around in my pocket in any attempt to heal it. I was so sick my mother came to live with us, and she would pat me and tell me what a good day I had had on the days when I could get up, take a shower by myself, and push the grocery cart around the store while she shopped. That is what recovery from surgery was like for me.

I was looking at the prospect of another operation to fix the leak when my surgeon offered me another experimental treatment. They were going to use pig intestine to fix the leak that wouldn't close. Ultimately, we closed it successfully with Remicade.

So, that is what surgery turned out like. Did I know the risk before I went under the knife? Yes, I did. I understood the risks just like I understood the risk when I enrolled in a clinical trial of an experimental drug, and if I could go back and do it again, I would make the same choices. I would do it again.

The risks that I took are the reason that my life is moving forward and it is always going to

be that way for me. I mean I am 29, I am going to have Crohn's disease for the rest of my life, and I am facing that continual choice between one risk and another. I would love to have completely effective treatments that had no dangerous side effects, but that only exists in some fantasy world. In the real world, like I said, I took Remicade, which has its risks of infection. I maintained on azathioprine, which has its risks of liver damage, of infection. Both those drugs have long-term risks of lymphoma that we understand only poorly.

Right now I use biphosphonate with all their attendant risks to treat t he osteopenia that I have from years of corticosteroid therapy. I dropped below the fracture wrist threshold when I was 25. So, that is what it is going to be like for me, a tradeoff of one risk for the benefit that I can get out of any given drug.

If you bring Tysabri back on the market, are the risks significant? Yes, they are. If that means that it has to be in a strictly regulated

program like the RiskMAP that they have described here, then, that is the way it should be, because that is an acknowledgment of reality that risk can never be eliminated, it can only be managed, and we deserve the chance to assume that risk in exchange for the benefit that we can get.

If Tysabri were to come back on the market tomorrow, would I do it? Probably not right now. Right now the risk-benefit tradeoff is not worth it. But I can't think just about the now. I have to think about 5 years from now, 10 years, 20 years, the rest of my life, and there may be a time when I am in bed enough shape that the risks of Tysabri are worth it.

What I fear most is going through my therapeutic options one at a time and having them fail until there is nothing left to do but to cut off my diseased intestine a piece at a time and if I keep doing that, eventually you run out, you just don't have anything left to take, and then what do we do? That is why this drug is so important to me, maybe not for the right now, but for the

future, and for the patients who right now are in a position where they are bad enough off that Tysabri could benefit them.

One of the things that I had a chance to do when I was going to school was to learn from a lot of really gifted economists, and they taught me a really valuable lesson about a thing called the opportunity cost. That is the cost of the foregone alternative. It is the cost of the choice that you could have made, but you didn't. What they taught me is that a lot of times you don't see that cost, but it is always there.

If you don't put Tysabri back on the market, no Crohn's patient will get PML. We know that and people could look at that and say, well, isn't that great, that is nothing but benefit. But that is not true. There is a cost and we are it. The cost is the quality of life and the potential that this incurable disease is stealing from us.

Most people are never going to see that cost. Only you do and only you have the ability to do something about it. To answer Dr. Sachar's

question from earlier, the glass for me is always half full, it's the hope of real therapeutic progress that keeps me going all the time, and it's the reason that we will never be better off with fewer options. We are going to have Crohn's disease for the rest of our lives. We don't have the rest of our lives to wait for real progress.

Thank you.

DR. SACHAR: Ms. Casanova, both our committees are grateful for your investment of time and energy and credit card charges in giving us your perspective. Thank you.

Speaker No. 6.

MS. ARNETT: Good afternoon. My name is Melissa Arnett and I would like to thank the committee of allowing me the opportunity to participate in this open hearing. My remarks are submitted on behalf of my mother, Jamie, who is not able to be here today in person.

As such, I am here of my own volition and at my own expense.

During the next few minutes, using my

mother as an example, I will talk about the reality of having Crohn's disease, and the impact that the approval of Tysabri for this use can have on patients with moderate to severe Crohn's disease.

My mother, now 51, works as a program director for another federal agency. Prior to her Crohn's disease diagnosis, she did not have a history of digestive complaints. Ten years ago, what we thought was the stomach flu kept getting worse instead of going away.

After several weeks of illness and perplexed doctors, she went for a colonoscopy and was immediately admitted to the hospital. This first episode resulted in her diagnosis, a week's hospitalization, and a month of recovery time afterward.

Although a typical description of Crohn's disease talks about diarrhea and cramping, that description doesn't really provide an understanding of this disease. It impacts almost every aspect of normal life, especially for those with more severe cases who symptoms are not well controlled by

available medicines.

For my mother flare-ups mean that she consistent has a fever, lacks every, feels generally unwell, and has arthritis-like back and joint and joint pains. Her digestive symptoms are intense - the movement of food through her system is extremely painful and the need to eliminate is unanticipated, frequent, and extremely urgent when it arises.

To cope with her symptoms as well as possible, she eats only at dinner time and severely limits the amount of fiber. Despite this, a "normal" day means that she has several diarrhea episodes around midnight, and wakes again about 6 in the morning. Between 6:00 and 9:00 or so, her episodes are so frequent and unpredictable that she is not able to leave the house until her system has emptied.

Her episodes are less frequent during the remainder of the day but still occur as her colon cannot tolerate holding any material. At this point, her episodes continue to be very

unpredictable, painful, and may mostly consist of blood and mucous. A "typical" day means 15 to 20 such urgent and painful episodes, from minutes apart in the morning to perhaps a few hours apart later in the day.

During the first 5 years after her diagnosis, Mom was treated with a combination of anti-inflammatories for maintenance and corticosteroids for flare-ups. Despite the anti-inflammatory medication, she remained highly steroid dependent.

For her, this means that while steroids are somewhat effective in bringing her flare-ups under control, she will typically re-flare within two weeks of tapering off of them. Next, immunomodulators were added to her treatment regimen. These were ineffective at the original prescribed dose and she was unable to tolerate higher doses.

Both steroids and immunomodulators had side effects that negatively impacted her quality of life. Still flaring though taking these

medications, she had no energy, found it difficult to concentrate or work and started having adverse side effects like blood vessels spontaneously breaking in her hands.

At this point, she pursued clinical trials out of desperation. She was accepted for participation in a random study trial for Antegren (now called Tysabri) through the University of Virginia and began to wean herself off of steroids and immuno-modulators in order to begin the trial.

Her first double-blind random study trial began in December 2002. Within the first week of her study, she noticed marked improvement in her flare-up. Within 1 month, the flare-up was definitely over, and she discontinued taking anti-inflammatory drugs within 2 months.

From the first double-blind study, she continued on in the open label trial. University of Virginia medical staff called her a "poster child for Antegrem." The only side effect she had from this drug was a persistent headache the day of the infusion and this was relieved by drinking fluids

before during, and after the infusion.

She applied for and accepted another federal position in Colorado, with the intent to fly back to Virginia monthly at her own expense to continue study treatments. Fortunately, she was able to transfer to another test site in Denver. Life was good.

In the 27 months she received Tysabri infusions, she no longer took medications and did not have another flare-up. In fact, she says that she "forgot she had Crohn's" and anticipated being able to continue on the open label study up through the FDA approval of the drug.

In February 2005, she received the devastating news that the trial was discontinued, and underwent the recommended follow-up, including an MRI and neurological assessment. These follow-up measures revealed no indications of any problems.

Despite immediately beginning anti-inflammatory drugs at the end of the trial, Mom's Crohn's began to flare again 4 months after

her last Tysabri infusion. Since that time, she has tried everything else available without finding an alternative effective treatment.

These measures included Remicade at double the recommended dose, two series of treatments (both random and open label) under the Adacolumn aspheresis (blood filtering) trial, antibiotic treatment, and the recently approved Humira injections also at double the recommended dose. Despite these efforts, she has remained in almost constant active flare for two years. Two colonoscopies during the period confirm widespread active Crohn's disease throughout the length of her colon and rectum, beginning at her ileum.

Her only relief during these years has been on times when she has been on very high doses of corticosteroids (60 mg daily) for several weeks. This treatment level is not recommended for long term use because of the likelihood of its serious side effects and health impacts, so the steroid treatments have alternated with attempts at the other previously untried treatments mentioned.

Her prior Tysabri use has screened her out as ineligible to participate in other trials for medications, like CDP 870, which might work for her.

The outlook for my mom obtaining much relief from her Crohn's disease is currently not very good. To recap her options and results experienced:

Anti-inflammatories and antibiotics were not effective.

Immune modulators, not effective and not tolerated.

Currently approved biologics, infliximab, not effective, both with disclosed risk of fatal infection.

The Adacolumn asphersis trial, not effective, difficult, time consuming.

Other medications in trial, effectiveness unknown, prior Tysabri use likely to be an eliminating factor.

Corticosteroids, effective, with significant side effects impacting daily life and

strong potential for health impacts from long-term use.

Surgical removal of ileum, colon, rectum. Recommended for physician for consideration. Ongoing impact on daily life. High probability of recurrence of Crohn's disease at the surgical site.

Tysabri, very effective. Not currently available for Crohn's disease.

My mom and I that sharing her story gives the committee information about the importance of making Tysabri available for Crohn's patients. But mom is just the top of the iceberg. In the small Colorado clinic where she received the second part of her trial treatment, there are 3 other study patients with similar stories.

Multiply this type of impact by the number of other, and larger, trial facilities, not to mention other "hopeless" Crohn's patients who have not had the opportunity to try Tysabri yet.

Mom and I urge the committee to approve Tysabri for Crohn's patients in appropriate circumstances. Ensure that the risks are known, but

allow the patients who must live with this painful and humbling disease the chance for effective treatment.

Thank you.

DR. SACHAR: We are very proud of what you have done here this afternoon.

Speaker No. 7.

DR. GASPARI: Thank you. I appreciate the opportunity address the joint meeting and commend the committee members for the important work that they do.

My name is Mike Gaspari. I am a gastroenterologist in Charlotte, North Carolina. I am a member of a large single specialty GI practice there.

I have a personal interest in inflammatory bowel disease ever since I was a Fellow working at MCV in Chuck Elson's lab, and I have carried that interest into my practice. As regards disclosure, I do have a consultant's agreement with Elan as I do with Abbott and Centocor, and other pharmaceutical companies, but the primary role of

that consultant's agreement was attending a meeting in which the data concerning Tysabri was presented in depth. I also was a subinvestigator in several trials that one of my partners did with Elan in which he was the principal investigator. I was marginally involved in those trials and derived no financial benefit.

I am not here acting in the capacity of a consultant. My travel expenses, my time away from my practice today is self-funded, and I have neither approached Elan nor intend to regarding reimbursement, nor have they contacted me regarding attendance at this meeting.

My decision to be here is based on my personal commitment to the care of IBD patients, which includes my involvement, meager as it is, in the development of new therapies through clinical trials.

So, I have come to contribute my 2 cents to this discussion. I have no slides to present, and I believe my discussion will be much shorter than the allotted 10 minutes.

I will give you my bottom line at the top, and that is, that based on available data concerning efficacy and safety, natalizumab is a worthy candidate to add to the list of currently approved drugs for the treatment of Crohn's disease.

As a corollary, I do not believe that this is going to entail a radically different skill set that I an and other gastroenterologists currently possess and use in our practice.

One of those skills is recognizing that drugs associated with higher risk are used in situations where there is proportionately a higher benefit to be achieved or at least hoped for until the risk of PML associated with the use of natalizumab is better defined, the increased scrutiny that is offered by a program, such as the CD-TOUCH program that was described, I believe would be welcomed by both patients and health professionals alike.

As it concerns disclosure of risks to our patients and their understanding of those risks, I

have very little doubt that they when presented with a side effect of death, that we will get their attention and that they will understand what that risk is.

Much of the time that I spend with my ill IBD patients involves discussions of therapeutic options including the risks and benefits of those options. Some of those options have other life-threatening implications, such as surgery in the patient that has already undergone multiple operations.

I am very comfortable with those discussions. I believe my patients are comfortable with those discussions. The one discussion, though, that I dread is the one in which I have to explain to a patient that we have essentially exhausted all available therapeutic options or that they have to accept steroid, which they dread, in an attempt to get their disease under control one more time, hopefully, delay surgery, and that at that point we are just keeping our fingers crossed that something else will come along, another clinical trial, that

may offer some benefit in the maintenance of their disease as we taper their steroids and expect the inevitable flare.

My request to the committee is that in their difficult discussions about this issue, that they remember those difficult discussions that take place in exam rooms across the country in the care of patients with these devastating diseases and very few options when they have exhausted all available ones.

DR. SACHAR: Thank you, Dr. Gaspari.

Is there any other speaker from the public who has pre-registered for commentary at this meeting?

Is there any other speaker from the public who would like to take advantage of two minutes without pre-registration to address the committees?

That means speak now or forever hold your peace.

[No response.]

DR. SACHAR: In that case, the Open Public Hearing portion of this meeting has now

concluded and we will no longer take comments from the audience.

T he committee will not turn its attention to address the task at hand, the care consideration of the data before the committees, as well as the public comments that we have heard and appreciate.

The issue before our committees this afternoon or all day today would probably be not so contentious were it not for a particular concern about a particular level of risk.

For that reason, it seems to me appropriate to turn now the Chairman of the Drug Safety and Risk Management Advisory Committee to address some of his questions, to lead some of the discussion, as well as to compensate for my apparent functional right homonymous hemianopsia earlier today, and not having seen some of the people to my right.

So, Dr. Platt, what I would like to suggest is that for about the 15 minutes or so, until about 3 o'clock, that you take the gavel and I am going to suggest that we take our break at

that point and return about 3:15 for an unbroken continuous serious discussion, point by point, of the questions the FDA has placed for us.

Richard.

DR. PLATT: Thank you, Dr. Sachar.

I know that we covered a great deal of ground this morning and there were a number of points that weren't explored in the kind of detail that everyone would have liked. We don't have a lot of time now either, but let me suggest that we go around the whole table and identify questions that the group would like to address.

We may not have time to deal with all of them, but if we go around and put them all out, maybe we can quickly come to some consensus about the priority that we would attach to them and use the remaining sort of clarification time that way.

Does that seem like a reasonable approach?

Why don't we start on the right, and, Mark, if you have anything you want to propose for discussion, let's go.

DR. AVIGAN: I think this is really now

for the committee to discuss the benefit and now the risk questions, and so I will defer and only be here to answer questions accordingly.

DR. PLATT: Gerald?

DR. DAL PAN: Same here, I will defer.

DR. BEITZ: I think it would be helpful to hear a discussion about appropriate patients for this product if it were to be approved.

DR. SACHAR: That is good. That appears in several of the principal questions that the FDA has asked us to address.

DR. SMITH: I have several unanswered questions about infections, so I would love to be able to ask those.

DR. PLATT: Why don't you put the questions on the table.

DR. SMITH: Great. I guess I will direct them towards the company and then we can go from there.

There are a couple of questions I have and how I look at some of infection related questions, I have divided them up into two group. Those are

virus infections that are latent virus infections and the other group that are acute viral infections. Some of the patients that were presented it is not clear to me whether they were primary infections or reactivation disease, because I think you are talking about two different issues. So, that is the first question.

The second question, I would disagree that Burkholderia is an opportunistic infection, and not knowing the details of the case, I would like to know if there was underlying lung disease in that individual, had they had prior exposure, was this a hospital-associated infection, so I think that is important to know.

Then, the third thing I think we have to look at are the two cases of aspergillosis because aspergillosis, even in people who have long-term steroids, is an unusual disease, so I need to know whether that person was neutropenic, if they were neutropenic, for how long, if they were on steroids at higher doses of 50 mg, for how long a period of time they were, because that is an important

question, and then the patient that had pneumocystis pneumonia, again, it's an unusual disease in someone like a transplant patient, even though they are on many drugs to keep their hearts and their bone marrows and their kidneys going.

So, the question in my mind for that case in particular, is there known CD4-CD8 ratio that plays a role and is that helpful information.

Then, just a quick comment about what the experience in the HIV community is, and I think it is very analogous in this situation, because you are talking about a drug that is going to be used for one's lifetime. We have learned now for 25 years in the HIV population --

DR. PLATT: Dr. Smith, we are just trying to get questions on the table.

DR. SMITH: -- that the longer you look, the more these things come out, and you find out, so the issue of malignancy also comes up, because the latent viruses, hepatitis B, hepatitis C, these are going to be large impacts in this particular group for a long period of time, so I think those

are other questions.

DR. KRAMER: I had a question concerning CRP. It is my understanding, if I am not mistaken, that exogenous estrogen raises levels of CRP, and since this is a young population, I presume with a reasonably large number of female patients who might be on birth control pills, I wonder if that has been looked at, if you have any information on concomitant medications or on gender differences and responsiveness or in the elevated CRP.

Also, how that would impact that as a criterion for treatment in the future if there are things that elevate CRP artificially.

DR. PASRICHA: I have several questions, too, about both the efficacy and the risk. The risk with regard to PML, I think needs to be discussed in greater detail. It seems to be a comfort level that there is a 1 in 1,000 risk that is based on 1.8 months in average duration. I really think that needs greater discussion. I look forward to that.

I also raised the question of lumping

patients with MS and CD together as far as the cancer risk is concerned. I think that is not appropriate and we need to discuss that, and the risks are separate, because the populations are separate.

That is something that hasn't really been emphasized as much.

As far as the efficacy is concerned, I would like to go into greater detail about the differences between--I would like to discuss some of the definitions that the sponsors have used in terms of maintenance of response versus maintenance of remission. I think they are two very different things, and we really need to clarify that for some of the items here.

Finally, I would like to see if we can have a comparison from the data or we can infer a comparison from the data with regard to natalizumab versus infliximab, because that is becoming one of the indications that we are going to discuss is patients who are either resistant to or intolerant to, and I don't think there is enough detail yet on

that for us to be comfortable.

DR. SACHAR: I would like to point out that we will be dealing with all of those questions with Questions 4a, Questions 1a and b, and Question 2b(1), so I am hopeful that there will be adequate time to discuss every one of those points you raised, all of which are important .

MR. LEVIN: Two points of clarification that would be helpful to me. One is we heard very eloquently in the public session from clinicians treating the disease, how much this would mean to patients with Crohn's, and I would appreciate hearing similar opinions, which may differ in degree, but from the panelists who are clinicians treating the disease, how they translate what appears to be a moderate benefit on paper to the reality of what patients experience and what practitioners experience in treating this disease. It would be very helpful to those of us who don't treat patients with Crohn's.

The second thing is I would be grateful for some clarification on whether early recognition

of the symptoms of PML is a reality. I mean it is sort of like, you know, is this something that really will occur and will it occur early enough to make a difference in outcome.

I think that is part of the consideration in risk-benefit. It is also part of the consideration about how you inform patients about what the risk really is. So, you can be promising that we are going to very vigilant, we are going to spot this early and we are going to be able to take care of it for you, or if that is not the reality, I think you need to convey what the reality is honestly and openly to patients

DR. CHANG: This is an efficacy issue and also safety issue. It is about the concomitant immunosuppressants because if it is going to be indicated in patients whether or not on these drugs, I still wasn't clear on the data between the 303 and the 307 if patients off immunosuppressants actually do well on Tysabri, because in the 301 it didn't look like that even know in the maintenance, it looked okay and then in the 307.

So, I wasn't clear about that issue, and a little bit about the CRP, but I don't think that is a big issue.

My other issue, I do think it looks efficacious in certain patients. The problem that I have is just imagining clinical practice, and is in the risk-management program, because I think that there are good guidelines for the first three months. But I didn't actually know what it meant by other objective markers of inflammation. I didn't know what that was referring to exactly, and I am just wondering it if would be better to discuss details on the guidelines, particularly the maintenance, because I could just see what will happen, at 60 percent or 50 percent over a year is having a response, but the rest of them aren't, what guidelines are they going to follow, how long are you going to allow someone to be on steroids or restarting an immunosuppressive agent, and what is really the criteria for lack of response, are clinicians going to use different criteria and guidelines?

I just would be afraid that down the line the next thing we know people have added other agents and then there are multiple agents and increased risk.

The last thing about the risk is I think obviously we talk about PML. But the other issue with Crohn's that is different than MS is that those patients are on other immunosuppressors or steroids more so than MS, and they seem to have higher risk of infection, and not just talking about PML, and if there are going to be risk-management strategies to monitor for other infections.

DR. SACHAR: That's very good. We should definitely take those questions into consideration, Dr. Chang, as we approach Questions No. 3, 6, and 7 from the FDA.

DR. DAY: I am concerned that many of these meetings which are with one committee and the Drug Safety and Risk Management Advisory Committee wind up rushing at the end to do something about the risk management part of it, and I would like to

have adequate time to discuss the risk mesalamine action plan submitted. It is well organized and every comprehensive, but has some unknowns and some difficulties. I will mention just a couple and we can decide what to talk about.

It looks like the entire thing is currently paper based, but there are some indication in the background material there will be on Tysabri.com, some patient-friendly thing. I have gone there, it is not there now. It is much more descriptive and it looks like for providers.

I would like to discuss possibility of medical errors that can happen. For example, the logo for Tysabri could get into difficulty. It is all in sans-serif, so it is spelled correctly and the T is capitalized at the beginning and the i at the end. The i at the end in the logo looks like an l, so it looks like it could be pronounced Tysabrl, and if you Google that, you will get Tysabrl all over the world.

You will get it in Chinese or Korean and so on. So, there is a possibility for someone in a

central pharmacy to pick up something or misunderstand, and so on, so there are other places where there are possibilities for medical errors, so this would be catching these in advance in the risk-management general plan.

Finally, I would urge that we discuss increasing the amount of attention devoted to opportunistic infections in general in the TOUCH program, and not just the emphasis on PML. PML, there have been 3 people that we know of and all the other opportunistic infections, quite a big more, and there is not much of an educational component in that for the patients and/or others.

DR. SACHAR: We will have to guarantee you then that not only Question 4a, but that Question 7 gets ample time.

DR. KOSKI: I will echo some of the previous investigators or at least participants in this committee without hopefully going too far in but, as a non-gastroenterologist, I really would like to have a clear idea how this drug will actually be used in a different set of people than

who have already spoken with us.

I would like to also know that if this does go forward, what are the criteria for these people being selected.

I know we have heard a lot of general things, but there is really no sort of hard and fast rule, you know, that we have heard. It sounds like to some extent it is going to be--well, I think this patient is doing a little worse today, or it failed one therapy should I try two or three others, or should I go to this other one that is newer.

The other thing is, is that again I think we also need to specifically discuss, and I know that this is identified later in some of the questions, but we need to have I think a better neurologic evaluation of these patients before they to go into the program, basically a baseline level.

Then, in addition, if it's at all possible, I really think that we need to know what some of the training issues are going to be for these various centers that are actually going to be

administering the program.

DR. GARDNER: I am having difficulty getting a good handle on the differences and similarities between the MS patients and Crohn's patients from the standpoint of what the practice is, and then thinking about implementing a risk-management plan, the realities of practice and patient selection are extremely important in knowing whether it is going to work, and I can't figure out how much we can extrapolate from the MS TOUCH program to move directly interrogator the CD program, because of the way the patients are and the patient is treated.

DR. PLATT: I, too, am not clear about the intended target population for the CD-TOUCH program, and I am specifically sort of struck by the fact that the proposed indication that you noted for us is quite a bit more liberal than what I thought I heard the sponsor proposing as its intended use.

It was a surprise to me and I would appreciate some reconciliation, and I join several

of my colleagues in saying it would be very good to see in writing the best articulated set of guidelines that will be used to govern entry into this CD TOUCH program.

DR. SACHAR: I have already spoken a lot and will be speaking a lot more, so we can go on.

DR. HENNESSY: I will pass.

DR. LEVINE: I will pass, so we can get on with the business.

DR. DAVIS: Well, I want to hear from you guys because I am having trouble weighing the p-values versus these people's lives and the benefits.

The other thing about the risk management is t he devil is in the details, and so what is the communication with the patient, is the patient clear about what they need and when they need to communicate it to the physician about any symptoms they are having about infection, and then what is the communication between the infusion center and the physician.

DR. KRIST: I agree with a lot that has

been said, so I will be very quick. One of the things I want to kind of clarify some is I want to talk more specifically about going from very objective criteria about defining populations to now a subjective criteria, and what is the implication on efficacy as it gets extended outside of a research setting and what is the implication as far as risk, as well.

MS. EICHNER: I will pass.

DR. NELSON: One of the concerns I have about much of medications that get approved in this country is about post-marketing surveillance. I know this program is meant to improve post-marketing surveillance, but one of concerns is it is not totally clear to me is who actually is going to be analyzing the data when it comes in, who is going to be looking over the sheets that get sent in and is there going to be enough insight into whether a signal is real or needs to be further investigated.

Along those lines I mean I think that relying on people to send in data, this is kind of

a quasi-passive, quasi-active data collection, and it's not totally clear that all data, all adverse effect data will be reported. Maybe they will just looking for the big ticket item like PML, and that is going to be rare.

Using death reports as a data collection tool is rather poor, or death certificates. You know, death certificates are often filled out by the clinician, and not by the pathologist, and without a pathological diagnosis, many of these people may not actually, that have PML, may not actually be picked up.

So, I don't know, you can't really mandate an autopsy on people, but somehow using death-certificate data might be a little bit limited.

DR. COUCH: Very quickly, the incidence of PML appears to be 3 per 1,000 over a 3-year period. How does that come out over a 20-year or a 30-year period, is this an ongoing cumulative risk ?

Secondly, I haven't heard anything about the inservice training that the infusion centers

are going to have with regard to neurological complications, that is, if they are not already in the MS business, so I think I would like to hear more about what kind of training they are going to have.

DR. LESAR: I just have a couple of questions about the TOUCH program. One is--and I think it mirrors some other comments--is its efficacy of the screening tool that showed 8 percent signal of which a very small percent were actually changed, and you are also looking at the number of reauthorizations, about 3.5 percent were not reauthorized, and whether those signals, the signals seen on the screen matched the non-reauthorization and what were those signals that were changed or were not changed.

I also have a question related to the initial requests for authorizations for initial, how any of those were approved and how many were not.

DR. NEATON: My question is about the risk assessment plan, the 4,000-patient cohort study. I

think the sponsors establish the efficacy in the short term in this population. But a number of risks, which were significant, not only PML, but serious infections, malignancies, hypersensitivity reactions need to be more reliably ascertained, and I think you need a control group there. I would like to hear more about that.

DR. VEGA: I don't have any other general questions.

DR. PLATT: Dr. Sachar, it seems to me we have done a good job of getting the questions on the table, and so my question to you is whether you think it will be possible to weave in sort of the answers to those questions as part of the discussion we are going to have or whether we need to take a little more time to focus on any of these that we won't be able to address as part of these questions.

DR. SACHAR: Yes and Yes, where they fit very well into the framework and context of the written questions, they will weave right in, and when there is something additional that has to be

addressed, that doesn't fall under the rubric here, I count on my notes and your notes to make sure they get addressed.

DR. PLATT: I am taking it that you don't want to actually talk about the answers to those questions right now, but we will bring them in later.

DR. SACHAR: That's correct. What I would like to do now take a break. I would like to reconvene at 3:15 when we will address all questions as written, modified, and supplemented.

[Break.]

DR. SACHAR: Now, the fun begins--not that we haven't been having fun so far, but we are going to have a lot more now.

The sponsor has asked for a 10-minute opportunity to try to address in a fast and efficient way, some of the specific factual questions that have come up in terms of trying to clarify some of the points of concern that the panel raised in the course of the last session, and at the same time, Dr. Platt and I would like to

ask, in that same window of opportunity, to try to state for us, carefully drawn, word for word, in a method that we can write down your view, your view of precisely which population you believe that this drug is properly indicated for and what circumstances should govern its continued use and mandate or at least suggest its discontinuation.

I think we have the answers to those questions in compartments and bits and pieces, and we recognize that it is our job as advisory committees to the FDA to determine our recommendation of how it should be stated, but we think it would be very helpful in our deliberations to be very clear in our own minds what your proposal is exactly.

With that, why don't you start in and then at 3:30, we will take the initiative back.

DR. FRANCIS: In terms of the indication statement, the compilation that was studied in the development program or those who failed conventional therapy, defined as steroids and immunosuppressant therapy, and that is the group in

which we have shown efficacy both in terms of inducing a response and remission and maintaining response and remission, and that is why the indication statement was worded the way it was.

However, because of the safety issue and because of the consultations that we have had with the gastroenterology community, we understand that the initial use of this product will be virtually restricted to those who have also failed TNF-alpha inhibitor therapies.

We understand that and recognize it, and also are comfortable with the fact that approximately 40 percent of the patients evaluated in the studies were failures of TNF-alpha and also attained the same level of remission and response. So, that is the initial patient population that we are talking about.

I think in terms of how the specific wording for that will be, I think we have to hear from the panel, as well as discussions with the FDA.

One of the things that has come up that

appears to have caused some confusion is what is our position on monotherapy. The monotherapy in the MS was a much easier issue to address. We have the position of the companies we do not want this drug used in combination with chronic corticosteroids or with immunosuppressant therapy.

The reason that monotherapy is not in the label is because patients can also be on 5-ASAs and antibiotics, so when we are talking about the issue related to immunosuppressants and steroids, we are very clear on that, we don't want that to happen, however, of course, we recognize the medical necessity of not being to stop steroids in patients abruptly and that is why there is that initial taper period during the first six months, to allow them to respond and then to be able to get them off medication over the subsequent weeks after a response has been achieved.

So, these are things that we feel that should be implemented into the label.

I think that one of the other issues that you have raised there is reasons for stopping, and

the first reason for stopping would be obviously if the patient did not achieve the response that we expect to see by three months.

As Dr. Sandborn has said, it is very clear within the time frame of three infusions and the follow-up from that third infusion, whether patients will respond or not, and I think as you have seen from the data from Dr. Jones, you are seeing responses as early as four weeks although patients do continue to get response up to about 12 weeks, and that is why that interval has been selected.

DR. SACHAR: Would you care to give us your perspective or your proposal as to the sequence and separation from anti-TNF therapies and immunomodulators, antimetabolites in terms of a washout period or a maximum period of allowed overlap? Again, we are only asking for your proposal, so that we can understand where we are starting from.

DR. FRANCIS: Right. I think as we had discussed earlier, the short term safety risk

appears to be relatively low for concomitant use of these therapies, but we are not recommending that.

We would recommend that immunosuppressive therapies be discontinued at the time before or at the time at the latest of starting natalizumab therapy, so that there is not overlap of the immunosuppressive therapies apart from possibly that functional overlap that will go on for a period of days to weeks once those drugs have been discontinued.

In terms of the corticosteroids, as I mentioned, patients can't stop steroids abruptly in the same manner that one can stop the immunosuppressive therapies. But what we have seen mentioned that a response can occur within four weeks of initiation of therapy and that our education program in the TOUCH program with gastroenterologists will recommend that as soon as patients achieve a response, that steroid tapering be begun immediately, so that it could happen as early as four weeks.

In addition, in the CD303 study, it was

demonstrated that about a third of patients could come off their steroids within two weeks and 70 percent within eight weeks. So, it is conceivable that patients could be off their steroids as early as six weeks after initiation of natalizumab therapy and the six months is giving them three months to respond and three months maximum to get off the steroids.

So, that is an outer limit one would anticipate and hope and believe that the physicians also will attempt to get their patients off of steroids as quickly as possible.

DR. SACHAR: And your concept of an approved scenario in the event of a single relapse or acute clinical flare during maintenance therapy would be what?

DR. FRANCIS: That the patients who have a single flare would be appropriate for consideration of a short course of corticosteroids, which is generally, in talking with the IBDologists, somewhere in the range of one to three months of steroid therapy depending on the severity and the

responsiveness of that flare.

DR. SACHAR: And in the view of the company, would that be a sufficient manifestation of failure of maintenance therapy to recommend discontinuation at that point, or from the vantage point of the company do you want to propose that a patient be allowed one strike and one pulse of steroid before abandoning maintenance therapy?

DR. FRANCIS: I think there is no definitive data on that.

DR. SACHAR: I know.

DR. FRANCIS: I think certainly we would like the patient to have one strike. The consideration of whether two strikes in a year would be also acceptable in which your patient could be on steroids for, say, two to four months out of a year, I think anything beyond that, I think most clinicians would deem that as a patient who was no longer responding to the therapy and should discontinue the therapy.

In terms of management of the acute flares also we would not want to see immunosuppressants

added to that. We would consider that a treatment failure if they required immunosuppressant therapy, natalizumab should be discontinued in that setting.

DR. SACHAR: Well, then, to a large extent, our exchange in the last few minutes has clarified for me the company's position and that will have to be integrated with the panel's recommendations, the FDA's decisions, and if there is approval for marketing, the individual physician's response to the challenge as presented by the individual case.

Dr. Platt, does that answer the fundamental scenario that you wanted the company to lay out?

DR. PLATT: That is clear for me personally. Could I just ask others on the committee?

DR. SACHAR: Right. I am sure it doesn't answer every last question, but let's see if it sets it.

Bob.

DR. LEVINE: Just one element that you

mentioned that I am not sure what the answer is, and I would like to know the incidence. Three of the experts on the most recent AJA consensus trial on biologic use in inflammatory bowel disease, in the July issue of the AJA, and that is Dr. Sands and Dr. Hanauer, out of 15 of them, they agreed that indications for natalizumab would be in CD proposed restrictive labeling, and in that labeling they mentioned just what you said except they did not mention patients who were unable to take infliximab or TNF antagonist therapy, anti-TNF therapy.

You are mentioning that. That is a big difference. Now, I would like to know what the incidence is of that group in our trials or otherwise or if Dr. Sandborn can tell us perhaps the incidence, how many people are in that group?

DR. FRANCIS: The proportion that are TNF-intolerant to the TNF--

DR. LEVINE: You mentioned--no; if there is going to be restrictive labeling to that point, as you pointed out, you also mentioned a second

group who could not take the treatment, who could not go on to your treatment.

DR. SACHAR: Who could not take it, who were intolerant.

DR. LEVINE: Who would be intolerant to it. What percent is that group?

DR. SANDBORN: You mean contraindications.

DR. SACHAR: Right.

DR. LEVINE: A group that can't be put on infliximab for a variety of reasons. What percent did that group get? You keep mentioned that and that was not mentioned in the consensus group.

DR. SANDBORN: I think it is a very small group and you can decide if it is worth allowing the leeway.

DR. LEVINE: It would include patients with concomitant Crohn's disease and multiple sclerosis, patients who have received infliximab and developed demyelating disease, and patients with cardiac disease where you would have a contraindication for infliximab. I can't think of anything else.

DR. SACHAR: I think that is what you meant. It is a small group.

DR. HENNESSY: So, it would not be restricted to C-reactive protein positive individuals, and if not, why?

DR. FRANCIS: Oh, sorry, yes. We still feel that the C-reactive protein issue is on the table, because we feel from a safety perspective again that it is getting more likely that the patients who will be treated with elevated CRP are more likely to respond and those who don't have the elevated CRP may be taking a risk that is not warranted.

DR. SACHAR: That was one of the questions that came up in the discussion of evidence of inflammation, of active inflammation as manifested by increased CRP or other biomarkers. Somebody asked, well, what else would count, and I think we can get into that because it comes right up in the very first set of questions.

Do you have another five minutes?

DR. FRANCIS: Yes, we have other updates

that we will try to address the series of questions that came up. Some of them can be dealt with reasonably quickly and then others are going to be longer discussion points I think.

So, we will first turn to the issue about infections. The question was raised about virus and latent viruses, what was the status within the clinical trials, the latent viruses we have been looking at. As I mentioned earlier, the herpes simplex or the herpes family, CMV, EBV, and as I demonstrated in the placebo-controlled study, there was no difference between the two groups except for about a half a percent. It was higher in the natalizumab group than the placebo group, most of that driven by herpes simplex.

Presumably, with herpes, all of it is reactivation although we can't say that for certain. There were very rare occurrences of CMV infection and EBV was also very infrequently reported. So, most of the viral infections that we were seeing were acute.

Of course, the JC virus itself is deemed

as a latent virus, so that would also be a reactivation state.

DR. SACHAR: Were there one or two cases of HSV encephalitis? I thought I saw two in one of the tables, but maybe I misread esophagitis or something, because I am only hearing about one of them.

DR. FRANCIS: That is correct. There has only been only been one case of herpes encephalitis, one of esophagitis, one meningitis, and I am blanking. What was the fourth? Oh, the dermatomal zoster, yes, sorry.

So, in terms of the Burkholderia cepacia as an opportunistic infection, I think as I tried to allude, the definitions of opportunistic versus atypical gets a bit gray. That is why we included both of those tables to make sure that people understand there is 11 of these events that include Burkholderia.

[Slide.]

That particular patient, in fact, did have hypertension and history of tobacco use and also a

diabetic and had received the three infusions of natalizumab at the time that she developed a cough and was found to have congestive heart failure as well, so whether or not these are confounding factors related to the Burkholderia.

[Slide.]

The other issue was the aspergillosis patient. There was only a single case of aspergillosis, you had mentioned two. This particular patient was not neutropenic. So this was a 75-year-old patient with Crohn's disease, and he had received 10 infusions of natalizumab, had also had NSAID use, but more specifically high-dose steroids that were still in a taper regimen, so had been up as high as 50 but was tapering down to 5.

The patient developed duodenal ulcer, severe GI hemorrhage and peritonitis following the final dose of natalizumab and spent some time in the hospital including ICU and ultimately sputum culture revealed Aspergillus. The patient died several months later following multi-organ failure.

[Slide.]

The other case that you had asked us about was the pneumocystis carinii case, and this as a 69-year-old patient who had received 34 infusions of natalizumab, so one of the longer dosing patients in the Crohn's program.

Had a history of cirrhosis with portal hypertension, splenomegaly and ascites, had had episodes of hepatic encephalopathy one month after last dose, and then recurred one month later with associated acute renal failure and anemia, again was hospitalized, treated in intensive care unit, intubated and transfused, and a sputum culture grew PCP. Again, the patient developed multi-organ failure and subsequently died.

I think you had also indicated that there was not enough attention to the opportunistic infection issue in the RiskMAP, and certainly that is part of the RiskMAP is collecting all opportunistic infections and monitoring for those and pursuing them aggressively whether it be PML or other types of opportunistic infections.

I think you had also mentioned that there

was an issue about paying more attention to the malignancy issue and certainly I think I tried to elaborate on the issue that was different in CD than in the MS patient population.

Within the briefing book are all the cases of malignancy that have occurred in the Crohn's program, and also indicating in the presentation that we feel that this is a potential signal and still needs to be followed actively in the risk management program and in the post-marketing surveillance situation.

So turning to the issue of CRP, elevated CRP with with estrogen, certainly there are things that can raise CRP and I suppose to your point, yes, there could be patients who have an elevated CRP with symptoms of active Crohn's disease who maybe otherwise wouldn't have elevated CRP, and I guess I can't promise that that won't happen. I think we are more specifically trying to say if they don't have that elevation, then, we feel less likely that they are going to benefit, but we may still include patients who have other reasons to

have elevated CRP.

You had asked about other markers of inflammation, actually, I think the chairman said we could discuss this later. Elevated sed rate could be another thing to be looked at. It wasn't looked at in the clinical trials, so we can't comment on that.

Dr. Sandborn had alluded to an endoscopic lesion activity as being another manifestation of active inflammation, and there is data from our clinical trials. In a small number of patients it does show, in fact, endoscopic activity does respond to natalizumab therapy, as well.

I will turn now to the PML issue, the risk of PML was said to be--it's the broad statement--1 in 1,000 patients. That is based on three cases in approximately 3,900 cases of patients exposed to the drug. There is a fairly broad confidence interval around that. That ranges from 0.2 to 2.8 per 1,000 or, flipped the other way, 1 in 350 to 1 in 5,000 patients, so still a fairly broad estimate of the risk of PML, which is what the TOUCH program

is designed to do, a better estimate of what the risk for PML will be, because all patients who take the drug will have to have a registration and will be followed for that, and all cases will presumably be detected, such that we will begin to get a better estimate of what the true risk of PML is in this population?

The issue also, is there a cumulative risk? We don't know what that is. We don't know if PML will occur, is it a random event in any patient who gets exposed to any amount of drug, or does the risk increase cumulatively over time with the increasing numbers of infusions. I think the numbers of cases so far are too few to comment on that.

One other aspect was about the importance of early recognition of PML and outcome. We had heard earlier that it didn't matter and I think in this setting where there is no therapy, maybe that could be said, but I think we have to think somewhat more optimistically.

We also heard that there have been

anecdotal reports including a recent report of treatment benefit in a patient who received a 5HT2A receptor antagonist therapy and improved from their clinical PML.

The other thing that we think is actually quite important is the issue of IRIS, immune reconstitution inflammatory syndrome, and although that can be bad because it is inflammatory within the central nervous system, it is bringing the viral infection under control.

We also have implemented a study of plasma exchange in patients receiving natalizumab, because one of the issue with natalizumab, one of the beneficial aspects is a long half-life, but when you have a complication with a long half-life product, then, the product is onboard for upwards of 8 to 12 weeks, and therefore, there is continued exposure to the product.

With plasma exchange one is able to reduce the level of natalizumab in the blood quite rapidly, so that a 12-week exposure may be reduced down to a 4- to 5-day exposure, allowing the immune

system to reconstitute, if you will, and allow cells potentially to retraffic into the central nervous system, so that early identification and early implementation of something such as plasma exchange and fiber HT2A receptor antagonist therapy may, in fact, prove an effective therapy in the future. But this is clearly conjectural at the moment and studies are ongoing now to test these hypotheses.

So, I think it still does make sense to try to early detect specifically the first thing, of course, as we said before, is stopping additional doses of therapy, so the earlier one detects that, then, the fewer doses that the patient will be exposed to subsequently.

One of my pet peeves is the issue about neurologic examinations at baseline and maybe one neurologist will have to go against another on this one.

I don't know that that is going to be very valuable any more than necessarily baseline MRIs are going to be valuable. The issue is that when

the patient has a new neurologic symptom, that the dose is held and they have a full neurologic assessment at that time including MRI evaluation particularly in the Crohn setting.

Crohn's patients are neurologically normal for the most part. Any new neurologic symptoms are coming on a clean background, and those should immediately prompt dose cessation and a full evaluation to ensure that this is not a case of PML developing.

I am not sure that a neurologic examination done two years earlier, or one year earlier, or three years earlier, will provide, possibly by a different neurologist--will provide any comfort at that time when new events onset in terms of being able to determine or having the comfort to say, well, I am not going to worry about the symptoms because I found something two years ago.

So, I think that that is actually not going to be very helpful and the same comment related to baseline MRI.

I think I have run out of gas. So, I am going to turn it over to Dr. Jones, who is going to deal with some of the efficacy issues that were also raised.

DR. SACHAR: Are there questions from the panel that you feel you need to hear something further from Dr. Jones about, or even better, Dr. Jones, before you make a presentation, because our time is short, would you just tell us what is the question that you heard that you feel you need to respond to?

DR. JONES: Well, I am actually very lucky. My response is actually going to be very brief, because it has to do with subgroups regarding gender.

The consistent findings that we saw in both the maintenance study and CD307 lends itself to a very quick answer. We didn't know if we would see any difference between males and females. We saw a positive response in both.

The second question that was asked about the subgroups was immunosuppressants. Again, in

the main presentation I presented a population who were not taking immunosuppressants. We saw significant benefit with response at Month 6 and Month 12 for that patient population.

I think the question was regarding for the induction and where we saw a little bit better benefit for those patients who were taking immunosuppressants in 301.

When we looked at the data for 307, we found the reverse. In fact, those patients who weren't taking immunosuppressants did slightly better, so the patients not on immunosuppressants had a 50 percent response rate on natalizumab versus 32 percent on placebo. The ITT was 48 versus 32, so we actually saw a slightly better response rate.

DR. SACHAR: So, the bottom line is that neither gender nor prior experience or response to immunomodulators seems to have any bearing on prediction of response to Tysabri.

I think that will take care of us. Yes, sir?

DR. AVIGAN: I just wanted to follow up on Dr. Nelson's question about pharmacovigilance to the sponsor. The question was on the atypical infections and malignancies which were not covered by TOUCH but rather by TYGRIS, and the idea that there is an ongoing observational study, and what we know so far is that although you have had X thousand, I think the total number is 8,000 U.S. patients enrolled in TOUCH, only 33 patients so far, or 35 patients, have been actually recruited to TYGRIS.

I wanted to hear from the sponsor what their plans were about that as of the end of May.

DR. FRANCIS: So, the question is why is the number in TYGRIS relatively low?

DR. AVIGAN: Why is the number of recruitment so low?

DR. FRANCIS: Well, actually, it was deliberate in some ways, in that we felt that it was most important to get the TOUCH program up and running efficiently, get the centers trained, get the physicians trained, get the program established

before initiating the TYGRIS component of the protocol, which didn't get started until this year.

So, that is the straight answer. We focused on that for the first 6 to 8 months as the more critical element.

DR. SACHAR: At this point we have about 100 minutes in which to accomplish the goal of making a recommendation to the FDA, and the sum and substance of that recommendation will appear in essence as our joint response, which will be formally voted on to Question No. 8, but it will be helpful in getting to Question No. 8 to go through Questions 1 through 7, and before we do that I thought it might be helpful at the outset to focus and initiate the discussion with a 5-minute overview on my part of what it is that lies before us that we have to do and what we have to grasp with.

Although the discussion has been rather complex and there are a lot of complex issues here, at the bottom line it is really a very simple thing we are being asked to do. We are asked to weigh

the balance of efficacy and safety, benefit and risk.

On the efficacy side, as I see it, there are essentially four questions to be grappled with in terms of induction of acute remission.

How great is the need for this drug? What proportion of people who might need it can be expected to benefit from it? What factors help identify the subset of patients most likely to benefit from it, and to echo Dr. Levin's question, is the benefit clinical significant in terms of disease control and quality of life as opposed to statistically significant by only numerical criteria?

I will launch a discussion by just giving a quick overview of my thoughts about each of those and then we will go on from there.

In terms of how great is the need for this drug, I think we have heard that only about 30 percent of Crohn's disease patients have what we would, as practicing gastroenterologists, and what they, as the patients, would consider a

satisfactory result from current medications so that that would suggest that there is a need for a further drug.

And the people that we think might need it are those who are refractory to everything else or who are responsive only to steroids and cyclosporin, let's say;; in other words, responsive only to drugs that cannot be maintained at high doses over a long period.

What proportion of those people who might need it can be expected to benefit from it? Well, we will all have to take our own perspective on the data, but in terms of absolute proportions, it looks like about 50, 60 percent absolutely with a therapeutic delta of about 10 to 12 percent, and we will have to decide if that is a real benefit.

What features help identify the subset of patients most likely to benefit it? Well, I think we can say that they should have some manifestation of active ongoing inflammation, and we will come to terms with whether that has to be an increased CRP or other clinical or laboratory markers of which

there are a myriad, and we can discuss that when we get right down to the individual questions.

Then, is the benefit clinically significant in terms of disease control and quality of life, or is it just the p-value? Frankly, I think we have heard from patients and from practicing doctors and we have seen quantitative quality-of-life data, and we have seen objective risk-acceptance data in terms of time, tradeoff and other materials from Dr. Sands, that I think would suggest that the benefits that we are talking about transcend simple p values.

So, those are four questions needs to be re-asked and re-answered, not only for acute induction of remission, but for maintenance of remission, and those are separate questions and as we address the list of questions given to us by the FDA, we will specifically focus on individual answers for maintenance.

Then, that's efficacy, and what is safety? What is risk? Well, again, I sort of see four questions there. What proportion of people treated

with this drug will suffer from it more than they benefit? What proportion will get a cancer or a PML or an infection or something bad, and how much more is that than you would expect in a control population, what is the NNH, what is the number needed to harm?

How can we reduce that proportion to a minimum? What level of risk will patients accept and what level of risk will we accept on their behalf? We look forward very much to what the drug-safety and risk-assessment people have to tell us about that since that is their specialty.

With that as a framework or beginning, unless somebody would like to interject something at this point, I propose that we turn to the specific list of questions to the advisory Committee and see if we can come to some satisfactory consensus on the basis of everything we have heard and on the basis of everything that we have to contribute as panel members.

DR. CHANG: Could I just make a comment, because I don't think it is one of the questions?

DR. SACHAR: Yes.

DR. CHANG: On the comment about is this really meaningful, at least in the --

DR. SACHAR: Is this really what?

DR. CHANG: Clinically meaningful, the changes as opposed to p values.

In the data that was provided, if you look at the IBDQ data, which was the disease-specific quality of life, they actually showed changes that have been shown to be clinically meaningful. So, if you are going to at least look at quality of life, that reflects daily functioning and daily activities, the change that they did demonstrate with the drug were clinically meaningful.

DR. SACHAR: I, as an individual am agreeing with you on that point and that is why I added that question to my menu.

Questions to the Committee

DR. SACHAR: The first question says that the proposed indication states that Tysabri is indicated for inducing and maintaining--two separate things--sustained response and remission,

and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation as evidenced by elevated CRP level or another objective marker.

Do the available data support the efficacy of Tysabri in patients with moderately to severely active Crohn's disease with inflammation as evidenced by elevated CRP level or another objective marker?

Let's raise that question first for the induction of sustained response and remission. We have p-values that are statistically significant from two clinical trials showing a therapeutic delta in the range of 10 to 12 percent.

Does that mean that the available data support the efficacy of Tysabri in those patients and, when we add CRP, we widen that to--what was the number, does somebody want to give us? 18, 20, something like that? Okay.

Without dwelling on the decimal points at this point, let's just ask, after a little discussion, yes or no, is the committee satisfied

that the data support the efficacy of Tysabri for the induction of, we will say, response and remission, and by "sustained," we are not talking about maintenance; we are talking about 12 to 16 weeks

Sean.

DR. HENNESSY: I think I might modify the statement by taking out "or another objective marker" since the trial didn't admit patients by another objective marker, it was just CRP, and then given safety concerns, I think I would add, who have failed, are intolerant to, or have a contraindication to a TNF inhibitor.

DR. SACHAR: Absolutely, and that is going to--that second part comes out in Question 2. But in terms of CRP, I, for one, would be reluctant to restrict the use of the drug only to patients whose evidence of active inflammation was an elevated CRP because of the fact that there are so many other clinical markers available for active inflammation including endoscopic, imaging, MRI, radio nuclide techniques, ultrasound, measurements of thickness,

fecal markers, alpha-1 antitrypsin, lactoferrin, calprotectin, extra intestinal manifestations, fever, erythema nodosa, pyoderma, peripheral arthritis.

It seems to me that the point of the CRP is not to say that this drug won't work unless it somehow binds to CRP. It is trying to say we want to be sure we are not giving it to people with an irritable bowel or somebody who doesn't need it.

Let me come back to you for a moment after we get Alexander Krist.

DR. KRIST: What is going to be the incidence of not having an elevated CRP in those populations? This is the ultrasensitive CRP, and it was the upper limits of normal. I mean it was a very small level.

I kind of agree with Sean just thinking about evidence. I mean the evidence we have is just on CRP. I do have concerns about introducing other subjective things. I mean a CT scan is subjective and endoscopic examination is subjective. I would think if it's clear-cut, there

would be an elevated CRP.

DR. SACHAR: Let me return to Sean on that, and then ask some of the other experienced gastroenterologists and IBDologists to comment on the sensitivity of the CRP for active inflammation.

Sean, you wanted to follow up.

DR. HENNESSY: Sure. Thanks. The context of the positive study was an almost positive, but not quite positive study where they took all covers, and it was only when they included only CRP-positive people that they were able to achieve a conventional level of statistical significance.

DR. SACHAR: Although even without them it was 0.051. Would any of the other gastroenterologists on the panel or off the panel give us the benefit of your thoughts about whether CRP should be the only required touchstone for admitting a patient to Tysabri eligibility?

I saw a hand. Dr. Pasricha.

DR. PASRICHA: I have two comments, one about the CRP. If you are going to put CRP in as part of the labeling indication, what happens to a

patient who is felt to be clinically active, but has a borderline CRP? What will the physician do with that patient? This is a patient who otherwise failed all forms of therapy. Are we blocking that patient from getting this drug?

DR. SACHAR: That was my point and the question that I raised, and the counterpoint was raised, but that is a fictional scenario, it doesn't really happen, and the question is does it or doesn't it.

Bob, you would know, and, Bill, you would have something to say?

DR. LEVINE: I was just going to say I don't think we should stick with the CRP completely, but it was a good reasonable guess estimate. A recent paper in 2006, on the diagnostic value of C-reactive protein for predicting activity of Crohn's disease, their conclusion was, and they used a 21.6 cutoff, CRP appears to be useful to evaluate CD activity especially to predict inactive or low activity of Crohn's disease, so that doesn't really help us too

much.

DR. SACHAR: That is sort of a negative predictive value.

DR. LEVIN: I am with you. I think we have enough clinical judgment in other manifestations.

DR. SACHAR: As I have said, I would be reluctant to take a patient with a high fecal calprotectin and fever and arthritis and a tender abdomen, whose CRP was not elevated, and deny them the use of the drug, but, Bill, would you want to comment?

DR. SANDBORN: We actually recently published subjective data on this from our center. So it turns out if you have symptoms and colonoscopy evidence of inflammation, which is not very subjective, a little bit, but not very much, over 90 percent of those patients, nearly 95 percent will have an elevated CRP.

On the other hand, if you say--I am saying that wrong--if you take patients with an elevated CRP and symptoms, over 90 percent of those patients

will have an abnormal colonoscopy.

Conversely, if you do a colonoscopy in a patient with symptoms, only about half of the patients who have significant inflammation at colonoscopy will have an elevated CRP.

David, you reported this years ago with a sed rate and it is not very different.

Do, if it took CRP to get the drug to our patients, could I accept that? Yeah. Is it the best thing for clinicians? Probably not.

DR. SACHAR: We can get caught up at great length when we have a lot of things to discuss on whether or not the label should restrict use only to people with an elevated CRP and strike the phrase "or another objective marker."

Unless there is burning discussion on that point, maybe we can just get a consensus of those people that want to strike another objective marker and require the elevated CRP or those people who don't want to strike it in such a way as to leave some room for the clinician to make a judgment however flowed it may be.

Can I get a sense by hand raising who would be in favor of striking or another objective marker and essentially requiring the elevated CRP level?

[Show of hands.].

DR. SACHAR: Are there some views of the panel from those who would leave it in for the purposes of some flexibility or latitude.

[Show of hands.]

DR. SACHAR: Okay. I see we have some abstentions but this is not a formal vote that needs to be recorded but it will be taken into account in our final recommendation.

DR. LEVINE: May I ask a question?

DR. SACHAR: Another issue directly related to this?

DR. LEVINE: The a,b and c? Do you want us to comment on that?

DR. SACHAR: That is absolutely where we are going now.

DR. LEVINE: I think that you alluded to it. I just wondered if you wanted discussion now.

DR. SACHAR: So we are saying for response and remission, we have hard data that we can interpret as we wish but the hard data are showing statistically significant and, in the minds of some of us, clinically, biologically, meaningful differences between Tysabri and placebo for inducing response and inducing remission.

DR. LEVINE: I have a quandary.

DR. SACHAR: Okay. What is your quandary.

DR. LEVINE: My quandary is that I think for maintenance of sustained response and remission, that is their strongest data. But it is modest. For the induction data, I think it is not very robust at all. And for the eliminating steroid use, I would call it mildly significant, mildly robust, so that you have to take that in a togetherness. Then I would say, probably, move forward.

DR. SACHAR: That sort of comes down to a yes or no, though.

DR. KRAMER: Mr. Chairman, could you clarify whether we might get a chance to express

our opinion that might be different than yours in terms of interpretation?

DR. SACHAR: Of course.

DR. KRAMER: There is something I really would like to say. I think it is our responsibility to evaluate the quality of the clinical-trial package that has been presented to us in this setting.

DR. SACHAR: Sure.

DR. KRAMER: I think, in particular, having heard the comments and the very emotional statements of unmet need both from patients and from clinicians treating these patients, I think it puts a tremendous responsibility on the sponsor to develop this drug in a way that we can really understand the benefits and the risks.

I would take issue with the statement that we have clear evidence that there are two corroborative clinical trials that demonstrate clear evidence of efficacy here and I would like to say that my reading of this data is that there is a single study for induction, that the first study

was failed, that there was a post hoc subset that doesn't qualify that as an adequate study.

There does not appear to me to be any evidence that sponsor went back to the drawing board after the withdrawal of the drug to look responsibly about how they might alter their clinical-development program to address the population they are requesting approval for now, because the population that they have requested approval for has not been studied.

30 percent of the people were receiving concomitant--approximately concomitant--immunosuppressive therapy in the trials that they are using for a basis of approval to treat patients who have failed prior therapy, that will not be continued on immunosuppressant therapy.

So we don't actually have a population that they are defining that they want for their label that has been studied. So there is a single trial, 307, that is statistically significant in a population that required elevated CRP, but 30

percent of those patients were also on immunosuppressant therapy concomitantly.

They are defining failure as either having tried and then taken off if it didn't work or continuing on it, which is not what they are asking for here.

DR. SACHAR: Dr. Kramer, I would 100 percent agree with you if statistical significance were found only upon post hoc subgroup analysis. But, as I understand it, the statistical significance is the same in both groups as well as in the total group.

DR. KRAMER: They randomized based on all covers with an elevated CRP. They did not stratify, and I would like to hear from the biostatiticians--I wasn't aware that there was any stratification on whether or not they were taking concomitant immunosuppressive therapy.

DR. SACHAR: As I understand it, there was no prior stratification but post hoc analysis shows no difference.e.

DR. NEATON: I think if all one had was

301, it would be an easy decision. We are not there yet. So a post hoc analysis was done, as I understand it, and the only subgroup that we saw today for which there are differences in the treatment efficacy is by CRP. That is evident in 301 and it also seemed to be evident in the two slides that were shown earlier today after my question.

So they took this post hoc result and did another definitive trial. The fact that that definitive trial showed efficacy actually with, I think, a better endpoint in some respects than the one that we used in the first trial requiring evidence of a response at two time points as opposed to a single time point lined up very nicely with the post hoc subgroup analysis. And the secondary endpoints, I guess, you could also add, were consistent, I think kind of substantiates a claim of efficacy in the short term.

That is less of a concern to me than, as I mentioned earlier, the fact that these were 12-week studies, double-blind phase, and we have these

little trends for safety on several outcomes that make the risk/benefit the more complicated part of this.

My sense is that I am less concerned that the first trial was a failure because the hypothesis was generated from it and a second trial, basically, kind of was able to verify it.

DR. SACHAR: This is a very fundamental question. We are dealing with the question of does the drug work or not. And, if there are opinions that there are insufficient data to support efficacy of the drug, we need to hear them whether they agree with me or not.

So are there other--Dr. Pasricha, do you want to comment further?

DR. KRAMER: Just if I could clarify. Are you, then, saying that you think that the post hoc subset analysis of the first trial counts as one of two trials when you are saying they are two--

DR. NEATON: No; I don't. I don't think that is the case. I think, basically, this is generated a hypothesis so you have one definitive

efficacy trial in the population at risk. I think your point is right. I mean, the population at risk is not exactly even what they studied the indication here in the second trial. There is subgrouping which is then done there in terms of the concomitant treatment. That point is a valid point.

DR. SACHAR: We are proposing to recommend it, if at all, in people not taking concomitant immunotherapy. Is there anything in any of the trials to suggest that it would not be efficacious in people not taking immunomodulators? I haven't seen anything that--I haven't seen any lack of efficacy in any of the trials when you look at the group of people on monotherapy.

DR. CHANG: In 301.

DR. KRAMER: The usual requirement is to demonstrate efficacy in the population you are asking for approval in, not to say that there is no evidence it doesn't work in the subpopulation that was a post hoc analysis.

DR. SACHAR: But the group we are asking

approval for is people not on--we are asking to use it in people who can come off their immunomodulators.

DR. PASRICHA: The question was--I think the question is that the study 307 was designed prospectively not to exclude people who were on other immunosuppressants and that is where it showed efficacy.

But the indication that is now being asked or put in front of us is patients without concommitant immunosuppressants.

DR. SACHAR: Right. So you are suggesting possibly that it would require another trial.

DR. PASRICHA: I think what you are saying is a rigorous--the most rigorous way to address this labeling indication is to do a prospective trial with those criteria ahead of time rather than saying, going back and saying, well, we looked at 307 and we looked at the subgroup of patients not on immunosuppressants and they didn't show any difference. I think that is the point you were trying to make.

DR. KRAMER: I think that it is particularly important when you do have safety considerations. The third option that hasn't been discussed for patients that are in need is A, if the clinical trials were proceeding, they could be eligible for clinical trials.

There is enough evidence for a compassionate IND for patients that need this drug and have no other alternatives. So the view that we have to approve it even if there is no evidence in the population for which we are seeking to approve it, with a life-threatening side effect, I think distorts the actual situation and I am very concerned about that.

DR. SACHAR: Okay. My view is it is a little strong to say that there is no evidence. But, Dr. Korvick?

DR. KORVICK: I appreciate the comments that we are getting into now and they get to the crux of the questions that we have been asking, would like to ask the committee. Perhaps it might facilitate it if we went around the room sort of--I

have seen this in other circumstances where we go around the room and everybody has a moment to say what they think or how they interpret the data.

So that would be most useful to the FDA to get everyone's point of view on the questions that are before us, in addition to other discussions.

DR. SACHAR: Fine. We certainly short-circuited that when we took a show of hands before. So we can now delve into it in a little more detail.

Why don't we go in the alternate pathway now. Oh, well, yeah; wherever the invisible line falls.

DR. SMITH: Now I am completely lost. Are we at Question 1, No. a?

DR. SACHAR: Yes. Essentially, we are being asked Question 1a; does this drug work or not.

DR. SMITH: For induction, I would say, based on the study population, the answer is yes. But, based on the study population. As far as sustained response and remission, I don't think

there is enough data. This is b.

DR. SACHAR: No; it is induction of response and remission.

DR. SMITH: I understand that.

DR. SACHAR: Those aren't three things. Those are actually two. One is response and one is remission and, by "sustained," it doesn't mean maintenance but it means beyond one week or two weeks. It means at the endpoint of the study which is 10 or 12 weeks--12. I wondered if there are some people who feel that the data support that indication and some who feel that the data do not. Dr. Korvick suggested that we get sort of an individual sense of how people are feeling about that. You can abstain, if you want, if you are still not sure.

DR. SMITH: Again, I do believe, for the response in the study population, that it is, that they did, indeed, show us an induction-sustained response and remission.

DR. SACHAR: We will stop at that. Judith, you said no.

DR. KRAMER: I forgot to mention that, since the sponsor clarified that they wished to treat patients who have failed all other therapy including the TNF inhibitors, I would say that the study population that they presented to us is not the same as what they have asked for in the label. So the answer to the first question, to me, is no.

DR. SACHAR: I understand. So you have explained your reason for no and I had explained my reason for yes because, although it wasn't restricted to that population, it included a large enough number of those populations to draw conclusions from it.

DR. FRANCIS: Mr. Chairman, would it be possible to clarify our position on that statement. I think there is a slight misunderstanding in what we said earlier

DR. SACHAR: Yes; go ahead.

DR. FRANCIS: So the statement of the terms of our claim, the indication statement is for patients who have failed conventional therapy, steroids and immunosuppressive therapies. We

understand, however, that the initial use by the gastroenterology community will be in those who have failed TNF-alpha inhibitors.

So there is a subtle difference there. I think the other aspect of this is that the reason to restrict it to those who have failed therapy is for safety purposes. The studies were conducted at a time when there wasn't the safety issue. We feel that we have demonstrated clinical significance, statistical significance, on the pre-planned, pre-specified analyses and that only for--in which case, generally, if you have shown significance in the population as a whole, if there is a biologically plausible reason to look at a subgroup which, in this case, is driven by safety, that that should be taken consideration in terms of whether the drug is effective or not.

What we have shown is, in those subgroups, that, in fact, efficacy is maintained consistently regardless of which subgroup that one looks at.

DR. SACHAR: I think Dr. Kramer's objection is that, in your interest to enhance

safety, you have sacrificed by absolute ability to claim efficacy because you didn't design the trial to exclude everybody except those whom you were looking for.

It seems to me that, with those hundreds of patients you have got, you have enough of that population represented to get the answer.

But we are going to continue around. You will have a chance then. Pankaj, I think you are still at no.

DR. PASRICHA: No. Actually, I really want to clarify this because I think it is really important. If there is confusion on our part, it is really going to be worth spending a few minutes on it.

So the question is, as we go forward, we are not going to put patients who are on immunosuppressants on this therapy; is that correct? That is correct. From Study 307, what is the data efficacy in those patients who were not on immunosuppressants? Can we see that slide? Can we see that data, please.

DR. SACHAR: Right.

DR. JONES: I can give you a quick answer to that. That was actually the data that I presented just a few seconds ago, actually, and this was the patient population in 307 who were not taking immunosuppressants which made up over 60 percent of the patient population. We saw 50 percent on natalizumab, response rates between 12 and 32 on placebo. The ITT was 48, 32. So we actually saw a better response rate in those patients not taking immunosuppressants in that induction study.

DR. SMITH: Do you have the slide number for that?

DR. SACHAR: While we are looking that up, should we continue on?

DR. PASRICHA: Yes. Just one more question or comment. Another important dimension, when we are looking at clinical efficacy, is the magnitude of response, especially when we try to balance it against the magnitude of the risks.

So my understanding of the data that is

presented now from 307, at least, is that the number needed to treat would be somewhere between 6 and 7; is that correct? And so, if you want to put this in perspective, and it is tough to compare apples and oranges if you are not doing a prospective trial.

But let's put it in perspective with infliximab. If you go back to the original Corrigan study in '97, that was like 2 or 3; is that correct? I just want to make sure that everybody gets a perspective on the magnitude of effects that they are trying to see because it is hard to do that by just looking at percentages. It is better to do it by a number-needed-to-treat comparison.

DR. SACHAR: I think NNT is a very useful concept that you have brought to our mind here. I would point out that you might be willing to accept a little higher NNT as you go farther and farther up the pyramid; that is to say, you are getting people who have now failed more things and more things and more things and you have an NNT of 8

and, perhaps, an NNH of about 100, maybe even 1000. So that is part of a balance to be sure.

Dr. Levin, did you have a comment?

MR. LEVIN: I just wanted to say that I find Dr. Kramer's argument persuasive that we don't have adequate evidence of efficacy and particularly in consideration of some very serious risks and that there may be, indeed, other ways for patients in dire need of this drug to get this drug, as she suggests. So it doesn't have to be all or nothing consideration.

DR. SACHAR: Dr. Chang?

DR. CHANG: I agree that the data wasn't delivered in the standard way that you would probably like to see it although, honestly, I don't think the FDA should have held this meeting if they didn't think there was adequate enough data, strong enough data, for us to make a decision and brought everybody here.

But I think the data, as presented, and the comments that were made across the room that the data that was presented, I think, is good

evidence that it does work in a subpopulation of patients with moderate to severe Crohn's disease. I, personally, believe that it looks efficacious.

Now, the point, though, about the not having immunosuppressant agents--and I said this before; I am the one that brought up the point--and in 301, it did not show efficacy in those who did not have immunosuppressives. It did show efficacy in 307 and in the patients that were from 301 that were in the long-term study, the 303.

So you are taking two out of three pieces of data. Overall, you will have to make a judgment if you believe it really has maintenance or induction capacity in those patients. Overall, I would say it probably does but it is not definitive at all.

But I think what the sponsor is trying to do is trying to weigh the safety. So they are taking--even though there is a chance that it may not be efficacious, so I probably can't 100 percent answer that question, but, in light of the risk/benefit, you have to be on the side of safety

over efficacy.

So I think that is why the decision was to not use it in the setting of immunosuppressives.

DR. SACHAR: Did you find the slide we are looking for?

DR. JONES: Yes. It was Table 13 of the briefing book.

[Slide.]

You can see here, if we look at the top line and it is actually the top left that we are interested in there, we are looking at the response now in those patients not taking immunosuppressives at baseline. Here we see the figures that I was quoting there. It was 50 percent natalizumab versus 32 percent on placebo we also saw as well for maintenance in 303. As well, maintenance of response, we saw significant benefit.

These are the patients in the left-hand column that aren't taking immunosuppressants.

DR. SACHAR: Are we going to be forced to say that the little 2 at the end of the 0.052 means that we cannot support an indication for remission?

We will be voting on that as we go around.

Dr. Day.

DR. DAY: I think there is some demonstrated efficacy for some people and I am disturbed about the mismatch in terms of what would be in the label. I guess I will leave it at that.

DR. SACHAR: Dr. Koski.

DR. KOSKI: I think I am going to come down on the same line. I do think that there is some evidence of efficacy. Part of the reason I feel that is because, in the maintenance portion of the study, that there was an increased, you know, difference between treatment and placebo groups.

I am also concerned about what the label will say.

DR. SACHAR: Okay. We will have to address the label as we go along. Dr. Gardner.

DR. GARDNER: Based on the data that were presented to us, I would say that efficacy has been shown but, clearly, there is more work needed to done in conjunction with the agency's direction.

DR. SACHAR: Dr. Platt.

DR. PLATT: So I am persuaded that there is evidence for efficacy in some people. So the questions are confining us some. But I think that the potential risk for long-term therapy is the greatest unknown. Therefore, I am hoping that we come to a place of quite restricted availability until there is more data on use beyond 18 months, because it seems to me that the notion that there is a sort of a 1 per 1,000 risk is doesn't really apply there.

We don't know that it is a much greater risk but it could be orders of magnitude greater. So my comfort zone is for more restricted distribution than hear you saying, but it is actually quite compatible with what I thought I heard the sponsor saying--that is, much more restrictive than what the agency has put out as its language.

DR. SACHAR: We will address that. I think the reason that it is useful to split the questions into such restrictive compartments is that, if the answer to this question is no, we

don't go home. So it is really important, I think, to get past this first gate-keeping question.

Sean?

DR. HENNESSY: I think that the drug has been shown to be efficacious in a population that is broader than the one that the sponsor is asking for. I think that the sponsor is asking for a narrower indication than the eligibility criteria for the study. I think that is fine given that the study showed efficacy both in the overall group and in the subgroup that they are proposing.

I would go even further. I realize that they say that they anticipate that initially use will be in TNF blocker--people who have failed TNF blockers. I would put that in the label as an indication rather than just an expectation. So I would go further. I would restrict the population further than even the sponsor is proposing.

DR. SACHAR: Well understood. That will be our prerogatives to say that we want to restrict it beyond corticosteroids and immunomodulators to people who have also failed anti-TNF. Did I

understand you?

DR. HENNESSY: Right.

DR. SACHAR: Bob?

DR. LEVINE: I have already mentioned what I thought about it and I said to probably move forward. But I can't predict my vote until I hear more about the safety, particularly about opportunist infections.

DR. SACHAR: Right. But, as far as 1a is concerned, you are okay with efficacy.

Alex?

DR. KRIST: I think that there is data supporting efficacy. I think we are restricting the population for risk reduction and I think what remains somewhat unknown is the risk-to-benefit ratio as you extend it to this population.

DR. SACHAR: We will get to that.

Marilyn.

MS. EICHNER: I think efficacy has been demonstrated in what was shown in the trial 307.

DR. SACHAR: Dr. Nelson.

DR. NELSON: I think it is an