relevant to the questions before the committee.

[Slide.]

Essentially, all the Crohn's disease studies, safety results were already submitted to the FDA for the review that was completed in June 2006, so little of the data that I will be presenting is new data.

I would like to first state the conclusions of the reviewers from Neurology, the safety issues other than PML identified in the previous review were infections that included herpes, atypical lower respiratory tract infections, and viral meningitides.

Carcinogenicity, there was no clear increase in risk. However, natalizumab blocks transport of leukocytes including T cells across vessels and because tumor immuno surveillance is mediated by T cells, there is a theoretical potential to increase the risk of cancer.

Immunogenicity, which was approximately 10 percent, and hypersensitivity reactions, which are associated with immunogenicity.

[Slide.]

As there have been no new cases of PML, the emphasis of the current safety review and the safety portion of this presentation is on infections, malignancies, and deaths.

[Slide.]

This slide shows the limitations on the power for safety based on the numbers of patients and the duration of treatment. Crohn's patients are approximately one-third of the overall total and less than one-third of the experience over one year is in Crohn's patients.

[Slide.]

This slide shows the overall exposure duration and concomitant medications during corresponding time intervals. More than 1,500 Crohn's patients are exposed total, and this drops to a little over 500 for more than one year, close to 300 for more than two years, and only about 80 for more than 2.5 years.

These numbers are the denominators of the cases that I will present shortly. Monotherapy is

approximately 20 percent of the population throughout. Concomitant steroids are approximately two-thirds, and concomitant immunosuppressants are approximately half.

[Slide.]

First, we are looking at placebo-controlled data, so that information on causality can be obtained. These are short-term placebo-controlled studies of about three months, so lack of difference between treatment arms could be a consequence of limited duration of exposure.

There are additional long-term data that this does not include which we will look at shortly.

[Slide.]

Overall, the incidence of infections was slightly higher in the natalizumab group, and there appeared to be a slightly higher proportion of upper respiratory tract infections in the natalizumab group, with a fairly similar proportion of lower respiratory tract infections.

There is a trend toward a higher

proportion of UTIs and herpes infections in the natalizumab group, and I will say a little more about herpes infections shortly.

[Slide.]

Again, we are looking at serious infections from control data, but these data are limited by the short duration of exposure. The rates of serious infections overall were similar and abscess rates were also similar.

In addition, a couple of interesting cases, uncommon serious infections raise the concern of opportunistic infections in light of the mechanism of action which may interfere with clearance of virally infected cells.

There were two cases of viral meningitis and one case of cytomegalovirus infection. Each of these infections is discussed in the next slide.

[Slide.]

Each of these cases occurred after one or two doses. The case of CMV colitis occurred with concomitant azathioprine. Both of the viral meningitis patients were taking steroids, but

budesonide would not be expected to provide much systemic exposure for the first case of meningitis. The other patient was also on 6-MP.

[Slide.]

Now, here are safety data from the entire database of 1,563 exposed Crohn's patients, which includes uncontrolled studies. In this database, most of the patients are on concomitant immunosuppressants and/or steroids. Six serious herpes infections were found, here arranged by extent of exposure.

These were 3 cases of zoster and 1 case each of herpes vaginitis, herpes conjunctivitis, and varicella pneumonia. The zoster cases were very unusual given the young age of the patients.

Half of these 6 patients were on concomitant immunosuppressants or steroids. These are not controlled data, but are of interest because these are unusual infections. But not shown in this slide in the post-marketing setting there was 1 fatal case of herpes encephalitis and 1 case of herpes meningitis during the initial

introduction. Each occurred after 1 dose.

[Slide.]

Again, looking at the larger database, there were 6 cases of atypical lower respiratory tract infections. These were Burkholderia cepacia, MAI pneumonia, varicella pneumonia that was already discussed, pulmonary aspergillosis, pneumonia with lung abscess, and a case of PCP pneumonia.

The cases of pulmonary aspergillosis and PCP pneumonia were both complicated by bacterial infections and were fatal. Note that the PCP pneumonia case was not on concomitant steroids or immunosuppressants. Again, these are not controlled data, but are of interest because these are unusual infections.

[Slide.]

Here I have the incidence and rate of malignancies and controlled MS studies, and in the short term, placebo-controlled Crohn's studies.

The rate is higher for the placebo group in the MS studies, but it is higher for the natalizumab group in the Crohn's studies. So,

there is no clear increase in risk numerically of malignancies from the placebo-controlled studies.

The sponsor has already summarized the types of malignancies that were found. The theoretical concern about some degree of increased risk remains, though, because of the mechanism of action of natalizumab.

[Slide.]

There were 18 deaths in the natalizumab development program, 14 in natalizumab-treated subjects and 4 in placebo. The death rates in the MS studies were higher in the placebo group, but the rates in the Crohn's studies were higher in the natalizumab group.

However, the number of deaths are very small in the placebo-controlled studies, so rate estimates are not very precise and conclusions cannot be drawn regarding the risk of mortality.

[Slide.]

There are some cases of note, and these are summarized in this slide. The fatal cases of PML, PCP pneumonia, and pulmonary aspergillosis

were already presented.

There was one fatal malignancy in the database. This was a metastatic melanoma in an MS patient with a history of excised malignant melanoma. While this may have been a pre-existing condition, in view of natalizumab's mechanism, there is a possibility that the melanoma may have had a worse progression due to natalizumab.

In addition, there was a suicide that renews the issue of whether there may be an association between natalizumab and mood disorders. There is a small increased trend of depression noted in the original review for the MS indication.

[Slide.]

With regard to immunogenicity, approximately 10 percent of those tested had positive antibody at least once. Antibody positivity was higher in patients on monotherapy than in patients on steroids, which in turn was higher than in patients on immunosuppressants. This was found for each of the induction studies.

In addition, clinical response in the

induction studies tended to be lower in those with positive antibodies, but the response rates for antibody-positive patients is based on small numbers.

[Slide.]

Antibody positivity was associated with infusion reactions listed here. Overall rates of anaphylactic reactions was 0.4 percent in MS studies and lower in Crohn's studies. These reactions appear to be associated with antibody positivity, because there were no cases in antibody-negative patients, but not all were tested for antibodies.

[Slide.]

So, in summary, based on review of clinical trial data and no new safety issues were identified since the June 2006 review, the principal safety issues are PML, infections other than PML, herpes, atypical lower respiratory tract infections, and viral meningitides, carcinogenicity based on theory, but with no clear increase in overall risk, and hypersensitivity reactions.

[Slide.]

The risk-benefit considerations are that therapeutic gains were relatively modest in the induction studies, approximately 8 to 15 percent. But therapeutic gains appeared higher in the maintenance study, about 33 to 35 percent.

Evidence for efficacy in subgroups is based on exploratory analyses.

No population clearly has superior efficacy, nor did any clearly lose efficacy.

Management of Crohn's disease, particularly moderately to severely active Crohn's disease, commonly involves steroids and/or immunosuppressants in contrast to MS.

Risk factors for PML are unknown.

Long-term safety data in Crohn's disease are limited, approximately 300 for more than two years and approximately 80 for more than two and a half years. Recall that two of the three PML cases were found after more than two years of exposure. If patients are not immunosuppressed at the outset, it is possible that a case of PML may not develop

for many years.

[Slide.]

There are safety concerns other than PML, such as other infections, malignancies, and hypersensitivity. If natalizumab is marketed for Crohn's disease, Risk Management will raise a number of questions--whether concurrent therapy should be allowed or restricted, what the role will be for immunosuppressant history and deciding who can enroll, and it will need to be determined what the role for JCV serum, MRIs, and neurological exams by a neurologist will be as screening tools for PML.

The possibility of additional safety and/or efficacy studies will also be need to be discussed.

[Slide.]

Many people have worked hard on this project, but are not presenting here today, and I would like to acknowledge the contributions of everyone on this slide.

Postmarketing Safety and RiskMAP

DR. KARWOSKI: Good morning.

[Slide.]

My name is Claudia Karwoski. I am the Risk Management Team Leader in the Office of Surveillance and Epidemiology in CDER. I will talking today about the Tysabri Risk Minimization Action Plan.

[Slide.]

My presentation will include a discussion of the key elements of the TOUCH currently approved in MS patients, the experience with TOUCH in MS patients, some proposed features of TOUCH in Crohn's disease, and some considerations in Crohn's disease.

Lastly, I will give a brief post-marketing safety update of events that are not captured within the TOUCH program.

[Slide.]

The Peripheral and Central Nervous System Advisory Committee recommended natalizumab's return to the market based on the magnitude of the efficacy in MS.

This treatment effect seen with monotherapy hadn't been seen with prior treatments for MS. The PCNS AC also recommended that the product be approved with a Risk Minimization Action Plan that included mandatory enrollment of prescribers and patients and distribution that would be limited to patients that are enrolled in the program.

[Slide.]

The TOUCH prescribing program is a performance-linked access system RiskMAP, which means that it requires documentation of safe use before the patient can be treated with the product.

These types of programs often require participation of all parties involved in the prescribing, dispensing, or administration of the product. It is the most rigorous of the three categories of RiskMAPs and has some disadvantages, namely, that it can have an effect on product access, but it also has some evidence of effectiveness in minimizing risk.

[Slide.]

You have heard what the risk minimization goals are; to promote informed risk-benefit decisions regarding natalizumab use, to minimize the health consequences of PML, and to minimize the risk of PML.

[Slide.]

Because of the small number of cases of PML to date, there are also the goals of further categorizing the risk of PML, as well as the overall safety of the product with long-term use.

[Slide.]

So, the key elements of the TOUCH program is mandatory enrollment of prescribers, patients, infusion sites that administer the product, and affiliated central pharmacies that will dispense the product to the infusion sites.

The product also has a restricted distribution system to only those authorized infusion sites and central pharmacies.

There is an education program for both health care providers and patients.

The program also includes a safety

surveillance component with increased enhanced surveillance of PML, serious opportunistic infections, and deaths, and finally, has an evaluative component to look at the health outcomes, compliance with certain RiskMAP requirements, and assessment of the knowledge and behaviors around the RiskMAP and the risk of PML.

[Slide.]

How does MS-TOUCH Work to Meet Its Risk Minimization Goals?

[Slide.]

This is a particularly challenging risk to minimize because the risk factors for natalizumab-associated PML are largely unknown. The three cases suggest concomitant use of immunomodulating or immunosuppressant drugs and longer term use, but again these are a small number of cases.

There is also no known effective non-invasive laboratory to monitor for PML, and even if there were one, it is not clear that it would be preventable or whether treatment would be

effective.

[Slide.]

So, the program works to reinforce appropriate patient selection, risk communication to health care providers and patients, and it also reinforces communication between health care providers and patients, and close patient monitoring.

[Slide.]

So, the prescriber has a huge role in minimizing risk. At enrollment, they acknowledge on their enrollment form that the patient that they are treating has relapsing form of MS based upon clinical and radiological evidence.

Although the program does not require verification of an MRI, the program does and the label recommends that patients have a baseline MRI prior to beginning therapy with Tysabri.

The acknowledgment also reinforces the approved indication is monotherapy and is used for patients who had had inadequate response or are unable to tolerate therapies.

[Slide.]

While concomitant use of immunosuppressants and immunomodulatory use is not prohibited, it is discouraged and the use is monitored monthly and every 6 months when the prescriber sees the patient again.

Every 6 months the prescriber needs to determine whether the patient is still appropriate for therapy and then re-authorize the patient to continue therapy. At that time an interim history is also collected as part of the re-authorization process.

[Slide.]

The prescriber also has a big role in monitoring the patient. The program recommends the evaluation of patients at 3 months of initiating therapy, 6 months, and then every 6 months thereafter until 6 months following discontinuation of natalizumab.

There is opportunity for more frequent evaluation if contacted by the infusion site or if contacted by the patient. There are

recommendations if there are symptoms suggestive of PML, to suspend natalizumab dosing and further evaluate the patient and, if clinically indicated, obtain an MRI and CSF fluid for JC viral DNA.

[Slide.]

The infusion site also has a large role in minimizing risk. Before every infusion, the staff need to determine whether the patient is actually authorized to receive natalizumab and whether they have received and read the Medication Guide.

[Slide.]

The pre-infusion patient checklist contains 4 questions that would screen for possible symptoms of PML, as well as for possible inappropriate use.

The four questions, I have truncated them to some extent, the first being whether there are any new signs or symptoms or medical problems, and this would be getting at questions of possible symptoms of PML.

The second would be whether the patient has a medical condition that can weaken the immune

system, the third whether the patient has taken any medicines within the prior 30 days that may weaken the immune system, and the fourth whether the patient has taken any systemic steroids other than for recent MS relapse.

A yes response to any of the four questions would prompt a phone call to the prescriber for further instructions.

[Slide.]

Lastly, the patient also has a big role in minimizing risk. When they enroll in the program, they need to acknowledge their awareness of the risks, understand that there will be more intensive and required monitoring as part of natalizumab therapy, that they should report any new or worsening symptoms to the prescriber and at each infusion center visit, they should provide a list of all medicines and treatments to the infusion site staff.

[Slide.]

I will briefly summarize what we have learned with MS-TOUCH program since the product was

reintroduced.

Overall, about 17,000 patients worldwide have received at least one infusion of natalizumab. This is during the initial marketing phase, as well, since its reintroduction.

Most of these have been U.S. patients. Since the reintroduction, there have been about 8,300 patients that have received at least one infusion of natalizumab. About one-fourth of these have been exposed for 6 to 12 month and none, at least as of May 23rd, had received more than a year of continuous use of natalizumab.

[Slide.]

As you heard, there have been no additional cases of PML reported in the trials or in the post-marketing period. We have recently learned of two serious opportunistic infractions that you heard about from the sponsor. One is a foreign case and the other is a U.S. case, a patient enrolled in the TOUCH program. Both of these patients were hospitalized, treated, and were discharged.

[Slide.]

Of the 8,300 patients, most of these are women and the median age for both genders is 46 years.

[Slide.]

The enrollment form captures baseline information on prior therapies or more recent therapies, and of the enrolled patients, only about a little over 2.5 percent were naive to any sort of MS therapy. I have there listed the more recent therapies, the more common ones.

About 12 percent indicated recent immunosuppressant use and about 25 percent had received natalizumab sometime in the past.

[Slide.]

So, as part of the evaluation, the sponsor also looks at compliance with the pre-infusion patient checklist and, overall, there is good compliance with the infusion site in filling these and returning to the company. About 8 percent of the Elan pre-infusion checklists do require some sort of contact with the prescriber for

authorization.

With regard to the questions, the highest proportion of yes responses were to the first question, which really gets at the question of possible symptoms. It is not unexpected because many of the symptoms of PML may overlap with symptoms of MS relapse.

As you can see, the concurrent use with immunosuppressant or chronic systemic corticosteroid use is relatively low.

[Slide.]

Every six months the prescriber is required to complete a Patient Status and Reauthorization Form. This is mailed to them about 5 months after the patient has received their first dose. Compliance with filling these and returning them to the sponsor is very high. Most patients do get authorized to continue therapy and they also ask a question about use of immunosuppressant within the prior six months, and this information is similar to the information seen with the pre-infusion checklist, so very low rate of

concurrent use of those products.

About 10 percent use intermittent courses of corticosteroids, but this is allowed under the TOUCH program.

[Slide.]

The sponsor also has a survey component and has conducted one survey, results which find fairly high knowledge of key risk-management messages and actions that the health care provider is to take in order to minimize risk.

Lastly, they look at distribution data and only 10 of greater than 10,000 shipments were unauthorized, and these were sent to the patients or prescribers and in the cases of noncompliance, corrective action was taken.

[Slide.]

So, in summary, at this time the TOUGH program does appear to be working satisfactorily in the MS population. There have been no cases of PML since reintroduction. It is being used primarily as monotherapy. There has been good compliance with RiskMAP process, and the surveys indicate a high

level of understanding of the risks and the requirements of the RiskMAP, but the experience at this time has been relatively short.

[Slide.]

The proposed TOUCH program in CD is very similar to what is in place for MS-TOUCH. The process for enrollment, reauthorization, and follow-up would be the same. The names are different. MS patients would be enrolled in the MS-TOUCH program and CD patients would be enrolled in CD-TOUCH. The educational materials will be updated for its use in the CD population.

[Slide.]

There are some differences. Because the proposed indication for CD is not as monotherapy, there is not as much emphasis on the enrollment form for monotherapy. So, I have included here the language that pertains to the indications in the enrollment form.

[Slide.]

Also, CD-TOUCH would allow for concurrent use of chronic steroids for up to 6 months after

starting natalizumab therapy. The statement here states that the patients should have tapered off of their chronic steroid use by six months of natalizumab therapy or they should discontinue treatment with natalizumab.

[Slide.]

Another difference that we noted was--actually not much of a difference--was in the questions on the pre-infusion checklist. The last three, as you may recall, pertain to concurrent use with immunosuppressants or concurrent use with chronic steroids.

As it is not clear whether these will be permitted under the program, there may need to be some customization with these questions should the product be approved in Crohn's disease.

[Slide.]

So, if the product is approved in Crohn's disease, it would be important to discuss the following issues, particularly with regard to the management of these patients; that is, the appropriate patient and how these patients would be

identified in clinical practice.

The best way to monitor the CD population for PML, it is sort of built in with the MS program, because these patients would be getting neurological exams with their neurologist.

Whether concomitant immunosuppressive and immunomodulatory therapy would be permitted.

Whether the concurrent use of steroids for 6 months is acceptable, and how flares for Crohn's disease will be treated.

[Slide.]

I am going to quickly give a post-marketing update.

[Slide.]

The TOUCH program captures events, the PML, and opportunistic events, the sponsor's safety database and the Adverse Event Reporting System within FDA capture other post-marketing events seen with natalizumab.

[Slide.]

The sponsor's last periodic safety update report noted their post-marketing experience is

that most of the types and frequency of events are consistent with what is known about natalizumab and that there is a possible higher risk of hypersensitivity with an extended treatment with natalizumab. You have heard this with the sponsor's talk and they have proposed some labeling changes.

[Slide.]

The Adverse Event Reporting System has to date about 1,700 reports. It includes the entire marketing period. Most of these are from clinical trials. A quick look at these show events that appear to be consistent with product labeling.

The hypersensitivity labeling changes that have been proposed by the company are currently under review.

[Slide.]

A colleague within the Division of Drug Risk Evaluation recently noted cases potentially serious hepatocellular injury. So, she conducted a search of the entire Adverse Event Reporting System and noted 28 cases reported between the initial

marketing period up until about the third week in June.

Four of these were potentially serious hepatocellular injury, three occurring in the U.S.

The remaining 24 cases were of mild liver abnormalities. None of these resulted in death or liver transplant. This liver injury signal was not one that was identified within the clinical trials.

Of the more serious cases, the four cases, the liver injury occurred within 18 days after the first dose in 3 of the 4 cases and after 5 doses, in one of the cases.

The peak serum ALT ranged from 521 to over 2,000, and the range of total bili was from normal in one patient to up to 15.6 mg/dL.

These cases were extensively worked up and no other or obvious cause of liver injury was identified. FDA at this point has not reached any conclusions and this issue is under further evaluation.

Thank you.

Questions to the FDA

DR. SACHAR: Since there is a regulatory requirement that we start the open component of the meeting close to the announced time of 1 o'clock, and since we want to give ourselves at least 45 minutes for lunch--good, I am told that we can go forever with our questions to the FDA.

[Laughter.]

DR. SACHAR: There will be ample time after the public component of the meeting to return to our questions to the sponsor.

DR. FERRETTI-ACETO: Because the open public hearing may start a little late, I just wanted to ask if any of the open public hearing speakers have early flight or issues with timing, if they could see at the lunch break and we can maybe work something out if we do go a little into--we might start as late as 1:30. Thank you.

DR. SACHAR: We can probably get to starting earlier than that if we don't go too long now or we don't dawdle too much over lunch.

I would like to launch the question period with one question to Dr. Smith and one for Dr.

Karwoski.

Is there tangible benefit from the early diagnosis of PML, or is it already too late?

DR. SMITH: No.

DR. SACHAR: My question for Dr. Karwoski and actually for the whole staff is this. Did the FDA review of the sponsor's proposed CD-TOUCH program include a review of the informational brochure given to the patients? Once I get a yes or no answer to that, I will tell you why I am asking.

DR. KARWOSKI: We haven't actually seen the proposed brochure for the CD yet. Those haven't actually been submitted. So, we have reviewed them for the MS population and we know some of the language that is going to be included in the enrollment form and in the infusion checklist. But we haven't seen the proposed educational materials at this point.

DR. SACHAR: One of the CDs I got or one of the packages that I saw did include a proof of the proposed information to the patient, and I am

concerned that in the component that started off by telling patients what the potential benefits were of the treatment, and please correct me if I am wrong, or maybe it was just a dream.

It compared a response rate to active drug and placebo and told the patients, gave the patients the information of the difference between the placebo and the active drug as proportion. In other words, it said that there was a 42 percent benefit from the drug where in fact, the therapeutic effect, the delta was only about 12 percent.

I am concerned that it would be quite misleading to patients to confuse them in the difference between a proportional difference between the responses and the actual therapeutic delta.

Am I off base on that or is there, in fact, a draft available for us to look at of the proposed brochure?

DR. FRANCIS: I think you may be referring to the MS--

DR. SACHAR: Oh, maybe it's the MS one. Oh, it is the MS, okay. So, that has been reviewed by the FDA, so that is not the table now. The FDA was that was okay? Okay. We will forget that. Maybe we will talk about that at another time.

Dr. Davis.

DR. DAVIS: I have a question that relates to the materials given to patients. One is how a patient understanding of what they need to know and do be confirmed, and then the screening questions, the material is written on a high school or a college level. The average reading level of Americans is about 8th or 9th grade.

The organization of the material, some of it, quite frankly, even though it was MS, seems sort of disorganized and thrown together, and not real patient centered. So, it is not easy to read and understand the material.

The screening questions that are asked, is it a nurse that asks those? Even though they are oral, they assume that a patient has knowledge of medical conditions that could weaken the immune

system or medications.

Is this an RN who is probing this, or does she just say are you taking any medicine that can compromise you?

The third question is kind of a naive question, but it is based on my clinical experience as a psychologist. The Crohn's patients I have seen have been disproportionately adolescents. So, I wondered if the safety, efficacy, and risk benefit issues, if they are any different for adolescents or the educational materials.

DR. FRANCIS: If we start back to front there, the adolescents, there have been very limited study of natalizumab in the pediatric population, say, under the age of 18. There is no proposal in the indication to treat patients who are pediatrics. That would need to be dealt with subsequently.

DR. SACHAR: Dr. Krist, do you have a question?

DR. FRANCIS: There were a couple more.

DR. SACHAR: Oh, I am sorry.

DR. FRANCIS: It is the infusion nurse who uses the infusion checklist with the patient and sort of goes over this to describe with them particularly things like the medications that you raise.

The flip side has all of the medications that are immunomodulatory or immunosuppressive, and they read that list with the patient each time. The patient is instructed to bring whatever medication list that they have with them.

So, I think that in addition, prior to enrollment, obviously, the patient and the physician have to have the risk-benefit discussion and go through and ensure that the patient does understand the risk of the PML and the fact that this is generally a rapidly lethal disease or severely disabling disease.

So, we feel that the program, either way the program is established with a physician-patient contact and then a nurse-patient contact every month, repeating these monthly, these questionnaires are done each time, and the patient

information leaflet is provided each time to the patient.

So, there is opportunity for clarification at each visit.

DR. DAVIS: I guess my question was just because the doctor said it doesn't mean the patient understands it, so you believe that the doctor has confirmed patient understanding rather than just say do you understand what I have said?

DR. FRANCIS: Correct, although the patient signs it, acknowledges that they have had this explained and they understand the risk.

DR. DAVIS: My other comment about that enrollment form, which is like a consent form, in many medical schools now the consent forms are written in a little easier to read, easier organized, more patient friendly manner than this currently is.

DR. FRANCIS: Certainly the language was sort of discussed and reviewed with the Agency and agreed upon. If it needs modification, we are willing to discuss that with the Agency based on

the input from people such as yourself.

DR. SACHAR: Just as a follow-up to Dr. Davis' question before we go on to Drs. Krist and Couch, I don't have the consent form in front of me. Maybe a look at it would help, but I wonder if it gives us the same information that Dr. Smith just did; that is, does the patient understand that even if an early detection of this illness takes place, that it might be too late, that the cat is out of the bag, and that they may go on and have a slow and horrible death irrespective of an early diagnosis.

DR. FRANCIS: I think that that is the point behind the statement that says that they understand that this is a fatal or severely disabling disease, a rapidly fatal or severely disabling disease, so that they clearly understand that there is no treatment for this disease at the present time.

DR. SACHAR: That is pretty strong.

Dr. Krist, you had a question, and then Dr. Couch.

DR. KRIST: I just wanted some clarification about what the risk-management plan, how things worked after the pre-infusion questions, and looking at the indication of the medicine saying dosing should be suspended immediately at first signs and symptoms of PML, and then I see, looking at page 13 of our sheet on the risk-management plan, it said that 5.6 percent of patients reported PML symptoms at the pre-infusion checklist questions.

Then, on slide 107 earlier from the sponsor, I saw the infusion was not given to patients only in 0.5 percent of cases. My understanding was that after the positive response in the pre-infusion checklist, the nurse would call the physician and then the clinician seemed to clear the patient for the infusion all the time.

I just was kind of interested in how the physician was making the assessment over the phone that it wasn't PML even though the patient expressed signs and symptoms of that.

DR. FRANCIS: I think if any medical

symptom at all comes up in that question is the 5 percent case that you had alluded to, so, whether that be neurologic or another medical problem that arises in the month since the previous infusion, and then the infusion nurse contacts the physician who then addresses the problem specifically and authorizes that the patient is fine to continue with the therapy or not and needs to be seen by them before the infusion can be administered.

So, the actual number that is withheld, the 0.5 percent, are the patients who don't get the therapy at all. It doesn't comment on at what point in the 5 percent who are being held, at what point they get that therapy.

I think the issue about a PML symptom is any symptom. It may be neurologic, but, of course, as was already alluded to, MS patients have neurologic symptoms. But it may be other medical symptoms as well, and this only puts PML--I think the idea is that there should be a low threshold to consider a new neurologic symptom as potentially PML, and that is the whole object of the TOUCH

program, so that the dosing is suspended until the physician has clarified that that is not, in his opinion, that is not the etiology for the symptoms and the infusion can progress.

DR. SACHAR: Jim, did you get your question?

DR. COUCH: There is, I think, a basic question I would like to get answered, and that is the relationship between the physician and the infusion center.

It appears that the infusion centers are somewhat separate from the physician; that is, you have got an infusion center that may be doing a lot of different things than their infusion work, that perhaps they are doing cancer chemotherapy drugs, they are doing some other things, and you have got a physician who initiates the program, plans on hearing from the infusion center if something goes wrong, how closely does the physician in the ongoing case, the neurologist, interact with the infusion center.

Is this something like the situation with

chronic inflammatory demyelinating polyneuropathy where an organization that deals primarily with neuromuscular disease runs the infusion center, so they are very familiar with the patients, or is this--I think this is more likely to be a situation where a physician with a modest number of MS patients is using an infusion center that does not necessarily deal just with MS-related things and they are getting some--how often does the doctor see the patient, how often does the doctor interact with the patient, and what kind of--who is providing the information to who?

DR. FRANCIS: I think, in terms of the infusion centers, some of these will be, as you indicate, centers that are polyfunctional. But many of them are, in fact, neurology specific with the MS physicians themselves having their own infusion center or affiliated with their hospital center. But, of course, there are a proportion of them that will be using centers that are used for other neurologic or medical indications.

In terms of the interaction between the

center, the infusion nurse calls the physician and does not administer--if there is any issue, does not administer the drug until has had contact with that physician, so if they are not specifically there on site, then, they still must make contact with that physician before the infusion will be administered.

I think that in terms of the follow-up for the patients, this obviously depends on what the medical practice is for that physician.

At a minimum, as was indicated in the slides by the Agency, the physician must see the patient at three months following initiation of therapy at six months after follow-up for the reauthorization, and then at a minimum of every six months and at times mandated by symptoms of the patient.

DR. COUCH: What is the training program, is there a training program mandated for the nurses that they are bringing in?

DR. FRANCIS: Yes, there is.

DR. COUCH: What is the training program,

how intensive is it, and can the nurses really recognize something going on from the neurologic standpoint?

DR. FRANCIS: I think the nurses are not expected to do a neurologic examination. They are to ask have there been new symptoms, medical symptoms, whether they be neurologic or respiratory, that are different than what the patient had the previous month and, regardless of what system is involved, they are to contact the treating physician to get guidance on whether the therapy should be further administered.

The nurses and the infusion sites are certified and trained in what the risks of natalizumab therapy, the risks specifically for PML, the symptoms that they should be looking for, and the things to be alert to when the patients are seen each month.

DR. COUCH: If I could just follow up. The problem, if we are going to address any therapy towards PML, and then it does suggest that early re-establishment at reconstitution of the immune

system may make a difference, it is the early recognition of changes which is usually fairly subtle. The patient has subtle changes, and that is when you are going to try to catch them. If they go to the situation where, yeah, this person is really having a lot of difficulty with cognition, you are probably way too late to be able to do anything.

So, I think that needs to be addressed by this panel.

DR. FRANCIS: Well, I think as we tried to address earlier, because the patients and their caregivers are alerted to the fact that PML is a risk and the neurologic features to look for specifically, that both patient and caregiver, you know, are encouraged to contact their treating physician should those happen.

However, as a fail/safe in a way, every month they are being seen by a medical person who asks the same sets of questions and can refer the patients, so we agree entirely that we want to detect this as early as possible and the first step

in terms of the management of those patients is suspension of further therapy.

DR. SACHAR: There are questions pending from Drs. Neaton and Hennessy, but at this point I think Dr. Koski may have a comment on the specific neurologic questions.

DR. KOSKI: Yes, thank you.

First of all, to Dr. Davis, it is very possible that the two populations, MS and CD, that we are actually looking at might be slightly different in the sense that there is--at least in the MS population, there is a higher proportion of Caucasians, the educational status is actually quite a bit higher, there is a very active MS society that, you know, contributes to their medical knowledge and experience in a lot of these things, so it is a very highly interactive group.

The other thing I would like to also say is that, you know, the University of Maryland has an extremely active MS center. They do a number of trials. The nurses generally that do these intake informations or forms are not only RNs, but they

actually are RNs that have actually practiced in treatment of patients with multiple sclerosis. Therefore, they are really quite insightful, they know their population of patients, they deal with these patients really on a very regular basis. I am very comfortable with their ability to recognize some of these symptoms.

My prior institution--I have to keep on thinking about that--actually, the MS doctors are involved in the infusion clinic, they see these patients each time they actually are infused. So, as a result, there are a lot of checks and balances.

Just to reaffirm what Dr. Couch was certainly saying, these patients are examined, have a formal examination at least on an every six-month basis, and that includes a disability scale that is followed on a regular basis, and it helps to determine the function, not only of the lower extremities, but also in the upper extremities.

DR. SACHAR: Our Crohn's disease infusion people who have been doing anti-TNF for a long time

also, you know, know their patients quite well.

Dr. Day, did you have a follow-up comment?

DR. DAY: I have some general comments about comprehension. I agree with Dr. Davis' general comments. I think we need comprehension testing for patients and perhaps others. It is not enough to give information to people and ask if they understand.

There is a lot to understand here and in comprehension testing, you test knowledge and also the ability to apply that knowledge to various scenarios, so you could take some scenarios for the patients if something, you get some new condition, et cetera, would it still be all right to continue, and so on.

Just to pick out some of the things that are problematic in the patient authorization form, and by that way it is at the bottom of the TOUCH program addendum, a lot of people here have not seen it, I have heard.

But there is a place where it says that I understand basically that some of my health

information is going to be collected and shared with the manufacturer of this drug, and it goes on about that, and then it says I understand that I may refuse to sign this authorization and refusing to do so will not affect my ability to receive Tysabri, I understand that blah-blah-blah.

Then, later, way down, there is something about it is mandatory that you be in this program and get your health information collected. So, there is a disconnect here and it presses comprehension skills of even highly educated people to understand these two things.

I will give you just one other example which appears repeatedly throughout all the materials. I am reading now from the Medication Guide. But it appears in many other places, as well.

Briefly, "Tysabri increases your chances of getting a rare brain infection that usually causes death or severe disability. This infection is called PML, et cetera. Here is the critical sentence. PML usually happens in people with

weakened immune systems. Let me take that out of context as some patients reading individual sentences might. PML usually happens in people with weakened immune systems. That is not true. All right. If you just add in a few words before that sentence and say when it occurs PML usually occurs in people with weakened immune systems, then, it makes sense. But I mean that is one of the examples where comprehension testing could reveal that there could be big misunderstandings or lack of knowledge, and so we really do need some comprehension testing of the Medication Guide and other features of the program.

DR. SACHAR: I think Dr. Day's comments are probably much more broadly applicable to the practice of medicine than just to this, and when it comes to--

DR. DAY: And, indeed, I have made these comments in other contexts.

DR. SACHAR: Right. And when it comes to fixing up some of the wording of proposed forms, I think that is something that we might be able to do

in a subsequent session.

I think we will have time to take a couple of remaining questions and I know that Dr. Neaton and I think Dr. Hennessy are on the tarmac.

DR. NEATON: Thank you. I have one question on safety and one question on efficacy.

On the safety, I noticed, unless I missed it in the briefing document and also in the presentations today by the sponsor and the FDA, neither group focused on the target population. That is to say, what is the short-term risk, for example, of the serious infections, malignancies, hypersensitivity reactions in the group with elevated CRP at entry. The subset of 301 and 307, just those pooled results, I think that is something that is important to look at in light of the indication sought.

DR. FRANCIS: I think I could comment, answer very briefly. I recall 307 is all elevated CRP, 301 is only 30 percent are normal CRP, and there is no difference in the safety profile for infections or adverse events in general between

those groups.

DR. NEATON: The second question related to the CRP findings. I just wonder what your thoughts are. I thought it was interesting, the FDA presentation on the maintenance study, and so by my calculation in 301, the group that had normal CRPs, there was no evidence of a treatment difference at all. Actually, the response rate was slightly higher on placebo.

Yet, when you took people on study drug and re-randomized them, the baseline CRP in 301 did not make a difference at all in terms of the maintenance of the response.

So, I just wondered if you have thought through the implications of that both for kind of the CRP indication and kind of to what this may suggest about what I thought I heard you say was a placebo effect, attributed to a placebo effect in 301.

DR. FRANCIS: I think what we attributed is that the patients who had normal CRP had a higher placebo response rate than those with

abnormal CRP. The response rate to natalizumab was actually relatively constant across the CRP spectrum.

So, I think what we are seeing in 303 is you have got a patient with normal CRP who has, in fact, responded to natalizumab, and that patient maintains that response while on natalizumab, so it is really a subgroup, if you will, and I think that the retention of efficacy is in a patient who has already achieved efficacy.

DR. SACHAR: In other words, those were not patients who had normal CRP before entry into 301. Those are patients who had a normal CRP after treatment, is that right or not?

DR. FRANCIS: No, no. They had normal CRP before entry. But remember a good proportion of patients with normal CRP also had a response while the proportion responding with response to natalizumab or placebo was the same in the CRP normal group. But, in a patient who got a response on natalizumab, they maintained that response regardless of whether or not they had an elevated

CRP at baseline or not.

DR. NEATON: But I am not sure I follow that logic, because part of the placebo response which were seen in the placebo group is going to carry over to the study drug group, too, and so, quote, "the responders, irrespective of CRP, did equally well in the follow-up study."

I think that is a bit of a conundrum in understanding your CRP findings. I guess I wondered whether--have you looked at the baseline CRP and whether or not there is a gradation of response, or how was this cut point at the upper limit of normal chosen.

Is there evidence, for example, as you move the CRP down or move the CRP up, that there is increasing kind of treatment effect?

DR. FRANCIS: Right. We have looked at it based on cut points of CRP levels for the population within the CD307 study. What one sees here is that as the CRP increases, you can see from 2.87 being the cut point upwards to 50 and over, that the placebo response rate drops from 32 down

to 13 percent. However, the natalizumab response remains reasonably stable over that interval.

So, again, we are not trying to say that this is a predictor of treatment response. What we trying to say is that patients who don't have an elevated CRP possibly don't have as much inflammation are less likely to benefit from the drug and should not be exposed to the risk of the drug in that setting.

DR. NEATON: Do you have a similar slide to 301?

DR. FRANCIS: I believe we do.

[Slide.]

So, what one sees here for the CD301 patients is the Week 10 response for the ITT population, and the response rate sort of is on a trend down for the placebo group as the CRP increases and a slight trend upwards for the natalizumab treatment group.

DR. SACHAR: Sean, do you still have a question?

DR. HENNESSY: I have two quick questions.

One, are cancer and liver disease going to be included in the label? Two, are there any plans to follow up patients after they have stopped receiving the drugs, so that way, if they develop PML or cancer or other adverse events after having stopped the drug, it will be identified?

DR. FRANCIS: I think the issue of what is going to be included in the label will have to be discussed with the Agency based on further evaluation of the hepatic cases, and currently, malignancy is not in the label and would also have to form part of our discussion with the Agency.

In terms of the follow up of the patients, all patients who are in the TOUCH registry program are followed for at least 6 months or there is a follow up after the patient has discontinued drug at 6 months. The physician has to attest to what the outcome for that patient was.

We didn't talk about the TYGRIS registry here. That is the similar type of observational cohort in MS that we are proposing for Crohn's. In that situation, the patients are followed for five

years during that, so upwards of 5,000 patients for five years of follow up regardless of drug therapy.

DR. SACHAR: Dr. Nelson.

DR. NELSON: Thanks. I just wanted to follow up to some points that were made earlier and these might be very simple answers. It could be yes or no perhaps.

Going back to this concept of the infusion center, it says several times through the documentation that the infusion center will be registered, and I know you had commented that, in fact, the individual nurses that are going to be doing the infusions that are perhaps going to be trained.

But, you know, if a new person came on board to the infusion center, does that person automatically get included in the registration process, or do they then have to undergo some sort of training process, because I imagine the turnover at these places, like everywhere else, is pretty high, and if they don't have--you know, are they really covered under the blanket registration of

that center?

DR. FRANCIS: No, it is not a blanket registration. Just as each new physician, each new person dealing with the infusions has to be educated in the risk and the management program for the TOUCH program.

DR. NELSON: I guess another question, is there data from the MS TOUCH program as to whether or not there is any sort of--and I don't have a better word, but perhaps kind of alert fatigue--from getting these repetitive questions asked month after month?

You know, when you go to the airport and they ask if you packed your own luggage, you know, we answer the question before they finish it most of the time, really don't ask it anymore I guess because of that reason.

I don't know that there is any--and maybe the more psychometric oriented people could answer this as well--but when you get the same questions over and over again, you start stopping to listen to them, and I don't know if there is any data that

this is kind of persistent.

DR. FRANCIS: Right. I don't think there is data available yet. I think one has to keep in mind as we said the median number of exposures is only four to five at this time, so I think it would probably be something that could be looked at prospectively in the future. So if we saw that, you know, currently there is this rate and then a year from now the rate has changed or not changed when we get an idea about this issue about questionnaire fatigue. But it is a good point.

DR. NELSON: If I could ask just one more question. I wanted to follow up on Dr. Day's question, but what exactly is the HIPAA position on all of this? I mean do people have the right to refuse to send the data to the manufacturer or, you know, the company?

DR. FRANCIS: That is a good question. They need to have their information recorded in order to get a unique patient identifier to be infused, so without that, they cannot get the drug, because they cannot be authorized to receive it.

DR. SACHAR: Dr. Gardner, why don't we take a last question before the lunch break.

DR. GARDNER: Could you just clarify for me how clinical response will be defined in infusion centers? I see that if there is no clinical response in three months, Tysabri is to be discontinued. You are not using the CDAI in the clinical center, are you? What is the response?

DR. FRANCIS: That is correct. The infusion center does not determine that the clinical response has occurred, but the physician will.

DR. GARDNER: I am sorry.

DR. FRANCIS: No, that's okay. You are right, the CDAI is not generally used in clinical practice, so it's the clinician's judgment as to whether that patient has responded, so I will turn it over to the GI clinician to respond on how he would define a patient in response at three months after initiating therapy.

Dr. Sandborn.

DR. SANDBORN: I think Dr. Sachar and the

other gastroenterologists know the American College of Gastroenterology has some treatment guidelines for treatment of Crohn's disease in adults, and that includes some sort of working clinical definitions.

The working clinical definitions actually track not so badly to what was presented by the FDA, so the definitions of moderate to severe encompass both the disease activity as well as the refractoriness to therapy, so you could have sort of moderate symptoms, but failing other therapies.

So, typically, you would expect to see, what I would expect to see in a patient that I would treat initially with Tysabri would be--and not all patients will have diarrhea or pain--so if the colon is predominantly involved, often the predominant symptom is diarrhea. You may have some cramping and urgency. If the small bowel was predominantly involved and there hasn't yet been a surgery, the symptom would be more pain, so you have to get a little bit of a feel for what is the major driver of symptoms in that particular

patient, and then you are looking for improvement over time.

DR. GARDNER: Just as a follow up, so then, in other words, patient report to physician based on clinical judgment and my question to you vis-a-vis the TOUCH program is three months enough for you to ascertain whether there has been clinical response?

DR. FRANCIS: Oh, I think so. With corticosteroids or anti-TNF agents, we certainly can make that judgment. I think we could here.

DR. SACHAR: Good. I think with this very graphic description of pain, urgency, diarrhea, and cramps, it is time for lunch.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:30 p.m.]

Open Public Hearing

DR. SACHAR: Open Public Hearing component of the day's meeting.

The FDA and this committee place great importance in the Open Public Hearing process. The insights and comments provided can help the Agency and these committees in consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions, and one of our goals today is for this Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chair.

Both the FDA and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the Open Public Hearing session of the advisory committee's meeting, FDA and I believe that it is

important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, each of you, at the beginning of your statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

We would specifically be most interested in knowing to what extent the sponsor has assisted or supported you in your ability to come and testify today. This financial information may include the sponsor's payment of your travel, lodging, honoraria, other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise us if you have no financial relationships whatsoever and have received no support, encouragement, or assistance from any third party.

But if you choose not to address this issue of financial relationships at the beginning

of your statement, it will not preclude you from speaking. But we do encourage it.

With that, I would like to call on Speaker No. 1.

DR. WOLF: Thank you, Dr. Sachar. My name is Doug Wolf. I am a gastroenterologist from Atlanta, Georgia, part of Atlanta Gastroenterology Associates, and I am on the clinical faculty at Emory University School of Medicine.

I do have financial relationships to share. I don't have these prepared, but I have served as a consultant and I have received clinical research grants from Elan Pharmaceuticals, as well as Centocor, Avid, Prometheus. Bristol-Myers Squibb, and other companies treating patients with products, treating patients with Crohn's disease.

My topic today is natalizumab, an unmet need in the management of Crohn's disease, and I want to share my thoughts and my experience with this agent and patients who have received this medication.

As you heard earlier, there are almost a

million patients with Crohn's disease in the United States and about 80 percent need surgery at some point in the course of their disease.

While the disease is active, quality of life is decreased and this impacts on school attendance and work performance. Over the past 10 years, I have been involved in the care of over 1,000 patient with Crohn's disease and have participated in approximately 25 clinical trials dealing with patients with moderate to severe Crohn's disease.

So, how many patients are there with moderate to severe Crohn's disease? It is hard to estimate. I know this morning we were trying to address how many potential patients might be benefited from a drug like natalizumab, and I would say that at some point in time, somewhere between 250,000 and 500,000 of these Crohn's patients fit in this category of moderate to severe Crohn's.

Now, that may not be at every point, but at some point in their illness, so that is a significant number, and over half of these patients

do not have any sustained benefit with the anti-TNF agents or any other agent.

So, as you probably can't read in the back because it is on the bottom line, there are somewhere between 125,000 and 250,000 Crohn's patients in the United States and North America who might benefit from an agent such as this.

So, what do I use in clinical practice for Crohn's disease? Well, Dr. Sandborn summarized this well for you before, I am not going to reiterate it. But there is a lot of mesalamine use and we are not sure that it really works at all significantly in Crohn's disease.

There is a lot of corticosteroid use. You have heard about the potential side effects of prednisone. There is also a more friendly corticosteroid called budesonide or Entocort, which is FDA approved and does benefit a slice of the moderate Crohn's disease population. But is only approved for mild to moderate Crohn's disease. Then, there are the immunomodulators, azathioprine, 6-MP, and methotrexate.

Then, there are the biologics in Crohn's disease that everyone here is likely familiar with, infliximab, which is FDA approved for multiple indications in Crohn's disease, and then recently approved adalimumab and Humira.

This slide, which unfortunately people cannot see in the back, does summarize the fact that only a minority of patient with Crohn's disease benefit from anti-TNF therapy, and this shows you that although a 4-week response of 81 percent was reported with infliximab, if you really look at remission, it is less than half, and if you look at 1 year responses and 1 year remissions, you are getting down to a third of patients who are truly benefiting from this agent, and with adalimumab, the numbers are similar

So, there clearly is an unmet need in Crohn's disease for an agent that can benefit this population. Natalizumab is readily administered in any infusion unit. The infusion is similar to that for infliximab or Remicade, but maybe even simpler. It is a single vial and dose, 300 mg IV in the

adult. It is monthly dosing, easy to keep on schedule.

The infusion unit dosing does facilitate supervision on a regular basis, and in my personal experience of having over several hundred infusions in my patients under the auspices of clinical trials, I have only had one patient with an infusion reaction and really the medication has been incredibly well tolerated.

PML is a significant issue, but it is a rare complication of natalizumab therapy. It occurred only in subjects on combination therapy with immunomodulators, immunosuppressants, so if you kind of take an analogy of risk with infliximab or the anti-TNFs, hepatosplenic lymphoma has occurred in approximately 12 unfortunate individuals. It is essentially an untreatable condition and has also occurred with combination therapy.

So, maybe we are seeing multiple signals that combination immunosuppression is not good or is not safe for some patients.

Then, I want to simply add that with monotherapy, with azathioprine or 6-MP, significant neutropenia has been seen and there have been patient deaths reported in the United States.

So, what about the challenges in monitoring? Well, with 6-MP and azathioprine, I have had patients develop rare but life-threatening leukopenia or pancytopenia requiring hospitalization or outpatient treatment, severe hepatotoxicity, pancreatitis, flulike syndromes, myalgias and arthralgias, and my practice is no different than anyone else who deals with patients with this condition. So, one must be attentive for any possible side effects that might arise.

With infliximab and adalimumab, I have had patients develop small bowel adenocarcinoma, small bowel lymphoma, optic neuritis, multiple sclerosis while on infliximab and a couple patients with MS on adalimumab. An Atlanta colleague had an 18-year-old patient develop hepatosplenic lymphoma on this combination infliximab and 6-MP, so we are already attuned to referring patients with new

problems be they neurologic or other to neurologists, hematologists, rheumatologists, and getting assistance in managing these challenging patients.

So, what about natalizumab? Well, of course, it is important to be a responsible physician, as well as an IBD specialist, and we need to take brief histories to find out if there are any new neurologic signs or symptoms, and if so, refer to an experienced neurologist.

We also need to monitor periodic blood work and follow the TOUCH prescribing program as was described.

So, this is Heather and Olivia. Olivia is now 7 months old. Heather was a patient in the Tysabri natalizumab clinical trials. I have a brief statement from her that I will have to shorten to I guess for time purposes. But she says, "I benefitted significantly from Remicade, but at the time it was not known that it was a maintenance drug," and she subsequently developed immunogenicity and intolerance. She came to me and

participated in the Tysabri clinical trial during the time when she was very symptomatic.

Within two weeks she benefited and that was during the double-blind, the placebo-controlled portion, and continued to benefit during the open-label portion. When the trial was discontinued, it was the beginning of another difficult flare that lasted for nearly another year before she found an agent that was effective. But she still says that of all of the biologics and other agents she has received, there has been no medication that has been as effective with such immediate benefit as natalizumab Tysabri.

This is Kara. She developed Crohn's when she was 22, about five years ago. She experienced a small bowel perforation at the time of her diagnosis and was in the hospital for over a month. She subsequently moved to Atlanta. She had Remicade and then was not able to continue receiving it over a period of time and went on Tysabri. Again, she received two doses of medication and immediately noted benefit. After

Elan suspended the dosing of natalizumab, she continued to feel well for three months. But since that time her condition worsened again. She went on Humara and unfortunately, it has not provided the benefit that had been hoped.

This is Joe. There were a lot of questions or comments this morning about an infusion unit, and this is our infusion unit. We may infuse three or four patients at a time with an IV pump sitting in a chair just like that, and patients generally are very comfortable.

Joe participated in a double-blind Tysabri study, benefited and continued on therapy for approximately 16 months, and he was actually on a combination of Remicade and Tysabri study. He is an engineer by training although worked for Cingular for many years, and he has graphed out beautifully--it is hard to read. I know the benefit that he personally experienced from these studies and those of you who are up front can see that although he was flaring on Remicade with 10 stools a day, he did dramatically improve with

Tysabri and then flared after the end of the Tysabri study.

With that I stop and thank you very much.

DR. SACHAR: Thank you, Dr. Wolf.

We would now like to hear from Speaker No. 2.

MS. PRESENT: Good afternoon, ladies and gentlemen. My name is Jane Present. I live in New York City. I appreciate the opportunity of being permitted to speak before you today.

I have been involved in seeking the cause, cure, and treatment of Crohn's disease since 1965. I consider myself an unofficial founder of the organization that is now known as the Crohn's and Colitis Foundation of America.

I served as National President of CCFA between 1987 and 1991, National Chairman of the Board between 1991 and 1994, and stayed on the board in a fund-raising capacity until 1999.

I stepped down from the CCFA Board in order to focus my attention on the development of the Foundation for Clinical Research in

Inflammatory Bowel Disease, which is an approved 501(c)(3).

I am currently acting in the capacity of Executive Director of this foundation, which is a family foundation, supported by grateful patients and by the pharmaceutical industry. We have no members or chapters. There is a Board of Trustees which meets annually and a medical advisory committee which consists of the top thought leaders in inflammatory bowel disease.

The mission of this foundation is twofold: to support small, interesting, provocative , peer-reviewed clinical grants to young investigators dedicated entirely to improving patient care and to educate IBD patients and their families all across the country. There is a web site - myibd.org, which is interactive and current.

The patient program is called Advances in Inflammatory Bowel Disease - New and Current Treatment."

In the spring of 1999, Centocor Pharmaceuticals asked me to put together a

patient/family education program and take it on the road. Procter and Gamble immediately joined Centocor in funding the program, which has visited over 90 cities since the fall of 1999.

It has been recognized as the gold standard by which patient education programs should be judged, and I am very proud of it.

At this time, the program is funded by eight pharmaceutical companies: Abbott Laboratories, Axcan Pharma, Elan, Procter & Gamble, Salix Pharmaceuticals, SHIRE, USA and UCB. We have also received sponsorship funding in the past from Centocor, Berlex, Prometheus, Solvay, and Protein Design Labs.

I am paid by the foundation for organizing and moderating these seminars. I receive no money directly from the pharmaceutical industry for this role. I have come here today at my own expense.

I believe that I am in the position to speak today because over the past eight years I have been face to face with several thousand IBD patients and therefore believe that I do have my

finger on the pulse of the IBD population in the United States.

Advances in IBD does not visit first tier markets, such as New York, Chicago, Los Angeles, Boston, San Francisco or Rochester, Minnesota, not due to budget restraints. But, because we have confidence that the Centers of Excellence in these cities is such that our program is not essential. We choose instead to visit second and third tier cities where we have reason to believe that IBD is not treated with the same level of expertise.

Nothing quite reaches the level of anguish than to walk into a room and see patients who are clearly still being treated with cortisone and prednisone. Each time we visit I ask the audience to raise their hands if they have ever been on steroids and practically every hand in the room goes up. We even offer a free heel scan to patients and the score of that scan indicates that the patients should consult their physicians about bone loss.

The point I wish to share with you today

is that back in 1965, we had nothing to offer the patients other than steroids or azulfidine. A few years later, the immune modulators were offered, but the medical community took years before it accepted the use of 6-MP and Immuran as therapy.

In the late '80s, the various 5ASA products were approved , and finally we had a few more options in the armamentarium to fight Crohn's disease.

Centocor released Remicade in 1998 and the medical community accepted it almost immediately, perhaps in retrospect, too quickly, since we have encountered patients who have developed an allergy or an immunity to it, as well as an increased evidence of infection.

Now we have a few more options. We looked forward to the approval of Cimzoa, Humira, and Tysabri inasmuch as they appeared to promise patients an easier delivery system and possibly even more effective treatment.

Patients who received Tysabri were thrilled with the results and heartbroken when the

drug was withdrawn because of the potential toxicity.

I do congratulate Elan, however, on the wisdom of withdrawing it until the associated problems were resolved.

Needless to say, in my position as a patient advocate and educator, I have followed this story through academic and press releases and was relieved to learn that the FDA has agreed to revisit its release.

As science continues to decode DNA and more genes associated with IBD are identified, physicians will be able to tailor medications specific to each patient's case. That is a thrilling prospect. We more weapons we have in the form of effectiveness drugs, such as Tysabri, to improve and protect the quality of life for our patients, the easier my job.

We need to be able to offer Tysabri to the general IBD population to ascertain both its efficacy as well as any possible toxicity. Denying them this drug is to deny them the quality of the

normal life we hope they will achieve.

Thank you for your time and attention.

DR. SACHAR: Thank you for your remarks, Mrs. Present.

We would now like to hear from Speaker No. 3.

MR. SANDS: Good afternoon. My name is Bruce Sands. I am a gastroenterologist at Massachusetts General Hospital in Boston. I am also Medical Co-Director of the MGH Crohn's and Colitis Center, and Associate Professor of Medicine at Harvard Medical School.

I would like to focus in my allotted time on what I believe is a largely unexplored yet critical issue in Crohn's disease, namely, the question of what risks are patients willing to accept in the treatment of their illness.

I will start, as I should, by disclosing that I have been a consultant to and have received research funding from the corporate entities that you see listed here including Biogen Idec and Elan. But it is important to understand why I choose to

work with these entities in investigating new therapies, and that is because there continues to be a large unmet need in the treatment of patients with Crohn's disease.

In addition, I have traveled here at my own expense to present what I feel is my own opinion.

To date, there is no therapy or combination of therapies that has been effective for all patients with Crohn's disease. Anti-TNF antibodies have been an important advance in the treatment of Crohn's disease, but still prove ineffective in about 1 in 3 patients. In addition, all effective therapies for inflammatory bowel disease have rare but potentially serious adverse effects.

It is my opinion that strong consideration needs to be given to the preferences of patients themselves in weighing these risks and benefits.

When natalizumab was withdrawn from clinical trials in Crohn's disease, many of my patients, who had previously not responded to

anti-TNF agents, relapsed to their previous state of chronic active disease and were again unresponsive to all available agents.

To my surprise, actually, despite clear explanations of the newly recognized risk of PML, many stated that they would wish to return to treatment with natalizumab if they could.

Accordingly, we entered into a collaboration with the pharmacoeconomics group of Elan and researchers at the Research Triangle Institute, which is a nonprofit research institute. Our objective was to estimate the maximum risk of death or disability that would be acceptable to patients with Crohn's disease for specific clinical benefits.

We used the technique of conjoint analysis considered by many to be the most valid and reliable technique available for quantifying patient preferences.

If you will permit, I will provide a brief introduction to conjoint analysis. This technique has a strong basis in mathematical psychology and

it is being widely used in matters of health care policy. It is based on what I feel is the sensible premise that any good or service including medical therapy can be described by its key attributes, and these attributes are what determine the extent to which an individual values this treatment.

Finally, the technique can be used to show how people are willing to trade between characteristics and to estimate the relative importance of different attributes.

Accordingly, we designed a well-validated questionnaire that was thought to approximate treatment decisions that would be typical for Crohn's patients to make. We included items regarding demographics and the Crohn's Disease Activity Index, as well as the short form of the IBDQ, to understand what our patient population consisted of.

More importantly, we had descriptions of the levels of clinical benefit and treatment attributes of hypothetical treatments. We also had descriptions of important risks and the patients

were asked to undergo benefit-risk decisions in the format that I will display for you in just a moment.

The treatment attributes that we considered to be important, in addition to what the drug did for disease activity, included what occurred in preventing the complications of the disease, whether it prevented all or some or had no effect in preventing complications, times between flare-ups, the need to take oral steroids essentially steroid-sparing effect, and importantly, the effect on the 10-year risks due to serious adverse events, and the ones that we considered were serious infection, PML, and lymphoma.

These risks ranged between 2 to as high as 5 percent. As would happen in a clinical setting, we provided patients with brief, succinct, but realistic appraisals of what these serious adverse events consisted of, and we included this description that you see here of severe infection, this description of PML, and this description of

lymphoma.

I apologize that you can't really see the bottom of this slide. For PML, we state that studies suggest that some medicines for Crohn's disease increase your chance of getting PML, progressive multifocal leukoencephalopathy, PML is a rare brain infection. The symptoms of PML are series and may include the inability to think clearly, paralysis, blindness, and coma. PML can result in death or serious disability.

So, a brief but to the point description of what the patient might expect. In addition, we used best practices to represent the risks visually to patients as patients often have trouble understanding numerical quantifications of risk. So you see here grids representing a 0.5 percent risk of death, a 2 percent risk of death or a 5 percent risk of death with the red boxes representing the risk of death.

A second graphical display provided comparative risks to what a patient who would be 50 years old would expect of dying from over the next

10 years, either from all causes or from other anticipated things such as cancer, heart attack, or accident, and then we positioned the risks that we were asking them to consider along this risk line.

Here is an example of the kind of tradeoff task that the patients were engaged in. They were considering the panel of the treatment attributes comparing treatment A to treatment B, and looking at each of these attributes.

So, these attributes were varied in a series of iterative panels and each patient was presented with 10 of these panels and compelled to make a decision about what they would choose for the preferred treatment.

These patients all had a diagnosis of Crohn's disease. They were all adult patients. They were all residents of the United States, and they had provided informed consent. Over 300 were obtained through an Internet panel self-designated as having Crohn's disease, 140 were patients from practices who had participated in the natalizumab trials, and nearly 100 had experienced treatment

with natalizumab in the context of clinical trials.

All patients accessed the survey via the Internet, and the primary endpoints were the relative contribution of treatment efficacy and risk attributes of patient preferences.

The mean maximum acceptable annual risk or MAR for clinically relevant treatment efficacy attributes was also looked at and the percent of patients accepting various levels of risk for clinically relevant treatment efficacy attributes.

Here is the first finding of what we studied. Essentially, the effect of a drug on symptom severity was by far the most important attribute of the drug. Second in importance was the risk of PML and followed very closely by lymphoma and serious infection risk.

In addition, if you look at the results of the mean maximum acceptable risk for clinically relevant benefits, you would find that these risks vary depending on the promise of benefit from these specific therapy. However,in all cases, the patients were willing to accept a mean maximum

acceptable risk that was somewhat higher than what we currently understand to be the upper limit of possible risk of PML.

So, we see for patients who might go from severe disease to remission, the risk is as high as 0.7 percent acceptance of mortality over a year or risk of PML. In addition, the risk estimates did not vary very much according to which panel we looked at, whether it was the Internet panel, the naive clinical panel, natalizumab naive, that is, or the natalizumab experienced panel.

Finally, if you look at this graphic display, you will see that the majority, roughly two-thirds of patients or somewhat more were accepting of all levels of risk consistent with what we understand to be the risk of PML for various levels of benefit from treatment that was promised.

So, these MAR findings are similar across all the patient panels. Treatment decisions were primarily driven by the desire for improvements in daily symptom severity.

Crohn's patients are willing to accept significant risks for clinically relevant therapeutic benefits, and the great majority of patients would accept the observed risks in order to achieve clinically relevant therapeutic benefits.

I would like to acknowledge the work of others at RTI, Reed Johnson and Semra Ozmer at Elan, Steve Haas, Jeff White, and David Miller and my colleague Cory Siegel at Dartmouth Hitchcock, and I will conclude by saying that it is my personal opinion that patients are indeed willing to take a surprising amount of risk in order to achieve clinical benefits and that in my view, it is actually an ethical decision that you are faced with if you choose to deny this potentially useful treatment to patients.

I thank you for your attention.

DR. SACHAR: Thank you, Dr. Sands, for your presentation of some objective quantitative data on patients' attitudes.

Speaker No. 4.

DR. HANAUER: Good afternoon. Before my slides, I keep getting seconds until my slides come up, right? I am Dr. Steve Hanauer from the University of Chicago.

Dr. Sachar, members of the committees, I want to thank you for allowing me to present today on the public's behalf, and I am indeed speaking on behalf of myself.

I am currently the Chief of Gastroenterology at the University of Chicago and I have a large patient practice in inflammatory bowel disease at the University of Chicago that encompasses about 6,000 patients in our IBD database that we have seen over the past 20 years, and I continue to see a significant number of patients, approximately 70 to 100 inflammatory bowel disease patients on a weekly basis.

I do have some potential conflicts of interest. I have worked as a consultant and a clinical researcher for numerous pharmaceuticals, both biologic and conventional therapies. But I am neither being paid, supported, or reimbursed by

Elan for being here today.

The purpose of my discussion today is to talk about the disease, the patients, our current therapies and therapeutic gaps. You shouldn't be counting me because I don't have my slides up yet, so give me another -- they have taken 45 seconds off. I feel like soccer. You should be putting time back on the clock for me, or football, depending on your background.

What I am going to tell you is that Crohn's is a lousy disease to have and the estimates that Doug gave you of the number of patients in the United States, and that you have heard today are somewhere between a million and 2 million patients with ulcerative colitis and Crohn's disease divided about 50-50.

You also have to understand that these are diseases of young individuals with a peak onset in the second or third decade of life, and these are progressive diseases. Despite our medical therapy, we have not changed the natural history of Crohn disease over the past several decades, which is a

near inevitable progress towards the need for surgery either resection or colectomy.

So, again, these are my credentials. I have a large patient practice. I have had a number of positions in the Crohn's and Colitis Foundation, the American Gastroenterological Association, the American College of Gastroenterology, and by the way, I have both been a member and have chaired the FDA Advisory Panel for GI Drugs. These are my listed potential conflicts of interest.

Crohn's disease, as mentioned, affects approximately a million patients in the United States, the exact estimates remain somewhat fuzzy. This is, as I have already said, a progressive disease with transmural complications including stricture formation, abscesses, and fistula.

There is a wide spectrum of symptoms of Crohn's disease that depend on the disease location within the bowel and also the severity within that location and local complications, such as strictures, abscesses, or fistula.

It is difficult to quantify Crohn's

disease. We don't have real good measures of the inflammatory activity, and one of the problems that we have in measuring these diseases that is dissimilar from rheumatoid arthritis or multiple sclerosis is that they have, the rheumatologists, the neurologists have a good aspect of structural damage.

You can measure white matter, lesions in MS, you can measure joint destruction in rheumatoid arthritis and quantify both. We do not have good quantification because of the inability to measure structural damage and to quantify it through radiographic or other imaging studies of the gastrointestinal tract.

Crohn's disease is quite a heterogeneous disease and there are no two patients with Crohn's disease who are exactly alike, and that heterogeneity is related we believe to both genetic underpinnings, as well as environment exposures that are different in individual patients, and we would like to have genetic serum or other markers that predict a patient's response. But at the

moment we do not have biomarkers that will predict an individual patient's response.

You have discussed a lot about C-reactive protein today, and, of course, that has to be looked at as a measure of inflammation, more than as an individual predictor of response.

Although the course in Crohn's disease is variable amongst patients, depending upon different treatment regimens, as I mentioned, there is a progression from inflammation to transmural complications including stricturing and fistulization, which inevitably leads to surgery in patients with Crohn's disease.

This is a population series from Scandinavia where 80 percent of patient with Crohn's disease over 20 years required at least one surgical resection, and Crohn's disease recurs at the anastomotic site in over 75 percent of patients, leading to 50 percent of patients who have had one surgery requiring a second operation, and that goes on and on.

Now, who are these patients? What is the

Crohn's disease Activity Index and how does that really describe a patient? Well, this would be a typical patient who is entered into the natalizumab trials. The average CDAI was about 300. Accordingly, that would be a patient who had five bowel movements, five diarrheal stools daily with daily abdominal pain, poor well-being, and for perhaps a perianal fistula.

On the other end of the extreme, in patient entered into these trials with more severe disease, would be 10 liquid bowel movements a day, moderate pain on a daily basis, the presence of an abdominal mass, fistula, anemia, and weight loss. This would be a patient with more severe disease.

As we have heard the description according to the American Gastroenterologic Association, a patient with moderate to severed disease is either a non-responder to first-line agents or continues to present with fever, significant weight loss, and abdominal pain, tenderness, intermittent nausea and vomiting, and anemia, and on the other extreme, high fevers, persistent obstructive symptoms,

rebound tenderness, muscle wasting, significant abscesses, perhaps a toxic megacolon, et cetera.

These are bad patients who are entered into the clinical trials. Along those lines, when you compare the quality of life in patients with moderate to severe Crohn's disease, and in the white are patients who were entered into the ENCORE study with natalizumab, compared to the general population, patients with chronic renal insufficiency, rheumatoid arthritis. It is hard to see, but, in black, patient entered into the AFFIRM study with multiple sclerosis, the overall quality of life on almost every parameter was worse in patients with moderate to severe Crohn's disease than any of these other diseases including multiple sclerosis.

Our therapies you have heard about. We have algorithm for mild to moderate to severe disease and refractory disease. But what are the outcomes? In patients with mild to moderate disease, about 50 percent of patients will respond to conventional agents or budesonide.

More moderate to severe disease, about 70 to 80 percent of patients will respond to a course of corticosteroids, but I have likened this to the tipping point in patients with Crohn's disease.

Once a patient is started on steroids, less than a third are well at the end of the year. We can treat these patients with immunomodulators or biologic therapies, but we continue to have progression towards surgery once patients have require corticosteroids. This is the therapeutic gap with anti-TNF therapy, and it is similar for both infliximab an adalimumab.

If you look on the lefthand panel, the percent of patients who have been into remission, approximately 40 percent short term. These are patients similar to the natalizumab trials of patients failing conventional agents and of those patients, of that 41 percent who respond initially, about 40 percent can be maintained long term with a number needed to treat of 5 patients to maintain remissions with maintenance therapy with infliximab.

We do this despite the consequences of therapy with corticosteroids, which are region and well known to all of the panel members. As far as side effects and risk with azathioprine and 6-MP, I will only point out that 3- to 4-fold increased risk of lymphomas in patients treated in this meta-analysis and, as you have seen, these patients are not treated with a single agent but will multiple agents, and the risk of infections are increased, opportunistic infections, with each, but also compounded by the numerous medications that patients are taking, making it difficult to assess the ultimate risk.

There is also an additional risk of malignancy that has been confirmed in meta-analysis, lymphomas, with patients treated with the anti-TNF agents as has recently been published in the Journal of the American Medical Association.

Now, as Bruce Sands has already told you, these patients with these severe diseases and severe consequences aren't willing to take risks,

and based on a standard gamble technique and utility scores in Crohn's disease, the patients with chronic resistant disease, these are the patients that we are talking about who are receiving natalizumab in the clinical trials and ultimately would receive it, are willing to gamble 20 percent of their normal life to achieve remission and achieve a normal quality of life.

So, we have seen that these patients are willing to take risks.

So, ultimately, where do I see this falling into our armamentarium? I see this for patients with persisting symptoms that are of moderate to severe severity, confirmed by the presence of active inflammation either by elevated C-reactive protein or by the presence of endoscopic lesions who are not responding to conventional or the anti-tnf biologics.

Similar to what we are seeing with multiple sclerosis,I would envision that the vast majority of prescribers are likely to be experienced clinicians in inflammatory bowel

disease centers or tertiary medical centers with great experience in treating these patients with other biologic and potentially harmful conventional agents and with the ability to do the necessary monitoring.

Thank you.

DR. SACHAR: That was a helpful perspective.

We will now turn the microphone to Speaker No. 5.

MS. CASANOVA: Good afternoon. My name is Lisa Casanova. I own no stock in Biogen Idec or Elan Pharmaceuticals. My trip here was paid for with my credit care.

There has been a lot of talk at this meeting about the patient, the Crohn's patient. I am 29 years old and I have had Crohn's disease since I was 7. I was a participant in the Phase III clinical trial and open label trial was natalizumab at the University of North Carolina, Chapel Hill. I am here to tell you to bring Tysabri back on the market for Crohn's disease

patients.

When I enrolled in the trial, it was because I was looking for options. I had a very inflamed stricture and my colon was making me very sick. I knew that I was going to need surgery to remove it. That was inevitable, but I was looking for choices to allow me to delay that.

When I enrolled in the clinical trial, it was a wonderful drug. I started to get better almost immediately. I know objectively that I was getting better, because my gastroenterologist would examine the stricture, I knew that it was getting less inflamed, and I felt better, my quality of life improved.

I was able to do things like get through an entire day of work without trip after trip to the bathroom. Most people take that for granted and don't know what it is like when you are just trying to get through the workday to have to drop everything and run off to the bathroom because, of course, you have a mental map in your head of where every single one is, and hope that it is available,

so that you have a place to wait out the pain and the nausea just so that you can go back to work and get through the day.

Thanks to Tysabri, I was able to get through the day, I was able to work, I was able to make significant progress toward my Ph.D., and do the things I wanted to do like be able to sit through an entire class lecture, to be able to play a string instrument because I could last through a whole concert.

When Tysabri was taken off the market, I couldn't have it anymore, I started to get worse again, I was getting sicker, I was in pain, the inflammation was getting worse, and I knew it was time for surgery.

So, I went under the knife in November of last year. I had a sigmoidcolectomy, and I ended up with an anastomotic leak and an abdominal abscess that took six months to heal. I was let out of the hospital with a pick line and an abdominal drain that drained the contents of my intestine into a little container that I carried