to be part of routine clinical care at any of those time points in everyone receiving the intervention.

Dr. Sejvar.

DR. SEJVAR: I guess even before we start

with that discussion, I mean just a practical question, who pays for all this. Is it the patient's insurance?

DR. KIEBURTZ: That's a question I am not sure we can take up right now, but presumably if it was mandated as part of care, appropriate use of the medication, at least some insurance companies would pay for it, but it would not be considered research optional.

It's the clinical care aspect of administration of the medication. Of course, many patients don't even have insurance, so that means they would be paying for it along with the rest of their care.

Certainly any of these things, MRI, physical exam, possibly cognitive testing, and depending on the outcomes of that, may be part of what happens when someone has new persistent and focal symptoms, which might travel with new, persistent, and focal signs, obviously are going to be evaluated as to whether this is a relapse, potentially treated for that, or possibly PML, and

I think an MRI is going to be part of that, and the question of whether CSF is part of that.

But just moving away from that, to what would necessarily be part of the routine evaluation at zero, three, six, and ongoing six-monthly intervals, is there something besides a neurologist's or a clinician's interview and physical exam that we think would be necessary and mandatory as part of appropriate use of the drug?

Dr. McArthur.

DR. McARTHUR: This is not in individuals who screen positive on whatever symptoms. This is just routine, everybody is doing fine.

DR. KIEBURTZ: They come back at their three and six months. They have no relapse, no problems, they are doing well. So, it would apply to them equally. This isn't triggered by any event. This is just routine mandatory care.

DR. McARTHUR: I think the standard of care now for most MS patients on immunomodulatory therapy would be to do regular cranial MRIs, because the question is should they be done more

frequently in individuals on this particular treatment.

DR. KIEBURTZ: Regular means?

DR. McARTHUR: Well, one to two years. I mean there are no hard data at this point as to how frequently or how infrequently one should do them, but I would appreciate input from anybody, including in the audience I guess.

DR. KIEBURTZ: No.

DR. McARTHUR: No? Stay quiet.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I just want to make one point. The way you posed the question was should there be any other routine mandated testing at these time points, and you noted the time points to be three months, six months, and then six months afterwards, which is when I think people thought that the neurologist should see the patient.

The question was meant to be broader than that and whether or not, for example, something instead of the checklist is the only thing that is done every month. The question is should any of

these things be done every month or whatever frequency. I wouldn't limit your thinking about it to the doctor visits.

You may ultimately decide that, if anything, should be done routinely, it should be done at those times, but I wouldn't want to restrict thinking about it at the outset of the discussion to those specific times.

DR. KIEBURTZ: Thanks for that clarification.

DR. McARTHUR: If I can finish my thought then. So, I mean if I was giving Tysabri, I would want to do a scan every six months.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I was going to speak against any routine monitoring. I mean just as we don't know about the specificity and sensitivity for the questions, I am not sure doing routine MRI scans, say, annually, every six months, or any of these other tests will help us right now, and it will throw a lot more cost into the system.

So, I would prefer, now that we have had

the reauthorization and we have the clinicians being brought into the system every--I think it was at three months, six months, and every six months afterwards, that that alone would hopefully provide a system of detecting either PML or worsening MS.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I believe, first of all, that it is not necessarily accepted as the standard of care that any scan get done every one to two years. There may be regional differences, but I don't believe that that is assumed. We may all have very strong opinions about that.

Number two, I disagree with Dr. Sacco, in that my concern if we are not clear about what the expectations are for monitoring this drug once it is used, is that insurance companies will not readily pay for MRI scans q three months or q six months even if you think it is clinically indicated for a drug like this unless we say that we think this is critical, and I think it is unreasonable to put the clinician or the patient--to give them the burden of trying to prove that they need the study

given the fact that it's readily recognized that there is this risk associated with this drug.

DR. KIEBURTZ: Let me just get back to Dr. Katz's point. I would like to hear from anyone who feels that something aside from the checklist needs to be done on a monthly basis.

Dr. McArthur.

DR. McARTHUR: I don't think anything needs to be done on a monthly basis because frankly, there is no test to identify PML with the exception of MRI and spinal fluid JC virus. We have already discussed that the clinical symptoms and signs are not precise enough to make the differentiation between those from MS, those from PML, those from nerve root disease, those from carpal tunnel, et cetera.

So, if we are not going to do spinal fluid monitoring, which we have already debated and discussed, I would advocate that we need to engineer into the recommendations, regular MRI monitoring. As a clinician, I would not administer Tysabri unless I was allowed to obtain some

objective measure of what was happening in that patient's brain.

I am very concerned about PML and as far as I am concerned, the only way of detecting PML in somebody whom I am administering this drug is by doing serial MRIs. Six months may not be enough, I accept that, but there has to be some practical interval.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: I agree with Dr. McArthur, and I would again state that knowing how insurance companies work, because I do reviews of requests for MRs, that unless something is specifically FDA indicated, that there is a very good possibility that that link-up will be disconnected down the road.

So, for the sake of the patient and for the sake of the physicians, who are taking the risk of giving this drug, we need to make sure that there is some mandate associated with that.

DR. KIEBURTZ: So, nothing is being suggested more frequently than every month--that is

the checklist--the only thing we have suggested more frequently than every six months is in the first three months regarding a physician evaluation that you are hearing comments about every six months or some interval of MRI.

Dr. Temple.

DR. TEMPLE: I just want to be clear we know what everybody thinks about, you know, how urgent and how stringent that is.

That is, you got through the every month part, but do you believe, are you advising us that every six months there should be an MRI as a condition of continuing on the drug, or is it a vaguer recommendation than that, that, you know, good practice suggests you might, that is less forceful, what exactly are you recommending?

Then, I have a previous question. Maybe you think you have answered it and maybe you have, and that is, that the physician is going to be seen every six months. Was it your thought that the patient and physician acknowledgment forms would be redone at six months, is that the form, or should

we develop a different form, or what exactly did you have in mind?

DR. KIEBURTZ: We didn't discuss that specific issue.

Dr. DeKosky, then, Goldstein and McArthur.

DR. DeKOSKY: if we can talk about the first one first. I would like to know--this is not my field--I would like to know what it is we are looking for with a scan on people every six months.

Is it that we are looking for nascent PML developing in the brains of those people, and is that the reason we are doing, the recommendation of Justin is that we do scans every six months?

DR. McARTHUR: At least two out of the three cases had lesions which were atypical on their MRI, atypical for multiple sclerosis. So, again, we can't scan patients every month, we probably cannot scan patients every three months. Every six months would be a reasonable compromise.

If a lesion appeared that was atypical for an MS plaque, I think that would be a major trigger.

DR. DeKOSKY: I agree. I may not recall these correctly, but I thought the reasons for the scans were the clinical symptoms that developed, though, rather than a random survey every six months looking for, or that any of them, in fact, were picked up on an incidental scan. It wasn't driven by a behavioral change.

But you are advocating a scan even in the absence of any behavioral change to see if something is rising even with this low incidence. I know it is not easy, I am trying to track your thinking.

DR. McARTHUR: No, it's not easy, and I completely take your point, I mean that the MRIs in the three cases obviously were triggered because it was a neurological syndrome.

I think we are obviously, or I am erring on the side of conservatism and managing patients in what I think is the safest possible way, and the only way I can think of to monitor patients for a nascent or developing brain infection is with cranial MRI that is practical. We can't do spinal

taps, we have discussed that.

I don't know if six months is going to be frequent enough to capture an evolving PML lesion, recognizing the infrequency of that event. That would be my recommendation.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I just wanted to take the same point that was just raised. We have no data at all that a screening MRI scan will, in fact, detect preclinical disease, nor that that detection would change anything.

I take your point, though, that there needs to be some language that doesn't preclude physicians from doing that if they think it is clinically indicated or as part of their own individual care.

So, I think wording to that effect, that MRIs should be obtained for clinically relevant indications, and you may consider surveillance a clinically relevant indication, and that hopefully will take care of the third party carrier issues related to getting it paid for.

DR. KIEBURTZ: Let me also come back to Dr. Temple's point, which not everyone may see the distinction. Maybe everybody does and it is redundant to say it again. There is a difference between it being recommended, strongly recommended, and required, and I think you are looking for some level of certainty that this must be done on everyone at this minimum frequency.

Dr. Koski.

DR. KOSKI: Like Justin, I basically do think that when you are following an MS patient, just as part of the normal care for them, that I usually get an MRI at least on a yearly basis, and part of it is because sometimes there are silent lesions, you get an idea about the disease burden over time that is going on, and it might indicate a need for a change in therapy.

I think it is very difficult, because I think that the evolution of these lesions probably does occur over one to two months perhaps. Should we mandate each six months, I am just not sure. I certainly think that in patients that do have

sustained progression during this period of time, we are going to be getting intermittent MRIs, so I guess the issue is the frequency.

DR. KIEBURTZ: Dr. Ricaurte.

DR. RICAURTE: Just getting into the issue of is it a screening MRI, and should we give some thought to linking the MRI with a change in signs and symptoms that are sustained. It gets into the quandary that you are going to end up doing lots of MRIs, but then at least it reduces it to the group of patients that has developed a new persistent sign.

So, just the thought of perhaps--I am not against the idea of doing at least initially for the first few years, making it a requirement to look every six months, but just raising the question of whether perhaps initially, wouldn't it be wise to link the imaging study to the onset or development of a new focal problem.

DR. KIEBURTZ: I think it is highly likely that everyone who has that will get an MRI.

Dr. Sejvar.

DR. SEJVAR: I guess in addition to the level of the individual patient, at which time detection of developing PML may or may not be helpful in the eventual management, but I guess the biggest reason that we are trying to detect this early is sort of to take action on the whole population.

So, I guess that is one of the things that I am struggling with in terms of considering routine MRI, how frequently or whatnot. I mean we are looking for a sentinel event to call the safety of the drug into question.

DR. KIEBURTZ: Dr. Jung.

DR. JUNG: To address Dr. Temple's question, I would suggest that the wording be strongly recommend at six-month intervals or as clinically appropriate. I think that gives you enough leeway and doesn't mandate.

DR. TEMPLE: For the MRI.

DR. JUNG: Right.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I was going to emphasize the

strong recommendation for those that have neurological symptoms, and I guess I would ask is that we are doing the cohort study, I presume, and maybe getting MRIs in those 5,000 patients at six-month intervals for the cohort study under research purposes would be another approach to look at the detection of MRI for detecting PML and other changes.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: I just wanted to get back to Dr. Goldstein. If we go to our experience with HIV and PML, it is clear that there can be lesions on MR well before there are clinical symptoms. So, in cohort studies that have been done looking at serial MRIs, it is not infrequent to see, if you will, silent PML lesions, and Dr. Clifford might want to address that.

DR. KIEBURTZ: I will take the point. You can get lesions before symptoms.

DR. CLIFFORD: If I could just give a couple of comments on this topic. My assumption is that the MR scan is probably the earliest signal if

you could do them with adequate frequency, that you would see the pathology before you would see the symptoms in a number of people, and that is why we insisted on MR screening of the entire natalizumab exposed population when we were trying to rule out the presence of active PML.

It really bothers me because although I don't know how long before clinical symptoms occur that you can get an MR signal given the pace of development of this disease. My assumption is that it probably is, on average, no more than a few months that you would have an MR signal before you would have clinical disease, which means that at best, you are maybe gaining a month on the screening inventory for how early you might detect a signal if you did this monthly.

Every six months, you are gaining very little from the sensitivity that you have gained by doing the clinical screen, and at a cost of, if there are two scans a year on 2,000 patients to discover one case one month earlier, and what do we have. We don't have a treatment for this

condition. For all we know, it's an all or none, roll the dice, I am sorry you have been the unfortunate 1 in 1,000 that has developed this illness.

Our hope, of course, is that earlier detection, stopping the interference will result in a lesser lesion or perhaps no lesion. That is what we would love to see, but I think we have no assurance of that.

The other thing that I think don't forget. We heard a lot about the troubles access for patients that hate needles, shot, monthly shots are aversive. Well, let me tell you MR scans are not popular among our patients either, and so I think in terms of access and cost for a group of patients, that you are adding a very substantial burden, and I think that given that we have no treatment for the complication we are looking for, and that we would gain on my estimate only a month or maybe a little more of lead time compared to clinical symptom management, I think that is a high cost to pay.

I would be willing to see annual screening for the first two years or something until we have a better feel for this, but I would hate to see legislation of what is not really an evidence-based recommendation on a firm basis.

DR. KIEBURTZ: Ms. Sitcov.

MS. SITCOV: My question may not be moot, but what I was going to say is if I were to go on Tysabri, I would want to have MRIs done as frequently as my insurance company would pay for them.

DR. KIEBURTZ: Dr. Couch.

DR. COUCH: I think one of the issues with the MRI, just as an additional issue, and that is, there ought to be a protocol specific as much as possible, so that you don't have MRIs that have to have a lot of different protocols, try to get the same protocol for everything, and get it out to all the centers that are handling the patients, so that the data becomes relatively comparable.

DR. KIEBURTZ: Dr. DeKosky.

DR. DeKOSKY: Why would we do one

annually? All that does, if it's because they are on the drug, is give us an even lower estimate of the time that we might catch someone in the act of developing a pre-symptomatic lesion.

I think the issue of standard of care for MS patients probably is where we need to leave this with respect to MR. I agree with Dr. Clifford, that is why I was asking Justin for more detail, that this is not a way we are going to catch this disease even if, in fact, we think that there is a chance if we give antiviral agents that we could slow someone down or stop them from developing worse disease.

So, if we say, well, it doesn't make sense to do it every six months because we wouldn't catch people. It makes less sense to do it once a year with the specific intent of trying to catch a lesion. Otherwise, I would say the MRs should be left to the clinicians and their judgment about how frequently to do them to their patients.

DR. KIEBURTZ: I presume, Dr. Katz and Dr. Walton, you have heard enough discussion on this.

I think there is feelings that range from making strong recommendations to staying with current practice. I am not going to try to strive to derive a consensus from the committee on this. I think you have heard the range of viewpoints. I don't think it would necessarily be productive.

DR. TEMPLE: I agree with that. I still would like to--no, you don't have to answer, you can leave it to us, of whether what you actually had in mind was redoing the enrollment forms or perhaps a modification of them at six months or some period.

DR. KIEBURTZ: So, remember when people enter, there is this process by which--I forget the particular form--

DR. TEMPLE: Well, there is a Physician Acknowledgment and Patient Acknowledgment. That is sort of the vehicle for enrollment.

DR. KIEBURTZ: It would be signed at baseline. Then, of course, there is this screening checklist monthly. The question is at the times that the clinician is actually again seeing the

patient, should this document be revisited at each of those in-person meetings?

My guess would be that would be a good idea. Does anyone feel strongly to the contrary?

DR. GOLDSTEIN: To be done annually or at every three months, six months?

DR. KIEBURTZ: It should be redone at some time point.

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Okay. That's good.

We are leaving Question 8. There is no vote, there is no consensus. There is a lot of discussion. Just to bear in mind for the committee members and for the public, in this kind of situation, and many times it is not necessary to drive to consensus or vote on something.

These are discussion items and hearing the discussion in a dispassionate forum is useful to the Agency, and the fact that there is disagreement and lack of consensus doesn't mean people haven't thought about it. It means that is where we are, and I think that the Agency and the sponsor, having

heard that, can negotiate in good faith on what makes sense.

Question 9. For subjects who have received natalizumab in clinical trials, and who have not received for at least a year or longer, do you recommend any further monitoring? That is, people who were in trials, who have now been out for at least a year or longer, should they be monitored in any further way, and if so, how and for how long?

This kind of ties in with the next question. What happens to people who now that it is going to be, presuming our advice is--well, let's just say in the world in which it returns to marketing, what happens when someone discontinues, how long do you monitor them after that?

So, for example, the registry kind of evaluations, which are to be done on a six-month basis, would you continue to do the registry kind of evaluations on a six-month basis or some less frequent basis getting those kind of endpoints, and if so how long would you continue to do that for?

Again, I think the notion behind this, I presume is that the risk of PML does not cease with the ceasing of the intervention, and you would need to continue to follow people who are at risk for some period of time to see if the event occurs. Do I have the reasoning right?

Dr. Sejvar, did you have any thoughts on that?

DR. SEJVAR: I guess I would just like to offer that the answer to both of those would be yes. I mean again, I think that the National Death Index provides one avenue for that, but again there is going to be a significant time delay associated with that.

So, I think that some sort of real-time follow up of patients who have come off the drug is necessary, and then I guess the question is how frequently, and I would think maybe once, you know, a yearly follow-up is reasonable.

DR. KIEBURTZ: I would tend to argue the annual follow-up. Again, the reason for more frequent evaluation and follow-up is to try to "nip

in the bud" or identify incipient or early cases with the idea that discontinuation of the drug might have some favorable impact, none of that being known, but a reasonable hypothesis.

Here, the intervention has been terminated, there is no point in trying to intervene earlier or stop it, but following the group on an annual basis, I think less an annually, you have a higher risk of not getting the information again, but the question is if you did it annually, how long do you do it annually for, two years, three years, five years. I mean you have to do it for some period of time.

I don't know if anyone has any thoughts on that.

Ms. Sitcov.

MS. SITCOV: My feeling is--did I read in the FDA response, your recommendation was five years?

DR. WALTON: No, we did not make any recommendations on that length of follow-up.

DR. KATZ: In the observational study, I

think the sponsors are going to follow patients for five years.

DR. WALTON: But that was for patients who were getting--

DR. KATZ: Continuing on the drug.

DR. WALTON: Continuing natalizumab, yes, or within that study, those who had discontinued it.

DR. KIEBURTZ: Do you want to comment, Dr. Dal Pan?

DR. DAL PAN: I believe in the observational study, it was following people for five years after they had discontinued natalizumab.

DR. WYSOWSKI: After starting Tysabri.

DR. KIEBURTZ: After starting. Okay.

Just for the record, we are trying to sort out what--

DR. McARTHUR: Three years sounds like a good number.

DR. BOZIC: May I just clarify?

DR. KIEBURTZ: Clarify about what?

DR. BOZIC: The length of follow-up in the

observational study.

DR. KIEBURTZ: I don't think that is the question. Thank you, though.

Does anyone feel that evaluation less frequently than annually is appropriate? Does anyone feel that no follow-up after discontinuation is appropriate?

[No response.]

DR. KIEBURTZ: Do you need further discussion on that?

DR. WALTON: I think some sense of how long you feel that that annual evaluation should continue would be useful to us.

DR. KIEBURTZ: Beyond the discussion of two, three, to maybe five years?

DR. WALTON: I wasn't sure if that was the general consensus.

DR. KIEBURTZ: Okay. People's thoughts on how long that might--I mean at some point, the risk of PML from the intervention must dissipate.

DR. McARTHUR: It is quite likely if somebody discontinues this agent, that they will go

on to another agent, which might be even more of a potent immunomodulatory drug. Again, I think we have to be practical. Five years would seem like a good time period to me, but I think we have to compromise a little bit, so three.

What can we say? There is no data to say how long.

DR. KATZ: I think we understand the conversation.

DR. KIEBURTZ: Back to 10(a). Do people feel any differently about discontinuing in the setting of marketed use versus previous clinical trials, or should it apply the same way? It's the same, okay.

So 10(b). If a patient discontinues and plans to initiate treatment with another immunomodulatory agent, should they have a pause before initiating that treatment? If so, for how long should that pause be?

Dr. Jung.

DR. JUNG: I guess it depends upon the reason for discontinuing the drug. If

discontinuation is due to adverse events, then, can you afford to wait a prolonged period of time before starting another agent if the patient is relapsing. So, I think there needs to be more clarification.

DR. KIEBURTZ: Other comments?

So, following up, more clarification in what way, Dr. Jung?

DR. JUNG: I am sorry?

DR. KIEBURTZ: You said there needs to be more clarification of the question?

DR. JUNG: Is the reason for discontinuation because the patient is failing versus is the reason for discontinuing the drug because the patient has adverse events to the drug itself. That would push you towards two separate paths in terms of where the patient is going.

DR. KIEBURTZ: Bear with me. So, say it is because they are failing, would you want to impose a waiting period?

DR. JUNG: I don't know the answer to that. I think it is something we need to discuss.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: Are we also talking about steroids here, or is it just other approved drugs for MS? In the example I would raise, if somebody is failing and having a relapse and they are going to come in--

DR. KIEBURTZ: Let's take relapse aside. I mean I think you have to treat a relapse as you treat it, but I think failing in terms of having a number, not the acute treatment of a relapse, but that they are having progressive disability or having a high relapse rate, and you think that you want to shift to a different drug.

DR. KATZ: Just for clarification, I think this is sort of the reverse question that we talked about before, which is if you want to start Tysabri, how long do you have to be off some other immunosuppressant. I think this is just the reverse side of that coin because of the risk of--how long do you have to wait before starting another drug after coming off Tysabri because of the potential risk for PML, to be seen in the

context, you know, the potential increased risk to be seen in the context of essentially concomitance.

I don't think we were looking for the various different reasons, the different waiting periods depending upon the reason the drug was discontinued. It was this question of when do you think the risk of PML dissipates, and I quite frankly don't know how you would answer that question, but that is what we were trying to get at.

DR. KIEBURTZ: Thanks for that.

DR. McARTHUR: You have asked an unanswerable question.

DR. KIEBURTZ: It's a very steep path. I think, though, that the context is if somebody is doing badly on the treatment and you are stopping it in anticipation of shifting to another treatment, there is a little bit more pressure to be able to start the other treatment in the setting of clinical failure of clinical poor progression as opposed to if someone has been very stable and say they develop neutralizing antibodies and you decide

they need to come off, but they have been quite stable and they come off, you might be able to pause more leisurely before you start another treatment.

So, I think there is some point in making that difference. It is going to be very hard to have someone who is doing badly, who you say, okay, we have got to get off of this, and then say, well now we are going to wait a year before we initiate treatment, or two years, or three years. I don't think that is plausible or necessarily defensible because then the accumulating disability sits in contrast to the increased risk of PML that might happen, theoretical increased risk of PML that might happen with the co-administration of another immunomodulatory drug shortly afterwards.

So, I think we do have to think about that. I think if the person is stable and doing fairly well and has to stop, or just decides they don't want to take it anymore, you have a longer period of time where you might wait.

But is there some minimum period of time

you should be forced to wait in the setting of clinical deterioration causing switching off the drug?

Dr. McArthur.

DR. McARTHUR: I think what you have just described is really an argument for making it just clinical judgment, and there is so many scenarios, there are so many reasons why one might wait or one might accelerate a switch, it just has to be part of clinical judgment.

I don't think any of us have any data whatsoever to say three months is safe, but two and a half months is unsafe.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I think what I would fall back on is what we have data for, and that's the way the 1801 trial was done. About 30 percent of them were on prior immunomodulatory drugs, and there was a washout period, I think--is that right, that was required--before they could start on this drug.

That is the only data we have, and we

think that that is relatively safe doing it in that setting, so I would extrapolate and say, well, if you had to pick a number, that's the number I would pick.

In terms of the urgency, I agree you don't want to wait. On the other hand, we also have no data that acute administration of this drug alters the acute exacerbation, so I think balancing those two together, I would just use the same protocol that was used in the trial. That is what we have some data for at any rate.

DR. KIEBURTZ: Two weeks?

DR. GOLDSTEIN: Yes.

DR. KIEBURTZ: Part (c) is going to be the question which will probably be the most pressing immediately after this goes on the market is anyone who is on ABCR is going to want to know how long do they have to wait before they can take Tysabri, and is there some minimum period of time. Two weeks, is that long enough?

DR. GOLDSTEIN: Again, that is the only thing that we have data for.

DR. KIEBURTZ: I understand. I am just seeing if there is any difference of opinion. I don't know enough to have a difference of opinion, but I would tend to think that a little bit longer may be a little bit better, but not a lot longer.

Dr. Sejvar.

DR. SEJVAR: I guess maybe at the bare minimum, understanding that there is an effect that sort of outlasts the pharmacokinetics and pharmacodynamics, but couldn't we use those parameters as a bare minimum, or is that where that two weeks came from?

DR. KIEBURTZ: I think we heard that, you know, as Dr. Sandrock alluded to, you can actually do some in vitro analysis of how long the pharmacodynamic effects are, but are there more sort of elusive measures of immune function that might be suppressed for longer periods of time, that when you start to co-administer Tysabri, those increase the risk.

I think this is very hypothetical, and just sort of a clinician sensibility that maybe a

little bit longer to let things wash out before you start something else, but that may be overly cautious.

Ms. Sitcov.

MS. SITCOV: I think it was I who asked the question yesterday about how long one needs to wait, and you mentioned two weeks, but I don't understand why two weeks versus three weeks or five weeks.

DR. KIEBURTZ: Are you addressing that to Dr. Sandrock?

MS. SITCOV: Yes.

DR. SANDROCK: So, if the question relates to how long after stopping Tysabri, when we could restart--we said two weeks based on the PK and the pharmacodynamic effects of interferon, which you can measure for at least a week after an injection based on interferon-inducible genes, we felt that two weeks was reasonable.

If you would like me to address the other, I will.

DR. KIEBURTZ: Do you think there is any

reason to think based on any information you have that the immunomodulatory effects of interferons last longer than two weeks?

DR. SANDROCK: Well, there is not a lot of data on that. Everything that I just based the two weeks on is based on pharmacodynamic measures.

DR. KIEBURTZ: Actually, since you offered, I will take you up on it. The other way around?

DR. SANDROCK: In the case of washing off of Tysabri, the drug is given every four weeks, because we maintain saturation of alpha-4 integrin receptors for the dosing interval, and we see saturation levels falling at about eight weeks. So, eight to 12 weeks would be our recommendation after the last dose of Tysabri.

Again, that is based on pharmacodynamic measures that we can look at.

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: Also, we have been talking about the washout after one comes off an interferon, and two weeks was the number that the

sponsors proposed based on dynamic considerations, but there are other immunomodulating drugs that patients may be one. They may not be approved for MS, but they may be on for MS. How long one should wait to wash those drugs out presumably varies with the drug, I would assume.

So, you could suggest that it is drug dependent, you know, you would have to know something about the pharmacodynamics of each of the potential drugs the patients might be on, and say for azathioprine, it is this long, for CellCept it is that long. That is one approach.

DR. KIEBURTZ: I am not sure exactly what Dr. McArthur meant by clinical judgment, but it may be in part that there is not going to be one answer for any drug, it is going to have to be in the context of what is known about the drug, but on the other hand, that will leave the door open for just about any interval.

DR. TEMPLE: It also seems worth noting that in the cases that did occur, it took something close to two years of both of them being given

continuously for anything to emerge. It is hard to think that a week or two of common exposure would do the same thing, but we, of course, don't actually know that.

DR. KIEBURTZ: Sufficient discussion on 10? Oh, Dr. Koski, I am sorry.

DR. KOSKI: That's okay. I really don't agree with--excuse me--I do agree with the two to three months, but I think the other thing is presumably, if you are removing the patient because they are not doing well, or not performing adequately, you are going to have MRI data that will help to confirm at least that none of the lesions at least are similar to PML.

So, I think that will also help to make that decision as part of your clinical decision.

DR. KIEBURTZ: I think that is a good point. So, those are patients who are going to have more extensive evaluation, and that may shape your risk about or your thinking about risk about initiating other treatment.

We will move on to Question 11. I think

the nub of it is if in the previous discussion, you have advised reintroducing the marketing and have suggested only monotherapy, which is what we suggested, please discuss if and when exploration of the safety and efficacy of concurrent use with beta-interferons should be evaluated - never risk it, evaluate it in concurrent clinical trials, only after the risk of PML or other infections is better quantified, evaluated in a concurrent clinical trial now, some other approach.

To frame that up, do you think it is just off the table permanently, whether it is a question that can be addressed by further research, and should that further research be commenced now or after accumulation of more data in the monotherapy situation, and potentially more evaluation of the subjects who were previously dosed, who have also been allowed to restart their treatment.

I would be interested in people's thoughts on that.

Dr. DeKosky.

DR. DeKOSKY: We heard yesterday that

there had been no cases of PML reported with the other medications, is that correct, up to this time, reported, although there may have been cases?

DR. KIEBURTZ: Sorry, there have been no cases reported?

DR. DeKOSKY: With the other drugs approved for long-term use in MS, is that correct?

DR. KIEBURTZ: I don't believe there has been any other reported cases of PML.

DR. DeKOSKY: So, my suggestion would be that I would go for (b), that if, in fact, this is largely about an interaction with this particular medication, that it would be useful to have some experience with this medication's ability to produce other cases before combining it, which was the circumstance, we think, under which it was unearthed.

So, I would wait. I wouldn't rule it out forever, but I would wait to see whether or not the signal was worse with longer experience with this drug. It is my opinion.

DR. KIEBURTZ: I think the confidence

interval around the current estimate, I mean the point estimate is 1 in 1,000, but that goes up to 3 in 1,000, and down to 1 in 10,000. I suppose any 99 percent confidence interval, 1 in 100 probably falls in there, so I think the more information you have might give you a sharper point estimate and narrow the confidence interval.

Is that--I am saying in a different way what I think I hear you saying.

DR. DeKOSKY: We are up to 5,000 cases being followed. That ought to narrow the confidence limits enough to let us make a realistic estimate of what the potential risks would be of doing another combination study.

DR. KIEBURTZ: Dr. Sacco and Dr. McArthur.

DR. SACCO: I think given our answer in No. 4, which was that we are not sure this could occur with use of this drug alone, that I would also agree with (b), that gaining more experience with continued use of the drug alone in a large sample, in probably more than 5,000. 5,000 will be in the cohort study, but in the registry, could be

even greater. We heard that in the first few months this drug became available, it was like 7,000 people were signing up to get it.

So, i would like to get that data before embarking on the next set of studies with combination therapy.

DR. McARTHUR: Is the question restricted to Avonex or, by implication, do you mean other approved agents in combination?

DR. WALTON: The question focused on Avonex because that happened to be the one concomitant use where we had some experience that natalizumab adds something, had benefit, but didn't have the efficacy data that other thing added to natalizumab offered additional benefit.

But it really does apply certainly to all the interferon-betas and really to any of the concomitant use drugs that might be thought of.

DR. McARTHUR: Then, I would go along with (b).

DR. KIEBURTZ: Does anyone advocate (a) never evaluate concurrent use? Does anyone

advocate (c), which is permitting clinical trials of concurrent use of an approved medication with Tysabri--mind you this is research, clinical trials--right now, is anyone in favor of that?

MS. SITCOV: Could you please repeat that

DR. KIEBURTZ: Is anyone in favor of option (c), that is, initiating clinical trials at the time of re-approval of marketing?

[No response.]

DR. KIEBURTZ: I think we have uncharacteristic unanimity of opinion around option (b).

Dr. Temple.

DR. TEMPLE: Well, (c) is in the setting of a clinical trial, informed consent, and so on. Some of the points that people made earlier that we didn't really know how the drug works in people with aggressive primary progressive disease.

Do you think that couldn't even be studied in a combination form with informed people? That seems very strict.

DR. KIEBURTZ: Say the question again.

DR. TEMPLE: Well, (c) is about whether, in an IND setting, you could look at concurrent use. So, what I am asking is if you took some aspect of MS that is not now well studied, people who aren't relapsing-remitting, but just going straight downhill, we don't really know what Tysabri does in that setting. That is a point that people have made repeatedly and yet that is a very difficult situation that you might think calls for risk taking.

So, under the setting of an IND, ordinarily, you think people are allowed to make those kinds of choices.

DR. KIEBURTZ: I think we might have been thinking about the circumstance only of the approved--I mean for relapsing-remitting, so maybe we should think about it a little more broadly.

Dr. DeKosky.

DR. DeKOSKY: I was wondering, Bob, if you meant that to be done in a combination therapy without, for example, doing the study of Tysabri first in primary progressive. I mean in terms of

relative risk and the length of the consent form, I would at least like to know whether or not that drug worked.

DR. TEMPLE: You might even compare the combination with each of the singles in that setting.

DR. KIEBURTZ: So, you could have a factorial design, I think.

DR. TEMPLE: But really the point I am making is that we often, but not absolutely always if you are really scared, we often have more discretion in a setting of an investigational use where you can tell everybody, and they can say yes, I have waited, I have thought about it, I am willing. To say no would be a very unusual and strong statement about this. I just wondered if you really meant it.

DR. KIEBURTZ: Dr. Goldstein.

DR. GOLDSTEIN: I guess you were asking our advice. Obviously, the Agency will do what the Agency does, but I think first getting this information that we want to collect, that we are

all concerned about first, I think is appropriate. I think first testing the drug as monotherapy in these other clinical situations is quite appropriate, and then if you get a signal on monotherapy, and this turns out to be relatively safe as monotherapy, then, if you want to go ahead and then look at combinations, I think that is an entirely reasonable approach.

We are concerned about this. That is what this whole discussion has been about.

DR. KIEBURTZ: Dr. Koski.

DR. KOSKI: I completely agree in the sense that I think it is fair to do it under an investigational status, and I definitely think that monotherapy needs to be tried first. There is very few other things that have shown efficacy actually in the progressive varieties.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I think just a point earlier of the same thing, with progressive MS, I think we should do monotherapy. I was concerned the drug was going to get used in all of these other MS

varieties, as well, so I would very much say let's do other trials for other kinds of MS, but probably stick with monotherapy or direct head-to-head comparisons of two single active drugs.

DR. KIEBURTZ: Dr. McArthur.

DR. McARTHUR: The same as Dr. Goldstein, but just restating it. I think we need to allow the system, the registry, the drug distribution, collection of information from the pre-infusion, I think we need to allow that system to show that it can work either just in terms of the logistics of collecting the data. Hopefully, we are not going to see any signal in terms of PML cases, but just to show that the system itself can work.

DR. KIEBURTZ: I would be interested if committee members are comfortable in trying to quantify what would be adequate additional monotherapy observation, like how many thousands of person years additional, you know, another 5,000, another 10,000, because if we say we would like to get some more, are we able to quantify how much more before it's enough?

DR. McARTHUR: If there were 7,000 patients who enrolled within the first few months, I think to get 5,000 times two years, that is 10,000 patient years would be a pretty reasonable number.

DR. KIEBURTZ: My guess is they would be able to accumulate 10,000 person years of experience in less than two years, my guess.

Dr. Goldstein.

DR. GOLDSTEIN: There is a corollary to that question, and it was one that was raised yesterday, is we are doing all of this surveillance and we are looking for these adverse events. What level of adverse events would trigger concern, one case, two cases, 10 cases? Where is the trigger going to be pulled? Do we have any feeling for that?

DR. KIEBURTZ: I am not sure.

DR. WALTON: I think if we see cases that raise our concern again, it is entirely possible that we will be inviting you back to discuss this again. That, after all, is what triggered this

advisory committee in the first place, the occurrence of these cases.

DR. KIEBURTZ: I think we made our decision-making around the notion that the point estimate of 1 in 1,000 is about right, and that if accumulated experience starts to move that point estimate upwards significantly, I think it would be reasonable to reevaluate this discussion. What does upward significantly mean? I don't know, but we will know it when we see it.

DR. TEMPLE: As Russ said when we started, we expect cases, and if they are at about that rate, we would hardly be surprised. We don't necessarily believe that it is only because of concomitant therapy that these cases occurred. For all we know, it is going to be exactly the same with monotherapy. That is our ongoing assumption even though we don't want anybody to do anything but use monotherapy, we don't really know.

DR. KIEBURTZ: I think the committee members, I hope have deliberated in awareness that it is likely that t here will be cases of PML, and

it is likely that there will be deaths from it. I mean that has to be the background against which we are making these decisions.

The point is that there is death and disability associated with other interventions that are approved and on the market, and against the face of the disability and death that occurs with the illness, is it a reasonable balance that an informed physician and patient, clinician and patient can make together, and I think our unanimous decision was that was yes with certain restrictions.

That may need to be revisited based on the actual observed frequency of the problem with more people, over a longer period of time.

Dr. McArthur.

DR. McARTHUR: So, if in the unhappy event that a patient on monotherapy does develop PML, should we have a developed plan of exactly what to do, what to tell that patient? I realize there are no proven therapies for PML, but there are some, let's just call them alternative therapies that are

being proposed.

Certainly in the HIV literature, at least one of the patients in our packet received several forms of antivirals. Do we have an emergency plan is what I am asking.

DR. KATZ: I don't think one specific plan has been proposed, and I am not sure we are in a position at this point to say what one should do in a case of a case. Clearly, that will have to be thought about, but I am not sure, I am not an expert clearly, and I don't know that there is a treatment algorithm for patients who get PML.

I am sure, as you say, there are multiple different sorts of treatments that people give. I don't think we are in a position to mandate a particular one at this point.

DR. McARTHUR: I am looking at you, but maybe I should be asking the sponsor what is the emergency plan for if and when a patient on Tysabri monotherapy gets PML. What will happen?

DR. KIEBURTZ: Dr. Sandrock or does anyone--I mean you don't have to reply to that, but

if you are interested--sorry, that's a little loose. I mean if you are willing to share your thoughts on it now.

DR. SANDROCK: Our recommendation is obviously to suspend natalizumab. We are talking to some of the investigators about the possibility of using plasma exchange as a way of removing natalizumab more quickly, but that is just one of our thoughts.

DR. KIEBURTZ: The other part of Dr. McArthur's question, is there any specific clinical management of PML should it happen beyond trying to remove the agent, any antiviral treatment plan or other treatment plan that has been articulated? It is perfectly acceptable to say you are thinking about it.

DR. CLIFFORD: Well, clearly, there is no correct answer that has been demonstrated for the treatment of PML. Only two years ago I was standing in an international meeting proposing interferon-beta as an excellent plan for a controlled trial of treatment for PML in HIV

patients, and I think that I have given up on that as a primary hypothesis, but the flip side of that is that I am not at all--with the Agency--I am not at all convinced that interferon has anything to do with incidental happening that both of the cases that were observed in MS were in interferon-treated patients. I think that that is something that could have very easily happened by chance.

On a theoretical basis, the interferons have activity against DNA viruses. We have used interferon-alpha. Quite recently, several of us have published on a number of cases where we have actively thought that there might be a signal of activity of interferons against JC virus, so that has actually been on the table fairly recently.

In terms of the theoretical approach, the use of cytosine arabinoside has the best in vitro evidence, and while my group did a control trial that did not demonstrate in the pre-HAART era that this was an effective treatment for PML, we have revisited the thought, because we really believe the problem is drug penetration, and it is very

possible that in the setting what we will see--if we see another case associated with natalizumab, it is very possible that there will be an inflammatory reaction, that there will be more breakdown of the blood-brain barrier as the drug is withdrawn, and the JC infection is exposed to an increasingly active immune response, and that we could augment that with cytosine arabinoside.

So, I think that is something that I would actively consider, but all of these things are really investigational approaches, and we could certainly have discussions about giving a formula, but it would turn into another trial, and I hope there will not be enough patients to really do a meaningful trial. If there were, then, I suspect we would be stopping again anyway.

DR. KIEBURTZ: Thank you, Dr. Clifford.

Dr. Sacco.

DR. SACCO: I just wanted to check. I know we are getting to the end of the questions, if there may be another, but we never touched on, and I thought you were going to bring it up, the issue

of neutralizing antibodies and whether that has a role in any of our deliberations.

I thought it was in our questions, and I am realizing, we got to the end now, and it hasn't been unless there is a new question we don't know about.

DR. KIEBURTZ: It does go back to what would be--8(h), should there be some routine testing for neutralizing antibodies, or should that be in response to some clinical event, because the presence of neutralizing antibodies seems to be a signal for increased risk and decreased efficacy, so the risk-benefit ratio would be perturbed.

The question is should testing only be driven by clinical events, or should it be done at some specified time points as a mandatory part of use.

Thoughts on that?

DR. KOSKI: Certainly patients who had maybe infusion reactions early on, patients that appeared to have progression in their symptoms. Their MRI did not show something that might be

compatible with PML. I mean you would want to look and see if these antibodies are there since it is associated with decreased efficiency, and also infusion reactions.

DR. KIEBURTZ: Dr. Sacco.

DR. SACCO: I don't know how this works with the FDA and the sponsor, but I mean whether there would be a recommendation to check antibodies should symptoms occur, and then consider discontinuation of the medicine?

DR. KIEBURTZ: A recommendation is certainly something that could be proposed. The question is would it be required, and the discussion I hear is mostly--I mean if it was required, everyone would have it done at a certain time point no matter what their symptoms were.

I don't hear a lot of enthusiasm for that, but it could be required or strongly recommended in the setting of certain clinical phenomena including lack of clinical benefit and the occurrence of certain kinds of adverse events.

DR. DeKOSKY: I am remembering that the

development of the antibodies was relatively early in the course, that if you didn't have them by 12 weeks, you probably weren't going to get them, so we might want to temper that. Someone that is having response problems a year out, that that may not be a terribly useful thing to go after.

The other thing we didn't discuss, and I am not sure if you need feedback about it or not, is frequency of high-dose methylprednisolone for breakthroughs. We didn't discuss that and whether at some frequency, reconstitute immunosuppression or immunomodulation.

DR. KIEBURTZ: And hence, whether the drug should be restricted if you are having a certain frequency? I think these things are going to intersect because if you are having a high rate of relapse, you are going to get imaged again, these other things are going to happen, so that it will probably be driven by those clinical events is my guess. It is not going to pan out that someone is going to have a high exposure to pulse steroids, and not be getting these other things happening.

Is that fair?

DR. McARTHUR: That's fair.

DR. KIEBURTZ: I detect a certain group fatigue, but we will persevere if there is other important issues that the Agency would like us to address.

DR. McARTHUR: Dr. Kieburtz, I just found another page of questions here.

[Laughter.]

DR. KIEBURTZ: Dr. Katz.

DR. KATZ: I think you have answered our questions. I would like very much to thank the committee. It has been very difficult and I think you have managed to get through the questions and give us all the information we need. So, I very much appreciate your doing that.

I would also just like to acknowledge the folks who spoke in the public session, who were particularly courageous, not only handling their illness or their family members' illness, but coming here and giving their testimony. That is a difficult thing to do.

Finally, last but not least, I would really like to publicly acknowledge the Agency's presenters. You saw the slide of all the people who were involved in looking at these data, and there were probably even more than that, but the folks who presented - Alice Hughes, Susan McDermott, Diane Wysowski did a tremendous amount of work in a very, very short period of time, and their presentations were only the tip of the iceberg of the amount of work that they actually put in, and I think they need to be acknowledged.

Also, two folks who didn't speak here today, who have done a tremendous amount of work preparing for this, Wilson Bryan and Kathy Needleman in the Division, so I would really like to acknowledge their efforts. I think it has been extraordinary.

DR. KIEBURTZ: Could I just say I have had several discussion with the committee members, and I just want to reiterate some of those comments. First of all, I know it is very difficult for the sponsor to have so many things they would like to

say, and we don't call on you in the circumstance, and I am sure you are familiar with that, but thank you for the comments you did provide and the information you provided, which was very helpful and effectively organized, and for answering our questions when we had them.

And to the FDA for presenting very clearly and providing us materials that were cogently organized and obviously reflect a lot of work, and just to reiterate, the open public hearing was particularly--of course, it was moving, but it was also instructive, and as many of you might realize, it is an incredibly courageous thing to get up and say those things in public, particularly when they have such an emotional content, so we thank those speakers for their willingness and courageousness in doing that.

I would just like to thank the members of the committee for sticking with it, these are tricky issues, for the Agency for having forbearance with us in not necessarily given concise answers in open discussion.

Unless there is anything else that needs to be said, I think I will adjourn the meeting at this time.

[Whereupon, at 3:15 p.m., the proceedings were adjourned.]

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