intellectually sound decision and I think that it is okay.

DR. SACHAR: Dr. Couch had to leave but gave me a proxy vote that he thought efficacy had been demonstrated.

Dr. Lesar.

DR. LESAR: I believe the evidence strongly supports efficacy in some subpopulations.

DR. SACHAR: Dr. Neaton.

DR. NEATON: I also think efficacy has been established and I think some restriction is in order given the safety concerns.

DR. SACHAR: Without ignoring the very cogent objections and concerns of a minority, I think we have at least enough to make it worthwhile to continue the discussion rather than to stop now because we all feel it is an ineffective drug.

So we could then just move on to 1b for the time being about maintenance. Here, maybe we will go around again as quickly as we can with, again, my trying to bias the situation a bit by saying that the maintenance data to me looked even

much stronger than the induction data.

We you like to comment on that, Dr. Neaton?

DR. NEATON: I guess my only comment, I remained a little bit unsettled about the role of CRP in understanding the maintenance trial and don't accept the fact that these were placebo responders, or non-responders, that are driving it. So I am still a little bit confused on the role of CRP.

The only factor that I have seen today that seems to influence response is the baseline level of CRP.

DR. SACHAR: Right.

DR. NEATON: I am not certain--I worry, for example, how well was the blind maintained in these trials. These are very subjective responders. So I am a little bit concerned about the discrepancy in the kind of role of CRP in the induction studies and in the maintenance studies.

DR. SACHAR: It sounds a little bit as if you are saying yes, it certainly looked effective

for maintenance but it doesn't make any sense to you and you don't understand why.

DR. NEATON: I guess you might say that.

DR. SACHAR: Can we get a quick yes or no answer from the company, from the sponsors, as to whether or not the blind was tested.

DR. JONES: For premises such as CRP and also lymphocytes that would be affected by the drug, these were analyzed by a central laboratory. So the actual physicians never saw those results until the end of the study.

With regards to the population that we analyzed, the efficacy population, all patients who responded in 301 were eligible to go into 303 at the criteria mentioned, a 70-point reduction in the CDI score at weeks 10 and 12 and a score between 220.

But we didn't unblind those patients until the very end so we didn't know which ones were placebo responders and which were natalizumab responders.

DR. SACHAR: I think the doctor is asking

whether the effectiveness of the blind was tested; that is, was there any questioning of patients and physicians as to which they thought they were on, or was that not done?

DR. JONES: Ah. No; we didn't do that testing.

DR. SACHAR: The blind was not tested. Okay.

DR. LESAR: I think there is strong suggestion of efficacy for remission and I have the same concerns about the CRP.

DR. SACHAR: Dr. Nelson.

DR. NELSON: Yes; i think there is strong evidence as well.

DR. SACHAR: Ms. Eichner.

MS. EICHNER: I am still having confusion understanding exactly what that question is, if you could.

DR. SACHAR: It is actually referring to Study 303.

MS. EICHNER: Just testing of the CRP, whether it is sufficient or not, or--

DR. SACHAR: Well, within the population--

MS. EICHNER: That was tested.

DR. SACHAR: On whom it is proposed to be used, which is people with evidence of inflammation by increased CRP or some other maker--in this case, it was CRP--and not on concomitant immunomodulator, was it effective in maintenance of remission as defined by CDAI and c. will get to eliminating corticosteroid use.

MS. EICHNER: From my understand, I think it was.

DR. SACHAR: Dr. Krist?

DR. KRIST: Yes.

DR. SACHAR: Bob?

DR. LEVINE: Yes.

DR. SACHAR: Sean.

DR. HENNESSY: Yes.

DR. SACHAR: I think so; yes.

DR. PLATT: Yes.

DR. GARDNER: Yes.

DR. KOSKI: Yes.

DR. DAY: [Inaudible response.]

DR. CHANG: [Inaudible response.]

DR. SACHAR: Okay. Concerns, Arthur?

MR. LEVIN: Same as before and would like more evidence.

DR. PASRICHA: I am trying to understand that data for clinical remission and trying to reconcile what the FDA presented to us on Page No. 10, Dr. Rajpal's handout and Slide No. 50 from the sponsor's handout and Slide No. 50 from the sponsor's handout.

DR. FRANCIS: First of all, I want to say that when we were looking at sustained--when we were looking at the maintenance issue, it is more important to focus on the actual remission rate than the sustained response rate because clinically that is more relevant than just showing the sustainability of an arbitrarily defined response.

So, from a practical perspective, if the patient still has active disease, even though they have met the criteria for response, it is still a conundrum for the clinician because what you want to do is get that patient in remission.

So let's just focus on that. What I am looking at at the bottom of Page 10 in the FDA handout is that the difference in remission is--is it a delta of 10.3? 11.9 in 301 and 307, 10.3? That is Page 10.

DR. FRANCIS: That is the induction study?

DR. PASRICHA: So that is your sustained clinical remission; correct?

DR. FRANCIS: That is sustained remission. That is at every time point. So, for each assessment, the patient has to remain in sustained remission, the primary endpoint there at 6 months, so 44 versus 26 percent and then carried out to 12 months, 39 versus 15 percent.

There is also data available for patients in terms of who were at the individual time point as opposed to every time point which we have here demonstrating that the proportion that are in remission at Month 6 is 55 and at Month 12 is still 55 percent versus 22 percent, a delta of 33 percent for sustained remission.

DR. PASRICHA: Okay. I just wanted to

clarify that. So I am in favor of the data showing efficacy for remission.

DR. SACHAR: Dr. Kramer, how did you feel about 1b?

DR. KRAMER: It seems to me that if the initial is no, I don't understand how you can take those patients and follow them and say that you assume that drug is--

DR. SACHAR: You actually could in the sense that you are saying that those people who, by chance, got acutely better when they got the drug didn't relapse as much when they stayed on it. So there was something about them that the drug continues to maintain a response. I mean, they can be separated statistically. It is just that, in terms of approval, it wouldn't mean very much.

DR. KRAMER: Could you clarify which slide the sponsor was just referring to and the numbers that you just gave, which slide that was, the sponsor just gave an answer to Dr. Pasricha.

DR. FRANCIS: The first slide we showed was Slide 50 in the core presentation and the

second was a backup slide that we showed to do the "at" time point.

DR. KRAMER: And we are voting on the 6-month sustained remission?

DR. FRANCIS: Six months was the primary--the primary endpoint was, in fact, response. The secondary, the contingent primary endpoint, is the sustained remission at 6 months.

DR. SACHAR: Now, Slide 50 is sustained remission out to a year by CDAI. Slide 51 is sustained remission by a different definition out to a year and that is by the IDDQ score. There is, again, a complete separation of the blue and the yellow lines.

Do we have Margo Smith?

DR. SMITH: Yes.

DR. SACHAR: You feel that there is a--okay. Now, the same question is going to come out for corticosteroid sparing. Again, the data speak for themselves, the interpretations each of has to make.

There is a procedure for votes that sort

of requires a rather elaborate procedure to raise hands and the yes people have to identify themselves, say why they voted yes, and the no raise their hands and have to say why they did it. And then abstainers.

That seems to me that that is an absolute requirement for the bottom-line recommendation. I am calling for these votes at the suggestion of Dr. Platt, really, only for the purposes of facilitating and clarifying the discussion to reach that final vote.

So I would really like to short-circuit that. Maybe if we could just get a show of hands as to how many people feel that the corticosteroid indication was met.

[Show of hands.]

DR. SACHAR: Okay. So we don't actually have to record numbers of votes here. I think that what the record is going to show was that there was a majority consensus of the people that 1c was met. When we get down to the bottom line, those people who are unsatisfied will have very ample

opportunity to detail all their reasons that they are dissatisfied.

This is not a break. We are just going off the record for a couple of minutes. Everybody stay where you are.

[Off the record.]

DR. KWEDER: We are just going to take a five-minute break.

[Break.]

DR. SACHAR: Just as we have a requirement for balancing safety and efficacy, we also have a requirement to balance time with openness and opportunity to hear all the opinions. That can be difficult but we will try to strike that balance.

Part of it is going to come by moving along a little quicker without formal votes on all of these things but giving opportunities to everybody for input.

So, without going on a line-by-line exegesis on each question, we are just going to take a general look at--we have already discussed CRP at great length. The proposed indication

states that Tysabri is generally recommended for patients who have had inadequate response to or are unable to tolerate conventional Crohn's disease therapies.

What we are asking you to do is chew on that question for just a moment, see if you are satisfied that the data support that in that patient population. We have already heard some very cogent arguments as to why some people feel that that is not rigorously proven, but chew on it for a moment and then ask yourself the same question from the safety point of view as well as the efficacy point of view; that is to say, should we still talk about restricting to certain populations. As long as the evidence isn't too flimsy, should we be restricting to certain populations because of the increased risk?

There are some examples on 2b there on other kinds of things, levels of disease severity and refractoriness to other treatments and so forth and so on.

It would be good to hear from everybody,

but let's hear first from people who actually want to comment on that particular question. If you raise a hand, you will be recognized if I try to scan carefully to both sides.

Do you feel--let me start over here again. Dr. Smith, do you feel that there is anything encompassed in this question that we haven't already dealt with in the prior discussion that you want to particularly focus on?

DR. SMITH: Taking the question as a whole, not as a 2a and 2b--

DR. SACHAR: No; just take the question as a whole.

DR. SMITH: As a whole, my biggest concern is I don't think we have enough information right now when we are specifically talking about opportunistic infections, PML in particular, and then the other latent viruses as a general. I think there is clearly not enough data and I think, based on that information, this should be a very restricted group of individuals.

DR. SACHAR: Right. And that is what the

question is asking. It is saying, in view of the concern about that risk of latent virus, is there some subset of the Crohn's disease population in whom you feel that risk is justified because of certain features of their case.

DR. SMITH: Based on the information that has been provided--

DR. SACHAR: Based on everything we have been talking about all day.

DR. SMITH: I don't believe we have enough data.

DR. SACHAR: To approve it at all?

DR. SMITH: To approve it in the context of this question, is there a subset population.

DR. SACHAR: That is, is there anybody who is so severe--

DR. SMITH: I understand.

DR. SACHAR: Or about to explode.

DR. SMITH: I understand. And based on the information--

DR. SACHAR: You would say no.

DR. SMITH: No.

DR. SACHAR: What about it, Dr. Kramer. You are very concerned that we don't have efficacy here at all. So would you just say there is nobody in whom the risk would be justified and let it go at that.

DR. KRAMER: I think we are in a conundrum because I think the safety issues have led people to try to model what they did for MS to avoid concomitant therapies that might immunosuppress. Yet, even with what the sponsor is asking for, you are looking for the population that has already been immunosuppressed with other therapies and, in fact, the one case, as I remember, of PML in Crohn's disease was not concurrently on those other therapies but had prior receipt of them.

So I really think there is a conundrum where there is a hypothetical population that received all these other things so we can make ourselves feel better but there is no evidence that is going to protect.

DR. SACHAR: Understood.

DR. SMITH: So my answer is we need more

data.

DR. SACHAR: Right; that you are not comfortable.

DR. SMITH: And that it needs to be studied further.

DR. SACHAR: Dr. Pasricha.

DR. PASRICHA: I think while we are on Question 2 now, I think that is a reasonable proposal.

DR. SACHAR: As it stands.

DR. PASRICHA: Yes.

DR. SACHAR: Arthur.

MR. LEVIN: I would agree with Dr. Kramer once again.

DR. SACHAR: Okay. Could you state that into the microphone? It is valuable comment.

MR. LEVIN: My apologies. I would agree with Dr. Kramer again that we don't have sufficient evidence to make that--

DR. SACHAR: Not sufficient evidence to select anybody with Crohn's disease as suitable for a drug with these unknowns.

Dr. Chang.

DR. CHANG: I would agree, too, but my comment would be that I don't think any of these patients who were doing well on therapy would have ever entered the trial in the first place if they were doing so great.

The second comment I would make is I feel like they have shown efficacy and, in a broader population, and they were actually asking for a more narrow indication for safety reasons. So I would just try to keep that in mind.

DR. SACHAR: Dr. Day.

DR. DAY: Pass

DR. KOSKI: Although I support the hypothesis, I honestly don't think the data is here to support it.

DR. SACHAR: So you are not happy to pick anybody.

DR. KOSKI: Right.

DR. SACHAR: You don't want to give it to anybody. Dr. Gardner?

DR. GARDNER: Well, given that I thought

we had efficacy in Item No. 1, then I guess I can't say that there is nobody in No. 2. So I guess I will pass on any consideration of the subsets that are listed here because I agree, we don't have data.

DR. PLATT: If we weren't so concerned about safety, I would say the 307 population would be an appropriate one. Because we have these concerns about safety, I think there is good reason to be restrictive. I would sign on to the formulation that Sean gave us the last time we went around; that is, I would say, until there is substantially more data, especially about long-term exposure, that it makes sense to be restrictive even though we don't have very, very good evidence that this restriction is giving us a lower risk group.

DR. SACHAR: I will wait until the end. Sean?

DR. HENNESSY: Sure. So my restrictions would be CRP-positive and people who have failed, were intolerant to or have contraindications to TNF

inhibitors.

DR. SACHAR: The specific level of disease activity. We have all been talking about moderate to severe.

DR. HENNESSY: Yes.

DR. PLATT: Sean, also have failed steroids?

DR. HENNESSY: No. Well, no; you don't have to have failed steroids. If you are steroid-dependent, I think that can get you on.

DR. SACHAR: That is one of the prime indications that we are considering here is corticosteroid dependency at a toxic level.

DR. HENNESSY: I think that, with enough steroids, you can get just about anybody to respond.

DR. SACHAR: It is an effort to get people off steroids, I think, is what--

DR. PLATT: Oh, okay. Then I will say there might be a little daylight between us on that because I think that the issue of balancing the known risks of steroids against the unknown but

potentially catastrophic risks of this agent are sort of beyond the discussion we have had today.

DR. SACHAR: Okay. We will get a comment from the GI point of view at the end. Dr. Krist?

DR. KRIST: I think for the population we have talked about, it would be appropriate. I am not sure how to feel about steroids. I will have to pass on that because I agree, we haven't talked enough about it.

MS. EICHNER: I think the population that we are addressing, it is appropriate.

DR. NELSON: I that FDA and clinicians make difficult decisions about very toxic drugs all the time. Chemotherapy would be an example and antibiotics of other sorts would be as well. I think we need to allow this drug out there to the indicated population with the caveat that we have this very effective postmarketing surveillance system in place that we have been talking about and perhaps even better than we have been talking about.

DR. LESAR: I would concur with Dr.

Nelson. I agree with the restriction, that I am not happy with the postmarketing plan. I think you need more control data, not just observational data.

DR. SACHAR: Absolutely. We will get to that a little farther down.

The very sophisticated risk-assessment specialist, Dr. Platt, is concerned that the known risks of steroids don't justify the unknown risks of the Tysabri. The unsophisticated view of a practicing gastroenterologist is that the known risk of steroids are so terrible that I would be willing to accept the unknown risks of the Tysabri. Individual opinions will be coming to a bottom-line vote.

Now, are there sufficient data to support maintenance therapy with monotherapy. We have sort of been over that a lot. There is a strong feeling that the monotherapy population has not been prospectively selected and studied as such. Others have said that the monotherapy patients that are in the trial are sufficient to support that

indication.

I don't know if we need to go over that again separately, but is there anybody who feels that that question has been inadequately addressed and who wants to comment on it. If so, raise your hand.

Then moving on to Question 4, we are now getting into the safety questions. What are the risks that we mostly have to worry about. I see some good examples here.

I am not entirely sure I understand the question. It sounds a little bit like restating the question of how much do you have had to fail before you go to this drug. Now, can you clarify, Joyce, the question or the intent of the question?

DR. KORVICK: I think we want to make sure, since the focus of the TOUCH Program for MS right now is look at PML and opportunistic infections as the sort of high level immunocompromised sort of metric. I think that we were looking to see, you know, its obvious PML OIs. But those as well as other things because Crohn's

patients might have other risks that may be different than MS. So are there another things that the Committee thought was important for us to think about when we try to do the risk calculus.

DR. SACHAR: Such as malignancy in general and lymphoproliferative malignancy in particular, for example?

DR. KORVICK: Yes, and also other, perhaps, infection.

DR. SACHAR: Um-hmm. Well, on that infectious note, Dr. Smith, are there some things you wanted to watch for some other latent virus reactivations?

DR. SMITH: Yes. I actually think this is a very important point to all of these questions because you just simply don't know what is going to happen in the long term. The intent of this drug is to be used for years. I will use the HIV analysis. We are now seeing secondary malignancies at a higher rate in a group of people that are profoundly suppressed even after you give them antiviral therapy and they have normal CD4 counts.

There is a higher rate of lung cancer, something that we don't talk about, and it is not directly related to smoking. There is a higher rate of lymphoproliferative disease even though they have normal T-cells again.

So I think this is something that has to be really weighed heavily. I think, right now, based on the information, we don't have enough data to say that there is a group of people that it is worth risking, I don't think.

DR. SACHAR: Understood. So you are saying that, if it were approved over your objections, you would, at the minimum, want to see malignancy and other infections added to the risk but that your vote would really be that those risks are so high that you would rather not let this drug out there yet.

DR. SMITH: Correct.

DR. SACHAR: Understood. Dr. Kramer?

DR. KRAMER: My answer to 4a would be I would be concerned about all of the above.

DR. SACHAR: At least.

DR. PASRICHA: Same.

DR. SACHAR: Dr. Levin.

MR. LEVIN: Same.

DR. SACHAR: Drs. Chang, Day.

DR. CHANG: Same

DR. DAY: Also.

DR. KOSKI: Yes.

DR. GARDNER: Gardner, the same.

DR. PASRICHA: Yeah.

DR. HENNESSY: So we have learned about some risks and we know that there are some unknown--or some known unknowns. When talking about the really rare events like PML, having an exposed-only cohort may be good enough because the role there is to measure what the incidence of the event is.

When we talk about events like opportunistic infections where they can occur outside of the context of treatment with the drug, I think that the sponsor is likely to get in trouble with an exposed-only cohort because then any events that occur are essentially blamed on the

drug. That argues strongly for the need for a control group as somebody else suggested.

DR. SACHAR: Well said.

DR. LEVINE: My reservation was with safety. I think, at this point, I would regret waiting two or three years and going back and finding out we voted the wrong way.

But I think even though this is a marginal to modest drug, it is no blockbuster, for sure. I think we will know that pretty soon, as soon as it is used. I think the gastroenterologists will get an idea. Unfortunately, we won't know necessarily about the safety-efficacy. So I am right on the fence about it.

But I think, for the sake of being able to have a drug with a new mechanism and the possibility that it probably may work in some patients, I would probably still go forward with great angst.

DR. SACHAR: We might be able to knock you off the fence with Question 5 which is giving you the opportunity to suggest other studies that you

would like first. Dr. Krist.

DR. KRIST: Thinking about 4a and other risks to track, I think the issue of a control group is important to think about. The other two things I might add onto the list of things here might be the hepatotoxicity. We didn't talk a whole lot about that but we saw some slides about potential risks with that.

I would like to see an overall mortality. There was at least a trend towards a greater number of deaths in the CD population on the medication.

MS. EICHNER: I am speaking, actually, from a patient's point of view.

DR. SACHAR: Of course.

MS. EICHNER: I think if the patients that I know were presented with all these risk factors, they would say go forward with the drug even though we might find out later that some things are happening we are not happy with, the same as in, you know, cancer therapies. A lot of people still go forward knowing the risk factors.

DR. SACHAR: That is what your patient constituency would say and want. And how do you feel about that?

MS. EICHNER: I feel the same.

DR. SACHAR: Okay. Dr. Nelson.

DR. NELSON: If we are asking what should we look for in postmarketing surveillance--

DR. SACHAR: Essentially, yes.

DR. NELSON: Then I think that these are certainly great categories but I also think that that other category has got to be kept wide open. Clearly, the control group will help to figure some of these things out. But we can't be too smart about this at this point.

I mean, there might be one of these events that you don't find in 3,000 patients. It might take 10,000 patients to find it and it might be critically important.

DR. SACHAR: A lot of people are talking about a control group. Now, there are a fair number of existing databases and registries on Crohn's disease patients but they are not the same

as the TOUCH registry. The question, I guess, we will have to ask when we get to talking about that, are we suggesting that the company should be required as part of the TOUCH registry to enroll via the same system a certain number of control patients as opposed to using synchronous databases that many centers around the country are doing.

Maybe we will come back to that when we talk about what we want down at Question 7.

Next. Dr. Nelson.

DR. NELSON: I think there is enough to go forward but, again, I think it is very highly dependent on the risk-management procedures that occur in data.

DR. NEATON: I think you have the risk identified there. I mean, you said it earlier; what you want to establish reliably is the percent that will suffer. I think that is kind of an expanded "other." I can say, from my point of view, maybe kind of jumping the gun, I wasn't referring to kind of expanding the TOUCH program. I was referring to randomized trials.

DR. SACHAR: On Question 5, clearly everybody around this table would welcome more data. I don't think the question really is would we like more data. I think this question is addressed to the people who are not prepared, on the basis of data at hand today to go ahead with approval.

So I am going to ask those individuals what studies they wish prior to approving Tysabri with the understanding that all of us would like more studies. But specifically those people who say they don't want to go ahead now until there are more studies, what more studies do you want. That is largely, but not exclusively, on the right side of the table.

Yes, ma'am.

DR. KORVICK: I think what I would like to clarify before you jump into that all-important question is that this is very informative, the dialogue we are having now. I think for the committee's sake and for our information we would like to know if anybody has to leave before 5:30

today to catch a plane.

DR. SACHAR: With the understanding that, if you do leave before 5:30, you are expunged from the record.

DR. KORVICK: No; you are not.

DR. SACHAR: Not from the transcript of everything that has gone on up to now, but any vote that takes place--what's that?

DR. KORVICK: It is that the last question is important for us. We are going to take a vote. So if you are all here, then let's proceed. Thank you.

DR. SACHAR: We have to get to 8 before 5:30.

DR. DAVIS: I would like to see more randomized trials for me to feel comfortable about this whole question of risk. That is what I would need.

DR. SACHAR: Right. And the population that you want is an efficacy--it is not a problem with that?

DR. DAVIS: The efficacy part doesn't

really--it is the safety part in that group of individuals that the study was actually done in.

DR. SACHAR: Okay. So you want to follow them longer?

DR. DAVIS: Correct.

DR. SACHAR: Or you want another group treated longer.

DR. DAVIS: Another group--both, actually, would be best because, again, this is a very experienced group of individuals. They have seem other suppressive agents that have changed what their immune surveillance is. So you are compounding a problem.

DR. SACHAR: Dr. Kramer, what would you ask for?

DR. KRAMER: I would remind everyone that one of the good effective drugs that has been demonstrated here today is placebo with a 47 percent response rate in the 301 study and a 32 response rate in the 307 study. So I would recommend that the sponsor take the indication that they have requested. If they wish to have CRP as a

basis for identifying patients with inflammation that they look at patients with some threshold for elevated CRP, that if they wish to specify that it is patients who have failed steroids--well, failed immunosuppressive therapy, 6-MP, azathioprine and infliximab--that they study that population, they take that population, require that they not be continued on immunosuppressives or TNF inhibitors.

They have to decide whether they wish to have steroids as they have suggested, allow it in and then taper it, randomize that population and study the randomized population for both efficacy and safety and continue the follow up beyond the duration of the efficacy assessment.

I also was a little bit perplexed about why, in the initial efficacy design, the two endpoints required for 307 were 8 weeks and 12 weeks when they were still getting their third treatment at 8 weeks. It seems like the assessment of efficacy was simultaneous with the third dose of drug which I--

DR. SACHAR: Which, as I understand, had

to be 8 plus 12, which meant 8 while they were getting it plus 12, meaning 4 weeks after it had stopped.

DR. KRAMER: Right. But that 8-week assessment is not the assessment of the effect of three doses of drug. Maybe they are saying that just being--maybe they are saying that that means it works after two doses. But, anyway, that is a minor point.

So I am suggesting that the population they are requesting approval be studied in a randomized setting with safety. I also suggest that there be a treatment IND--well, a compassionate-plea IND--for access to this drug which has enough demonstrated efficacy for the FDA to bring it before an advisory committee but enough concerns about safety that it needs to continue to be studies in a randomized environment.

My experience is that the ability to do effective postmarketing surveillance in these settings is minimal. If you think the cry of "everyone must have it" is strong here today, just

try to get a control group in the postmarketing setting when the drug is approved.

So I am arguing that the responsible thing should be to study this both for efficacy and safety longer and make it accessible through a compassionate-plea IND for patients truly with no other options with multiple surgeries as have been described.

DR. SACHAR: The model of the TOUCH program is not sufficient to satisfy your need for postmarketing in and of itself or because it doesn't include a control group, or both.

DR. KRAMER: Without a control group, I don't think you get the true answer in terms of the risk of these opportunistic infections, et cetera. The other setting is, I do think the CD population is different than MS in terms of not being able to--one of the key aspects of the MS population is the ability to require monotherapy with this presumed increased risk for concomitant immunosuppressants, et cetera. But I don't think we are in the same situation here because these

patients are all getting immunosuppressant therapy.

DR. SACHAR: Dr. Pasricha, what would you like to see?

DR. PASRICHA: I think, like everybody else, I am torn between the lack of robust data across the safety and efficacy spectrum versus the unmet need of patients. I am really concerned about what the next few years will show about this drug. At the same time, I don't want to deny it to the patients who need it, so, if there is a way that we can do this and keep a tight lid on it as suggested, perhaps, by a compassionate IND.

But to come back to the question here, I would like to see particularly more safety data regarding the actual risk of PML in this patient population.

MR. LEVIN: I am going to pass.

DR. CHANG: I would like to see more data just on the level toxicity--potential toxicity. My feeling is that, like Jay said, you don't want to keep it from patients but I think that, if there is a very good and adequate management,

risk-management, plan I think it could be very effective because it appears, at least with what was shown today, that, with MS, it was actually very good.

I think the added risk is that you might have increased infections in the Crohn's population. But as far as the alosetron risk management, I think it has gone well. I'll tell you, physicians who are scared about using it. They just won't do it.

So it is not like everyone is going to be rushing to use the drug if they don't feel comfortable if you have a very well-thought-out risk-management plan.

DR. SACHAR: We will come back, at the end of the question of whether you would require additional studies before any approval as opposed to a compassionate-use program.

Dr. Day.

DR. DAY: I would second Dr. Kramer's views and add the hepatotoxicity comments from Dr. Chang. I feel pushed into a corner. It is a

chicken and an egg thing. What we will be deciding today might be quite different had the sponsor decided to go for a different indication in the label. I just find this disturbing because we know eventually the actual use will widen across the narrow focus and I regret we will not have enough time today to discuss what the possible consequences of that might be.

DR. SACHAR: So you wish that they had had a wider indication or a narrower indication?

DR. DAY: No. I did not say that. I said we have to focus on what the indication is that the sponsor wants in the label and, on the side, I am wondering if they are regretting that decision. But I think that it has just backed us into a kind of a corner with a chicken and an egg character.

DR. SACHAR: Dr. Korvick, you could enlighten us here as to whether or not it is within our purview to make a recommendation for approval, for example, with some different indications, more or less restrictive than the sponsor proposed.

DR. KORVICK: I think it is up to each

individual member of the committee to comment on what is before them. If they have a specific recommendation that you would like to specifically mention, that would be useful for us to take back.

DR. DAY: Well, it could be a fishing expedition. We could say, where does it look good, and approve for that. But I don't think any of us would be comfortable with that. So I would like to hear the comments of my colleagues on this.

DR. SACHAR: Okay. Let's have a comment from a colleague. Next?

DR. KOSKI: I would really clearly support Dr. Kramer's recommendations.

DR. SACHAR: Dr. Gardner.

DR. GARDNER: I don't think there are additional studies I would ask for prior to considering going forward with approval as long as we talk, as we have a broader discussion of what we want to see after. The reason is because I am not sure that the kinds of painful absences of data that everyone is feeling will be well obtained through additional process randomized clinical

trials given the rarity of some of them occurring.

I feel like we need to look at alternatives to that with an available product.

DR. PLATT: Because I think that efficacy has been adequately demonstrated for the 307 population, we have this great concern about safety, I think possibly a variation on Dr. Kramer's suggestion would be to approve its use if FDA were satisfied that that use could be limited to a very restricted population, for instance the one that you might consider appropriate for a compassionate IND.

So I would be willing to defer to FDA'S assessment of whether it is possible to really limit the use in an approval situation. But then, there is--in either situation, it would make great sense to say, before widening the indications, a full randomized trial ought to be conducted.

DR. KORVICK: Dr. Platt, I think that was very interesting. We were trying to, in our previous questions, understand what those very restricted characteristics would look like. So I

am not sure we got to the bottom of that. We have heard a lot of discussion, but do you have anything in mind?

DR. PLATT: Ah, well. It would be what I thought I originally heard Sean say; that is, individuals who are not adequately controlled on all available classes of therapy, individuals who have failed because they don't achieve adequate control.

So, personally, for me, that would include not satisfactorily controlled on chronic steroid therapy.

DR. KORVICK: Would you require that they do progress up through the immunosuppressants and the anti-TNFs.

DR. PLATT: Yes.

DR. KORVICK: The whole nine yards.

DR. PLATT: Personally, I would say--right. Individuals who have not been adequately maintained on any other therapy would be--I wouldn't call it comfort level at the moment, but I think it would be appropriate to make the

drug available to these individuals. If you can do it through approving and saying the indications are, and be satisfied that you could avoid having the drug then used more broadly, alternatively I think a compassionate-use situation would be--

DR. SACHAR: The only difference I hear between your proposed restrictions and those that have been more widely discussed is you would not suggest it be used in somebody whose symptoms are under control only on 60 milligrams a day of prednisone continuously.

DR. PLATT: Correct, and that is because--I take your point that 60 milligrams of prednisone is a big problem. There is great morbidity associated with it. But I think we have no idea what the risks are of chronic exposure to Tysabri. I think until--we will be in a very different place in a couple of years. It seems to me--so my comfort point is to say, for individuals who can't be controlled on current therapy, it would be acceptable to make the drug available now with the kind of postmarketing surveillance

program, the best postmarketing surveillance program, that FDA can devise.

DR. SACHAR: Right. Perhaps, what we, then, ought to say, who cannot be controlled with acceptable levels of toxicity on these other drugs because, perhaps if somebody is going blind and collapsing all their bones and has gotten pneumocystis or something from steroids, maybe--we will talk about it.

Dr. Hennessy.

DR. HENNESSY: I think that there is sufficient information available to date to approve it. So I wanted to ask for additional studies prior to going forward. I would echo Dr. Gardner's comment that additional randomized trials that are powered for an efficacy endpoint are, by definition, going to be underpowered to study rare adverse events.

I would also remind my colleagues on the committee that this is a severe disease. This is a group of individuals that has expressed willingness to tolerate a high degree of toxicity. I think, in

that context, even though it is unknown, the right thing to do is to make the drug available clinically on a restrictive basis and to do the best studies that we can to better characterize what that toxicity is.

DR. SACHAR: Bob, any comments?

DR. LEVINE: No. I would just be as restrictive as possible so that, with advertising, et cetera, there is no way you can slip in patients into this except as we have agreed right here with very tight restrictions. But I think I would go forward.

DR. SACHAR: We will complete the poll again with the understanding that we want to hear what studies are desired by those people who would not allow approval of this drug without them. So are you among that group, Dr. Krist?

DR. KRIST: No; I think I would support restricted use. But the question also is what data, what more data, do we need. I think we need more--

DR. SACHAR: Prior to approving; yes.

DR. KRIST: Well, prior to. I think we need a lot more safety data and I am not sure an RCT is the way to--

DR. SACHAR: Right. What I want to do is finish the poll for the people who insist on having these studies prior to any approval. 6 and 7, we can address, I think, after we look at No. 8 because either we are going to vote approval or not approval. If it is not approved, we don't really have to discuss 6 and 7 quite yet. But if it is approved, then we have to go back and talk about what restrictions and what kind of safety monitoring are required.

Ms. Eichner, you have already said that you would be willing to approve now. And Dr. Nelson?

DR. NELSON: I think I will hold my comments in the interest of time.

DR. SACHAR: Okay.

MR. LESAR: I have none that I would require.

DR. NEATON: I am okay for a very

restrictive approval but follow-up randomized safety studies.

DR. SACHAR: Okay. I was going to ask you if we can do this or not.

DR. KORVICK: We would like to, since, if you are planning to skip to No. 8--contingent into No. 8 is this built-in aspect of an affective risk-management plan is in place.

DR. SACHAR: Of course.

DR. KORVICK: So, perhaps, if we could have a teeny, tiny discussion from what people think would be elements or, if the neurologists in the room who might have had experience with the current program could tell us what they think about it, it would be helpful to know what elements people are viewing as an effective program.

So that brief discussion before you take a vote would be very helpful.

DR. SACHAR: Sure. That's fine. Specifically from the neurologists at this point and infectious-disease people, perhaps.

DR. KOSKI: So I guess we are addressing

7, specifically?

DR. SACHAR: Yes.

DR. KOSKI: Okay. Well, first of all, I want to remind everybody that the MS population is really quite different. I mean, I think everybody has been acknowledging that. But, you know, these people are followed with neurologic examinations. Most of them, before they were even considered for Tysabri for diagnostic considerations have received MRIs, some of them more than one.

You know, my attitude towards people with Crohn's disease is I sure have been sent a lot of them to evaluate peripheral neuropathy, one with myelopathy and peripheral neuropathy secondary to cover deficiency and also some patients with some central-nervous-system types of symptoms.

I think my attitude, particularly in a patient that is not being followed by a neurologist or having been evaluated by a neurologist, if you don't look for something, you are not going to find it.

So, sure; we say, well these are pristine,

pure patients. Well, I can assure you, they are not. And I would at least recommend that if you were going to put these patients into a program where there is the potential for opportunistic infections that maybe very subtle in their presentation that, at the very least, at least you have a baseline neurology examination.

Now, I certainly understand that two years down the road, you may say, oh, well, they sort of had something but, you know, the point is it is a big change from this point.

You know, when we follow patients, we are looking for clinical change. You can make the argument that, if that examination is negative, would I necessarily recommend an MRI. No. But I think all of these things are helpful when you are following these patients down the road and they do get different types of symptoms.

DR. SACHAR: So you are voting at least for c, a full neurologic exam. You have a whole menu of six things to choose from.

DR. KOSKI: Well, I know.

DR. SACHAR: You could just say all of the above.

DR. KOSKI: But I would say that, for instance, you could actually be a little bit more specific. I mean, normally, I would say yes, I would like a neurologic examination which, by the way, includes a Mini-Mental Status which is a--you know, it is a fairly brief cognitive-function type thing. One could actually do this, you know--for instance if you have a nurse practitioner that is used to evaluating patients, you could perhaps do it through that at the time of admission into the program.

I follow patients over years and it does make a difference, the changes that do occur over that period of time. But you have an idea about the tempo and what is going on with them.

DR. SACHAR: So we could always get an ad hoc committee, perhaps, to make recommendations.

DR. KOSKI: Oh, sure.

DR. SACHAR: But it is good to have these views in advance. Neurology and maybe from the

infectious disease and maybe from the Chairman of DMARS. And then we can go on.

DR. PASRICHA: Just a sort of perhaps naive question. I read or heard this morning that a third of the patients, or a third of human subjects, will excrete the virus in the urine; is that correct? So, even though the risks are not established, shouldn't we be excluding those at least. I mean, doesn't it make sense?

DR. DAVIS: It doesn't help. You can't include it and you can't exclude it. You don't know what it means.

DR. PASRICHA: So there are two aspects. Has that been studied, that it doesn't make a difference, or we don't know the answer.

DR. DAVIS: We don't know the answer.

DR. PASRICHA: So if you don't know the answer, it just would make sense, why take somebody whom you know is actively producing JC virus in some part of their body? Why wouldn't you want to take those out of the at-risk--you don't know, but you could be--

DR. DAVIS: I guess the point is that you can have some people who, depending on when you are looking at them, they may excrete at one point and they may not. So it is random. So today yes, tomorrow no. So when are you going to do the test?

DR. PASRICHA: The point is, if you catch it, shouldn't you exclude it?

DR. DAVIS: But catching it may mean nothing.

DR. PASRICHA: If they catch it only in a third of the patients, you should exclude those.

DR. SACHAR: It is a good question for the infectious-disease person.

DR. DAVIS: You can't interpret it. That is the problem. You don't know what it means when you find it. It is like CMV and the average person who excretes CMV in their urine. It means nothing. It doesn't mean they are going to have a problem with it. And, even in those individuals who have PML, most of the time, they are not excreting it. You can't find it.

DR. SACHAR: The positive predictive value

is so low.

DR. DAVIS: Zero.

DR. SACHAR: Zero, yes.

DR. PASRICHA: The positive predictive value, if you are not putting them on treatment. But if you are putting them on a drug that predisposes them, that may be different. It is like a PPD test for T.B.

DR. DAVIS: I guess the answer is that it hasn't been studied so I don't know that you know there is a risk. We don't know.

DR. SACHAR: We only have the data presented by the sponsor.

DR. DAVIS: That's right.

DR. SACHAR: Which said that among those--among the population they studied, there was no positive predictive value and poor sensitivity.

DR. PASRICHA: No; they didn't look at urine. They looked at serum. What we are saying is that one of the known harbors, safe harbors, for JC virus is the kidney. And if they are producing this in the urine, then you have--

DR. SACHAR: Ah. I misunderstood.

DR. PASRICHA: That patient population you may just empirically try to exclude.

DR. SACHAR: Good point.

DR. DAVIS: So, for the question, just to sort of give you the infectious-disease point, screening with an MRI scan is not going to be very helpful. You can start people off but there is nothing there until the person has the disease. So that is a way--

DR. SACHAR: Except it is a baseline.

DR. DAVIS: Well, baseline from what? It is not going to help you. It is just simply not going to help you. It is expensive and it doesn't give you any information.

DR. KOSKI: I would support that. It is just, as I said--but if you had a positive neurologic examination--

DR. DAVIS: That's different.

DR. KOSKI: That would be different.

DR. DAVIS: So I would agree that having a good general physical exam including a neurological

exam, and I do think for things like PML, you need cognitive testing. These are very subtle signs much like dementia for other reasons that, on the Mini-Mental, will not be picked up.

DR. SACHAR: And for f, you would probably add assay serum, and/or spinal fluid, and urine?

DR. DAVIS: Not helpful unless somebody has the disease.

DR. SACHAR: Did you have something as the DSARM Chair?

DR. PLATT: No.

DR. SACHAR: I think what we need to do now with only about five minutes remaining is to get a green-light red-light binary decision node here. Based on currently available efficacy and safety data, should Tysabri--could Tysabri--should Tysabri be approved for the treatment of Crohn's disease, period. If that vote is no, we are not, at this point, going to have to specify what the indications should be, what the restrictions should be, what the restrictive indications, restrictive distribution, administration, postmarketing

surveillance, controls, and so forth.

If the vote is yes, then we have to go on to those other things. Robert?

DR. LEVINE: I thought we agreed we would put the restrictions in. If we vote without the restrictions, then we would vote against it.

DR. SACHAR: Obviously, there are clearly going to be restrictions.

DR. LEVINE: But we just had a discussion where we said we would have the restrictions that we just talked about excluding all the previous drugs that they were on, et cetera.

DR. SACHAR: Absolutely. I think you misunderstood me. There are people on the committee who say that, in our current state of knowledge, no matter what you do, they will not approve it--no matter what you do, they will not approve it. If that is going to be the vote at this point, then we can stop at that point.

DR. LEVINE: Then you have to say that because that depends which way we would vote.

DR. SACHAR: Right. Now, I have to read--

DR. KORVICK: Mr. Chairman, before you go on, I think that we should be clear that what we are asking for is taken into consideration that, assuming an effective risk-management plan is in place and we take it that the committee, at least the people that sounded like they were willing to go forward, specified its somewhat prescriptive program.

DR. SACHAR: Of course.

DR. KORVICK: So I think that that is what you are voting on.

DR. SACHAR: Of course.

DR. KORVICK: I am just saying that to the committee at large. So I yield the floor to read the vote.

DR. SACHAR: Let me just refine it. Based on currently available efficacy and safety data, should Tysabri be approved for the treatment of Crohn's disease assuming that an effective risk-management plan is in place including postmarketing surveillance and restrictions on indication.

Now, the way this works--okay. Hands up for yes, should it be approved assuming that an effective risk-management plan is in place. So we are going to ask for that first. Risk-management includes restrictive indications.

[Show of hands.]

DR. NEATON: Does risk management include a risk-assessment plan?

DR. SACHAR: Yes. That is all part of management. Risk assessment at the outset, risk monitoring as time goes on and restrictive indications for starters and restrictions on concomitant therapy down the line.

Everybody with a hand up, you must say your full name and that you voting yes.

DR. NEATON: James Neaton. Yes.

MR. LESAR: Timothy Lesar. Yes.

DR. NELSON: Lewis Nelson. Yes.

MS. EICHNER: Marilyn Eichner. Yes.

DR. KRIST: Alex Krist. Yes.

DR. LEVINE: Bob Levine. Yes.

DR. HENNESSY: Sean Hennessy. Yes.

DR. SACHAR: David Sachar. Yes.

DR. PLATT: Richard Platt. Yes.

DR. GARDNER: Jacqueline Gardner. Yes.

DR. KOSKI: Carol Koski. Abstain.

DR. SACHAR: These are just the yeses. Are there any other yeses?

DR. CHANG: Lin Chang. Yes.

DR. SACHAR: No; are there any other yeses.

DR. PLATT: She said yes.

DR. SACHAR: Oh, I'm sorry. It sounded like no.

DR. PASRICHA: Jay Pasricha. Yes.

DR. SACHAR: Now for the record will all members voting no raise your hand.

[Show of hands.]

DR. SACHAR: For the record, please state your full name and state you are voting no.

DR. SMITH: Margo Smith. No.

DR. KRAMER: Judith Kramer. No.

MR. LEVIN: Arthur Levin. No.

DR. SACHAR: Finally, will all members who

wish to abstain raise your hand and state your name and that you are abstaining.

[Show of hands.]

DR. DAY: Ruth Day. Abstain.

DR. KOSKI: Carol Koski. Abstain.

DR. SACHAR: What now? For those who voted yes, you will now each have an opportunity to make a comment on your yes, if you wish to.

DR. NEATON: I will make a brief comment and run to a cab. I think it is absolutely critical that the risk-assessment program involve a randomized trial to look at safety. There is no question about it that another trial looking at efficacy is going to be underpowered. But what we have here is a set of trends for death, PML, which was one of the deaths, for serious infections, for malignancies, for hypersensitivity reactions, in your words, bad things that are happening to the patient.

So I think a study needs to be designed to understand and quantify those risks and rule out the possibility that they are above some limit that

would be considered unacceptable. That is not going to be possible, I don't think, with the nature of these kind of conditions in an uncontrolled study.

DR. SACHAR: Very good. The regular procedure is to go around and ask all the yeses to make comments, but if there are any no's who have to leave now who want to get their objections on the record, maybe we should give them an opportunity to do that.

Dr. Levin?

MR. LEVIN: My reasons, I think, have been stated before that I think the evidence is insufficient for us to approve the drug. I am also nervous about the large assumption about what the risk-management program will be. Given our concerns about safety and the lack-of-evidence concern, I don't know how we just simply leave the room assuming an adequate risk-management program will be in place.

DR. SACHAR: Does anybody else have to leave within the next five or ten minutes? Then we

will revert to regular procedure.

I have to read into the record that the overall vote was yes 12, no 3, abstain 2.

Now we can continue with the yes voters to comment.

DR. LESAR: I actually concur with both Dr. Neaton and Dr. Levin. My vote was based on the fact that required risk management is an absolute. I would also like to point out that if this drug is allowed to be used for steroid--to remove patients off of steroids, there should be clear caveats of why you have to take a patient off those steroids; that is, again, there would be probably specifically adverse events, intolerable adverse events. I think I would have some reservations about establishing a dose level unless there were actually demonstrated adverse events.

DR. NELSON: Lewis Nelson. I am not a statistician but it would seem to me that to develop a double-blinded randomized trial to collect this kind of safety data would probably take millennia to complete given the relative

rarity that we think the disease of interest, in this case PML, really kind of rears itself which is the reason I think we ultimately have to go these postmarketing studies.

I am not necessarily sure that an observational study wouldn't be helpful because of the essentially zero incidence of the disease in the population that would essentially be the control which is everybody that has ever had Crohn's disease and been on medications before and we are really looking at a signal.

Now, it may be different when we are looking at all these other issues, cancers and other opportunistic infections and that might change things. But the real issue, I think, that we have come to discuss is the PML issue

But I really also have a lot of concerns about the quality of most postmarketing surveillance that is performed in our country. I would request that, as this moves forward, the FDA try to create a system perhaps even more strong than the system that is being proposed by the

sponsor and, perhaps, put some really defined endpoints that would allow the drug, if it hit those endpoints, to be removed from the market that were predetermined and would really provide a fairly strong framework to allow us to move forward.

But I do think that something very strong to protect patients from these adverse events has to be in place; that is what is submitted from the manufacturer to the FDA, have the FDA analyze it, have the manufacturer analyze it. All those things have to be thought about very, very clearly.

MS. EICHNER: Marilyn Eichner.

DR. SACHAR: You don't have to make a remark.

MS. EICHNER: I think a very strong risk-management program does need to be in place. I think, from just speaking for the patients, we are more concerned about the opportunistic infections than anything else.

DR. KRIST: Alex Krist. I share the sentiments said before and I have said already that

I think we need more data. I think we have data showing that it is efficacious. The data showing that it is efficacious doesn't demonstrate that it is as efficacious as it is for MS. So I think it is modestly efficacious at best.

I think that the concerns about risk--I think it is going to take postmarketing more to be able to evaluate risk and I think my vote was very much contingent on the fact that there is not only strict postmarketing surveillance but also that there are systems in place to collect that information somewhat robustly, more than normal occurs postmarketing.

DR. HENNESSY: Sean Hennessy. No additional comments.

DR. SACHAR: David Sachar. I have voted yes with the understanding that I would recommend that the drug be approved for patients with mild to moderate cases of Crohn's disease, evidence of ongoing inflammation by elevated CRP or other objective laboratory or clinical markers, who have failed to achieve adequate sustained responses to

safe and tolerated regimens of steroids and immunomodulators as well as anti-TNF therapy.

We recommend that anti-TNF and immunomodulators be discontinued with initiation of Tysabri therapy and that the Tysabri, itself, be discontinued if there is no response within 3 months or if steroids cannot be discontinued within 6 months. Then I would go on to comment on what the risk-management program should be.

DR. KORVICK: Can I clarify? I think, for the record, did you mean moderate to severe Crohn's?

DR. SACHAR: What did I say?

PANELISTS: Mild to moderate.

DR. SACHAR: Oh, no. I meant moderate to severe. Sorry.

DR. KORVICK: Thank you.

DR. SACHAR: Thank you for that correction. Very sorry.

DR. PLATT: Richard Platt. I just want to attach my name to my earlier comments about the restriction on indications for individuals like the

307 population who cannot be controlled on any other therapy that has an indication and I support Dr. Sachar's formulation of indications for discontinuation for lack of response or flares.

DR. GARDNER: Jacqueline Gardner. I support Drs. Sachar and Hennessy and Platt's suggestion of restrictions. I think that the agency and we have learned a great deal from other risk-management programs and specifically those around inflammatory bowel disease that could be applied here.

One of the things that we have learned, I think, is that the populations with these restrictions then becomes small, so small, that it is difficult to study numbers that you would really like to have in doing risk assessment if you had everything going your way.

But I do think that intensive study of those people who are exposed to Tysabri after it is available with these restrictions, as well as even an historical group of Crohn's disease patients looking at some of the registries that Dr. Sachar

mentioned may be helpful in giving this perspective ongoing.

I think that our dream of a large randomized postmarketing surveillance study with non-exposed controls groups that we decide are comparable is probably unrealistic. So I wouldn't hang my hat on that as much as we would like it. But I think the agency has ample experience with these kinds of postmarketing observational studies that give us the best kind of information we can get under the circumstances of clinical practice.

DR. KRAMER: I realize I voted no, but I am confused by the committee's comments. I would like to clarify what is being recommended for postmarketing surveillance. Are we recommending just that every patient, as many patients as possible who receive this, be entered into a registry? Dr. Neaton, who had to leave, recommended having a control group. I am not clear what control group he is recommending.

One reason I recommended no is that it occurred to me that gastroenterologists are faced

with the dilemma once a patient has failed steroids--well, failed immunosuppressive treatment to choose between, right now, really TNF-inhibitors. But, if, for instance, natalizumab had come to this decision before the TNF inhibitors were approved, would we be reversing those two?

So, the question, if you were still in a clinical-trial setting, you could do a study where you did a head-to-head comparison once you had failed immunosuppressives to see whether the patients--I saw numbers there that looked to me that a lot of patients fail TNF-inhibitors. So you could do a direct comparison comparing efficacy and possibly safety.

So, I know I have said two different things, several things, here, but I would like to clarify from my understanding what is recommended for postmarketing surveillance because I was very--I didn't hear a clear description of that.

DR. SACHAR: Right. That is an excellent point that you raised. I would like to ask Dr. Korvick and the FDA whether the FDA has heard

enough general discussion about postmarketing surveillance at this meeting to be able to develop its own recommendations or whether you feel that you would like to committee at this point to achieve a voted consensus on more details of the postmarketing program.

DR. DEL PAN: I think I heard a few things from the committee. One is I heard a restricted distribution system as the TOUCH program currently exists. The other thing I heard, though, was the need for a lot more research data, let's call it. So some people advocated controlled studies. Those would obviously be in the realm of research.

But I think what I am hearing is more that the committee as a whole, and I would like to have correction on this, wants more information than the CD TOUCH program would provide. That would provide information on cases of PML and other opportunistic infections as they occur, a more real-time surveillance of those.

But, in terms of other things, I think the committee wants more than that. Now, the sponsor

has another research, an additional research, study in the MS population called TYGRIS. I don't think we heard much about that. That is the one Dr. Avigan referred to where there are about 35 or so patients entered in so far. They got the TOUCH program going first and then they started this.

I want to clarify that, as part of the risk management, you will have having a trial similar to TYGRIS.

DR. FRANCIS: Yes. Dr. Maier presented that information that we would be doing a similar observational study involving 4,000 patients with Crohn's disease, you know, essentially identical to what is being done in TYGRIS for MS.

Actually, I was informed it was actually 800 patients in TYGRIS, not 35. So, to answer your question directly, that is exactly what we would plan to do.

DR. GARDNER: Does that include patients that are not exposed to Tysabri?

DR. FRANCIS: No; there are no non-exposed. We have actually had discussions

about that, the issue about the types of patients that would be in your non-exposed group versus your exposed group, particularly if you are in a very restricted situation. So I think this is something that we have to, obviously, have further discussions with the agency as to how exactly that registry should be structured.

DR. SACHAR: There has been a strong sentiment in the panel today that a control group of non-Tysabri-exposed patients needs to have data accumulated on them. But there does not seem to have been arrived at a consensus as to whether we would virtually require the company to do that as part of their risk-management program or whether we would rely on existing and ongoing databases for that purpose.

Maybe it would be useful to have just a general sense of the committee as to whether anybody would be satisfied with the current positive exposure group being monitored by the company's TOUCH program while the control group be from existing database or whether we would really

ask the company to include controls.

Is there a sentiment about that?

DR. HENNESSY: I would say that form follows function and that the goals of the study need to be established before the design of it needs to be established and that, if you want a recipe for disaster, you get a bunch of people to design a study at quarter to 6:00 in the evening.

DR. SACHAR: Okay. Just wanted to get a sense. If we are finished with the business of the committee, I am sure I will be informed as to how it is formally brought to a close.

But, informally, I would like to thank the audience and the speakers and the sponsors and the FDA staff and the voting and non-voting members of the panel for their input especially those whose negative views enriched and informed our thoughts.

Individual citizens have individual opinions about the effectiveness of individual agencies of the federal government under individual circumstances but this citizen has a very positive opinion about the effectiveness of this panel for

the FDA today.

So thank you all. Are there any final statements or announcements before we adjourn the meeting? Okay. Then the meeting is adjourned.

[Whereupon, at 5:45 p.m., the meeting was adjourned.]

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