neurological and other medical conditions.

For risk assessment, the goal is to determine the incidence and risk factors for PML and serious opportunistic infections, and to assess the long-term safety in clinical practice.

The system by which we do this involves both labeling and an extensive risk minimization system that I will describe for you in this program.

[Slide.]

The current Tysabri labeling for MS contains a boxed warning indicating that Tysabri increases the risk of PML and that PML may occur with Tysabri monotherapy.

It also provides guidance to health care professionals to be alert to any signs or symptoms that may be suggestive of PML.

In those cases, dosing should be suspended immediately at the first signs or symptoms of PML, and evaluation should include brain MRI and CSF for JCV DNA.

In order to reduce the risk of PML, there

is a warning against use of Tysabri in patients who are immunocompromised or with concurrent use of immunosuppressant or immunomodulatory agents.

In the next few slides I am going to describe the Tysabri Risk Minimization System that helps to support this labeling.

[Slide.]

The Tysabri Risk Minimization System begins with a mandatory enrollment of all patients and prescribers into the TOUCH Prescribing Program.

At the time of enrollment, there is a mandatory enrollment form that obtains a series of information that I am going to describe in the next slide, and this form must be provided to the sponsor.

We maintain a controlled centralized distribution process that tracks the location and number of all vials of Tysabri and we provide Tysabri only to registered infusion centers. These infusion centers are trained by our specialized personnel on the risks and appropriate use of Tysabri, and they attest to providing Tysabri only

to patients enrolled in the TOUCH Prescribing Program and only at a registered infusion center.

Through this process, we have the ability to provide a series of educational tools on the risks and appropriate use of Tysabri to neurologists, infusion nurses, and MS patients.

In the next slide, I am going to go into some detail about the different components of this particular program.

[Slide.]

I mentioned that at the beginning of the process, there is a patient-prescriber acknowledgment of various activities on the enrollment form. This records the informed benefit-risk discussion between the patient and the physician, and the decision before the start of therapy.

The physician will sign that they are aware of PML risk, that they have discussed the risk and benefits of Tysabri with their patient and that the patient is an appropriate patient for Tysabri.

The patient will sign that they have read the medication guide on Tysabri, that they have discussed the risks and benefits of this drug with their physician, and they will report any new or worsening medical conditions to their physician immediately.

[Slide.]

There are some additional requirements for the prescriber, as well. They must report any PML, serious opportunistic infection or death to us for further analysis and follow-up. They must complete a Patient Reauthorization Questionnaire on every patients every 6 months and submit it to us.

On this questionnaire, they will provide information about the patient's current vital status, whether or not they have had PML or any other serious opportunistic infection. They will also describe any use of concurrent immunomodulatory or immunosuppressive medication and ultimately, provide an indication whether or not the patient should be reauthorized for dosing for the next six months.

In addition to this, there is a discontinuation questionnaire that contains the same kind of information that must be provided within 6 months of a patient's last dose. This information is provided to us and we screen this information and follow up with the prescriber if we see any issues that relate to the compliance with a requirement of the TOUCH Prescribing program.

[Slide.]

So, now I described what the prescribers have to do. Now, I am going to talk about what happens at the infusion center.

As I mentioned, infusion centers must be trained prior to registration, and Tysabri can only be used in a registered infusion center, and dosing can only occur to patients who are enrolled in the TOUCH prescribing program.

Prior to each dose for each patient, an infusion nurse at an infusion site must provide the patient a medication guide and complete a pre-infusion patient check list. In my next slide I will describe the pre-infusion patient check

list.

[Slide.]

This is a questionnaire that is administered by the infusion nurse prior to each infusion and it has two major components, first of all, to screen for new or worsening medical conditions, and secondly, to screen for the use of immunomodulatory or immunosuppressive medications to help reinforce the use of Tysabri as a monotherapy.

If either of these type of conditions are reported, then the infusion nurse would need to withhold dosing and contact the physician immediately.

We collect all the information and there is a real time submission of these pre-infusion patient checklists to us. Usually, we get them within about a day.

[Slide.]

That was the risk minimization process, and I mentioned that we have two different components to this program. We also have a risk

assessment component, as well, and this part is a very comprehensive program.

Basically, all patients who are enrolled in the TOUCH prescribing program also enroll in the TOUCH prescribing program patient registry. This is a key component of our program and has the goal of determining the incidence and risk factors for PML and other serious opportunistic infections in patients receiving Tysabri.

As I mentioned, it is a follow-up of all patients for the entire duration of their therapy and the data comes from physicians who report PML, serious opportunistic infection or death to us for analysis and follow-up as part of this program.

We do additional follow-up of patient deaths through the National Death Index and we collect death certificates on all deaths to determine the outcome.

We believe this process provides a safety surveillance and tracking of all patient that far exceeds routine pharmacovigilance.

[Slide.]

I have described for you now the MS plan. I have described the elements of that, maintain the risk minimization process, and I have described the basic major element of the risk assessment process.

Now, I am going to show you how well this programs is working in MS.

[Slide.]

As part of our program, we also maintain a process of evaluating the different elements to see how well they are working. This includes an analysis of both the information on patient safety and also compliance data from the various elements of the program itself.

We share this data with the FDA every three months and, if needed, this allows us to make changes very quickly to both the label and also to the risk minimization tools to either improve them or develop new ones to ensure that the program continues to meet its goals.

[Slide.]

Since the relaunch of Tysabri in June

2006, and up until May 2007, there have been approximately 11,500 patients on Tysabri therapy worldwide. In the U.S. we have had about 11,000 patients enrolled in the TOUCH prescribing program, and about 8,300 patients have been dosed with a median of four doses. We have had approximately 1,750 physicians who have enrolled patients and about the same number of infusion sites have been trained or authorized.

In Europe, we have had approximately 3,200 dosed to date and there are about 1,000 patients on Tysabri in clinical trials for MS. If you take all the exposure periods, all the clinical trials in both periods of post-marketing exposure, we have had about 21,000 patients who have been exposed to Tysabri.

Now, this is a fairly large population at this stage. But the duration of exposure has been fairly limited, and this is one of the reasons why we have a series of risk assessment activities to understand the drug use over a long term period of time.

[Slide.]

I mentioned that we have a process that looks at how well individuals are complying with the requirements of the TOUCH prescribing program. I am happy to report that we have seen excellent compliance with the TOUCH prescribing program in MS.

First of all, we know that patients and prescribers are being informed about the risks because essentially, all patients are enrolled at the time of an infusion and go through the process of the benefit-risk discussion with their physician.

We know that the drug is being prescribed as monotherapy according to the label, because over 96 percent of patients had no evidence of concurrent immunomodulatory or immunosuppressive therapy use.

We know that the drug is being shipped only to registered infusion centers because of about the 10,000 or so drug shipments that we have expected, they have all been sent to registered

infusion centers.

Finally, and perhaps most importantly, we know that the process facilitates clinical vigilance and use in appropriate patients. Essentially, all of the expected pre-infusion patient check lists out of the 39,000 infusions that have been given were received, out of those, about 8 percent of infusions were delayed due to information that was provided by the patient to the infusion nurse prior to the infusion. Ultimately, about 0.5 percent of infusions were not given following contact of the physician by the infusion nurse.

So, what this means is that the program itself is working very well according to the requirements of the program. What we know also is that some patients are having their therapy delayed and ultimately the therapy is not given because of considerations at the time of the infusion. So, it's a process that seems to be working very well.

I have showed you how well people are complying with the various aspects of the program.

Now, I will give you some information that we have about what the knowledge is of the different requirements of the program.

[Slide.]

We maintain a series of routine surveys that we have started of the people who are enrolled in the program. This is the healthcare providers, the infusion nurses and the doctors. This is the first of our surveys and we found that there is a high level of awareness of the various attributes of the program.

We know that there is a high level of awareness of PML risk. Prescribers know that there is an increased risk of PML associated with the use of Tysabri, and we know that the key components of the TOUCH program are well understood. Nurses know that Tysabri should be administered only to enrolled patients, and they know to contact the prescriber if a patient reports new or worsening medical problems.

Prescribers also know that they need to report PML immediately. So, that is the various

aspects of compliance with the program requirements. Now, I am going to talk about the safety profile a little bit. Gordon talked about this in a very extensive fashion, but the TOUCH prescribing program helps us to understand this, as well.

[Slide.]

As he mentioned, the post-marketing safety profile is consistent with that which we observed in the MS clinical trials. There have been no new cases of PML. We have observed two serious opportunistic infections. Those were the herpes cases that he mentioned. We also noticed an increased rate of hypersensitivity in patients who have experienced a gap in Tysabri therapy.

This ultimately has resulted in a labeling change that is currently being implemented and it was based on data from the TOUCH prescribing program. What this means is that this labeling change occurred in a very timely fashion. It probably wouldn't have been possible without the TOUCH prescribing program.

I have given to you now the MS program and I have shown you how well it is working. Now I am going to show you why we believe that it can be adapted to have similar effect in the Crohn's disease population.

[Slide.]

Here are the key changes to the Tysabri riskMAP for Crohn's disease. In the label, there will be a new recommendation that Tysabri should be discontinued within three months if there is no response to the drug. There will also be a recommendation that chronic corticosteroid use should be eliminated within 6 months of starting Tysabri or else Tysabri therapy should be stopped.

We will develop a new training and communication program. There will be CD-specific training of infusion sites and education of patients and gastroenterologists on the risks and features of PML.

We will continue to maintain a comprehensive risk assessment process. The TOUCH patient prescribing registry that I mentioned

earlier for MS will continue to enroll all Crohn's disease patients, and there will also be an additional observational study in Crohn's disease like we are currently running in MS that I will describe in the next few slides.

[Slide.]

Now, I am going to describe some aspects of CD care which help us to understand how this program will be adaptable for the Crohn's disease population. We know that monitoring for PML in the Crohn's disease setting is going to be different.

We know that Crohn's disease patients generally have normal neurological function, and the symptoms that might be suggestive of PML, such as cognitive or behavior changes, visual dysfunction, and unilateral motor weaknesses would be readily apparent to CD patients and their caregivers, because they are clearly unrelated to the underlying disease, and feel that this would help to prompt early contract for evaluation and early referral to a neurologist for further evaluation.

Our educational components of the program would help to build upon this particular aspect of Crohn's disease care.

[Slide.]

In addition to this feature, there are a few other features of Crohn's disease that are specifically related to risk-management and give us the confidence that the MS plan can be adapted quite successfully for the Crohn's disease population.

We expect Tysabri to be prescribed by gastroenterologists who specialize in IBD and thus would be able to recognize the appropriate patients. We know that gastroenterologists administer immunosuppressive therapies and are familiar with severe side effects, such as opportunistic infections and CNS demyelination.

As a result, they routinely refer to specialty physicians for further evaluation. As a result, our educational plan will build on this practice pattern and emphasize that gastroenterologists should have no expectation to

serve a role as a PML diagnostician.

Rather, they should have a very low threshold for referral and evaluation of their patients by a neurologist.

We also know that CD patients show a willingness to weigh treatment benefits and risks. In one study that we have conducted, we found that CD patients would be willing to accept the level of risk of PML that we have observed to obtain the level of benefit of Tysabri that we have observed in clinical trials.

Finally, we know that there will continue to be regular contact with health care professionals due to the monthly infusions that will be provided as part of Crohn's disease therapy for Tysabri.

[Slide.]

So, as a result, the major features of the risk minimization program for Crohn's disease will remain the same. There will continue to be mandatory registration of all prescribers and patients.

There will continue to be a controlled, centralized distribution process. The drug will only be allowed to be used in registered infusion centers, and we will still require real time submission of the monthly pre-infusion patient checklist.

We will continue to maintain the process of physician reauthorization and dosing of every 6 months. This process will require some minimal changes to the forms that are used for each of these, but this should be easily accomplished.

[Slide.]

So, that was the risk minimization changes. Now, as I mentioned earlier, I am going to talk a little bit about the risk assessment program. As I said, we will continue to maintain the TOUCH patient prescribing registry for Crohn's disease in the same way that we have done in MS.

Also, in MS, we run a 5,000-patient observational cohort study, and we will develop a similar type of observational cohort study in Crohn's disease. The purpose of this study is to

evaluate the use of Tysabri in long-term safety and clinical practice setting.

It is a voluntary study and is based on a subset of patients from the TOUCH patient registry. It has the goal of collecting all serious adverse events and assessing the risk of serious infections and malignancies. It will also seek to investigate potential signals of unanticipated adverse events.

It is a large study and patients will be followed for about five years and it is powered to detect rare events.

I have described to you the changes that we expect
to make in the plan.

[Slide.]

So, in summary, I hope I have been able to convince you that we have a successful risk-management plan in place for MS. When we adapt this plan for use in Crohn's disease, we are going to be using essentially the same goals and methods for both indications.

We are going to continue our ongoing

vigilance and our ongoing assessment of PML risk in overall safety, and we will do our best to ensure that we evaluate the plan so that it continues to work well and make changes if necessary.

As a result, we believe that this plan can be successfully adapted to ensure appropriate use of Tysabri in Crohn's disease patients.

Thank you.

Now, I will pass it back to Professor Sandborn to talk about Tysabri in the context of Crohn's disease therapy.

Clinical Perspective

DR. SANDBORN: Dr. Sachar, by my watch we have about 3 minutes to our 90 minutes. I will be finished in 5, so we will be very close.

[Slide.]

I want to just really now refocus to the clinical questions that the committee has to address today. I think there are three really and have to do with efficacy, finding the right patients and can gastroenterologists as a specialty handle this drug given the potential side effects.

Efficacy, Dr. Jones has gone through in detail and I won't belabor it except to say that I think there is robust evidence of efficacy for both induction and for maintenance in the broad patient population and in all of the individual subgroup analyses.

The point that I would like to make about efficacy is that we have an advantage over the neurologist in the way we will practice with this drug if it becomes available to us. With neurology, you are waiting for patients to relapse and it can take a year or so before you can tell whether the patient is benefiting from the chronic natalizumab infusions.

With Crohn's disease, as you just heard, our intention would be to give three doses at zero, 4, and 8 weeks, and by 12 weeks, if the patient is not improved, they are finished with natalizumab therapy. So, it is a short-term intervention to pick out the responders.

Once you pick the responders, those patients have a high likelihood of benefiting. Dr.

Jones told you that the median patient actually is still in clinical response at a year, having responded initially.

I would point out also that the absolute response rate is approaching 60 percent, so there is a substantial fraction of patients that benefit to induction therapy and those that don't, go off the drug. That is I think a real advantage for this disease group and this specialty for helping to tip in favor of the benefit for the risk-benefit consideration.

The second issue is what patient subgroup should be treated. If it weren't for PML, really, I think we would be looking at a broad indication of moderate to severe Crohn's disease unresponsive to conventional therapy. It would look a bit like the anti-TNF drugs.

From where I sit as a practicing clinician, I think the PML issues tips that a bit, and I would really look at this in my practice for patients that had failed an immunosuppressive. I usually use azathioprine and an anti-TNF agent. I

think that that is where the real unmet need is. There are subgroup analyses to show efficacy as well as the broad demonstration of efficacy with the drug. To me, that is where the benefit outweighs the risk.

Now, just how tightly you box that in if you decide to go that route, you want to think about. There are some other patients where there are relative or absolute contraindications to anti-TNF therapy; for instance, patients who have congestive heart failure might be otherwise stable outpatients, patients who have multiple sclerosis, patients who have experienced anti-TNF related demyelination. There are a variety of other patients that clinical judgment might suggest this would be a good treatment for.

It is important to put a face, I think, on the sort of patient you might treat. I saw someone in clinic last week--it's a 22-year-old woman who was diagnosed with Crohn's disease at age 16. She has had one surgery with 40 cm of terminal ileum and the right colon removed, and she has a

recurrence and now has another 40 or 50 cm of small bowel inflamed. She has got osteoporosis from prolonged steroid use. She didn't respond to the anti-TNF agent, so she was a primary nonresponder, and she got pancreatitis from azathioprine. I have nothing to offer this patient but more surgery, and at 22, we know that there are a number of surgeries to go.

So, she needs some other therapy. I have another 59-year-old patient who has been through everything. She actually only has 80 cm of small bowel left. She is TPN- dependent and her remaining 80 cm are inflamed. If Tysabri isn't approved, her next stop is small bowel transplantation, and we are preparing for that possibility.

Those are some of the types of patients that would benefit from the availability of this drug.

The last issue is can gastroenterologists handle this. I would point out that we are first internists, and so all of us were trained in the

era where we took care of patients with HIV, we have worked on oncology wards, and dealt with patients who get combination chemotherapy, and we have dealt with organ transplantation. Specifically, in gastroenterology training, we get liver transplantation therapy where patients are getting multidrug immunosuppression.

We also have nine years of experience with infliximab. We are used to giving infusions. We are used to holding infusions for patients where there is a contraindication to the infusion. We are used to dealing with opportunistic infections and assembling multidisciplinary teams.

In the last month in my practice, I was just thinking back on it a few minutes ago, I have made a diagnosis of candida esophagitis, I have had a patient with azathioprine-related leukopenia and disseminated CMV that was hospitalized for fever, and we had a case that is getting a series of drugs together that I think ultimately is going to be pulmonary Sporothrix. We can pull together the teams to make the diagnosis and we can treat the

patients, and these patients are all successfully being treated.

So, I hope that you will see, as a specialty, we need this drug, our patients need this drug. There is an important unmet need, and I think we can handle the treatment with the TOUCH program.

With that, I will stop. Thank you.

DR. SACHAR: I would like to thank the sponsors for a very clear, concise, and well organized presentation.

Their presentation has essentially five elements, features and needs of Crohn's disease patients, efficacy for induction and maintenance of remission, safety, and the risk-management plan. I guess that comes out to four major components.

Questions to the Sponsor

DR. SACHAR: I think in the interests of clear and focused questions to the sponsor, it would be useful, instead of sort of a buckshot approach to questions, if we called for questions sequentially in each of these categories.

What I would like to ask first is whether members of the panel do have any questions for Dr. Sandborn pertaining to the background, the clinical perspectives, clinical needs, clinical presentations, course, prognosis, natural history of Crohn's disease, and, if so, raise your hand and we will call on you.

Dr. Platt.

DR. PLATT: Thanks for the presentation.

Can you give us a sense of, given the waxing and waning course of the condition, would it be realistic to think about a management program that would involve periodic discontinuation to observe ability to do well without maintenance therapy?

DR. FRANCIS: Before Dr. Sandborn answers, certainly we don't have any data on intermittent therapy in terms of either its efficacy or safety profile, so we don't have any data from which to answer that question. But I think Dr. Sandborn could certainly comment on it conceptually.

DR. SANDBORN: Again, we are focused on

moderate to severe Crohn's disease, so it is not all the patients with Crohn's disease. We did the experiment of trying to discontinue in the 303 trial, and the preponderance of patients relapsed over the course of a year.

We have had exactly that same experience with trials where patients discontinued infliximab and where patients discontinued adalimumab. So, with all of the biologics in moderate to severe disease category, it has been sort of a clinical failure strategy to discontinue.

If that was all it was, maybe that would be okay. But the other problem is immunogenicity. So I think you heard from Dr. Maier that we are seeing now, in the TOUCH program, the patients who got Tysabri and had to have it interrupted during the period that it was unavailable and have been reinfused have higher rate of infusion reactions.

With the anti-TNF drugs, we know that those patients who have had a drug holiday and you come back to the biologic therapy are more likely to have loss of efficacy. So, between the higher

rate of infusion reactions, the loss of efficacy when you try to reintroduce the drug, and the loss of efficacy when you first stop the drug, I think for all those reasons, an episodic or intermittent treatment strategy just won't work in this patient group with the biologic.

Dr. Sachar, I guess has a lot of experience with this. He might want to comment himself.

DR. SACHAR: No. I think you have covered those two points well. I think Dr. Couch had a question.

DR. COUCH: MS is a disease that is highly variable in its course but, nevertheless, pretty much relentlessly progressive over a longer period of time.

While there is data showing that at 20 years, about 25 percent of the patients may be doing relatively well, another 25 percent have moderate to minor disability and the other 50 percent are doing poorly.

Between 20 and 30 years, a lot of the

patients that have been doing fairly well start falling off the curve and then really start doing fairly badly. So there is an overall significant increase in mortality.

Does Crohn's disease follow the same--is it a relentlessly progressive disease over 20 to 30 or 40 year time span, and could this treatment be used for 20 years or 30 years?

DR. FRANCIS: I think again I will have to turn it over to Dr. Sandborn for the clinical perspective. I think in terms of whether the drug could be used for 20 years or not, we don't know. The drug has only been used in patients upwards of three to four years so far, but Dr. Sandborn can speak to that.

DR. SANDBORN: Just as in MS, I think the parallels are actually fairly striking. There will be a smaller group of patients that may have a fairly benign course over time, but the majority of patients, probably 80 percent will progress to complications.

Perhaps one difference for multiple

sclerosis is that you can operate for those complications. But again many of the patients will require repeated operations and especially for the sort of younger half of patients who will have 30 or 40 or 50 years of disease.

When we looked at this in Olmsted County, Minnesota, we found that the median patient was diagnosed at age 30 and had 45 years of subsequent Crohn's disease. So it was a long term course and for sure the majority of patients will have progressive disease with multiple surgeries as you follow them for 45 years.

DR. SACHAR: I hope it is not too optimistic, Bill, to point out that the nightmare scenario of one operation after another after another after another until you have chopped up most of the small bowel is actually relatively rare.

You spoke about the two-thirds rule. Some of the proportions that I carry in mind are that, at some point, about 70 percent or so of patients will come to at least a first resection.

Of those, I think that over the next 20 to 30 years, it is about 45 percent or close to 50 percent who require a second operation, and most of the data I have seen say that of those over the rest of the lifetime, it is about maybe 25 percent of those who require a third.

So, if we sort of multiply out the figures, if we talk about the likelihood of somebody having more than two operations, it is probably closer to 9 percent than the majority of patients.

DR. SANDBORN: You are the master on this. I wouldn't want to quibble with you. The best study that I have in my mind comes from Viebke Binder in Copenhagan County, and the numbers I have in my mind are in their 1994 gastroenterology paper are that by 15 years from diagnosis, a third of patients have not had an operation, I think 40 percent of patients have had one, and the balance have had two or three by 15 years.

DR. SACHAR: They do operate a little earlier in Scandinavia.

Are there any other questions about the disease itself for Dr. Sandborn? Dr. Pasricha.

DR. PASRICHA: Bill, while we have you on the stage, could you--related to the question on duration--could you comment on the use of biologicals for modifying the actual natural outcome or natural history of the disease? You had a nine-year experience now with infliximab. Can you think now about how other biologicals may actually alter the long-term prognosis in these patients because that is of relevance to a life-long disease like Crohn's?

The other question I had was one of the greatest values that biologicals have added to Crohn's is the treatment of fistula. We haven't heard a lot about that with this drug. Can you comment on that?

DR. SANDBORN: We will start with the natural-history question. You can see, and I think you saw from the discontinuation rates, that the patients that are severe enough to go into these clinical trials are unable to tolerate a long-term

situation where they are not effectively treated.

So, to be able to do a placebo-controlled natural history study, which probably would take a minimum of two or three years to show important impacts in natural history, is very difficult because it is very difficult to keep patients under placebo treatment for that long.

So, the evaluation of natural history then has to come from the introduction of the drug into clinical practice and looking at large epidemiologic data sets. Infliximab is now nine years old, and the induction use of the drug is probably three or four years after, or the maintenance use of the drug is probably three or four years after, that. So we maybe have six years where the drug was used more on a maintenance case.

So, we are just getting to the point that those natural-history studies are going to be done. I think it is reasonable to think that they will change the natural history. It hasn't been proven yet for any of the biologics and frankly, in any of the drugs that we use.

The fistula question. I think the simple answer is that fistulas weren't evaluated. If you look at some of the other biologics, for instance, adalimumab, there were several short-term induction trials where about 10 percent of the patients had fistulas, and there wasn't a clear benefit in fistula closure, and a long-term maintenance trial with that drug, we did see some fistula closure.

Likewise, in the Phase II induction trial with natalizumab, there was a small group of patients that had fistulas. There wasn't a clear message, but that is not surprising in a short-term trial.

For a variety of reasons, patients with fistulas were not included in the Phase III program, so we don't have information. It is not to say it doesn't work, we just don't know. It hasn't been studied.

DR. SACHAR: Dr. Levine has a question.

DR. LEVINE: From your very nice review recently that just hit my desk about a prospectus from DDW2007, in your introduction, you commented

and talked about various natural history in the disease, and you alluded somewhat to the short term and advanced disease states of CD.

You make the statement or the summary statements that Tysabri is not more effective in maintaining clinical response and remission in CD patients with early disease. I presume that meant early, less than three months from what you are alluding to, compared with those with more advanced disease, and then you state or they state that these data further implicate TNF antagonists as effective agents in their ability to modify the natural course of CD, whereas, the results are inconclusive for natalizumab.

I am just wondering if that was your writing or if that was--

DR. SACHAR: Do you recognize his handwriting, Dr. Sandborn?

DR. LEVINE: If it wasn't, forget it.

DR. SANDBORN: Why don't we take another question and give me a second to read this.

DR. AVIGAN: I had a question about

patient management. Prospectively, when you see a patient, and you are trying to consider two possible situations, one where there is inflammatory disease, which if you reverse it effectively, the patient will get better. The other is that there is fixed disease, fibrostenotic disease, or fistula disease.

In patient selection, and kind of sizing up the patient, what actually is your kind of workup to sort of put the patient into a category?

You alluded to the point that patients seemed to be more responsive if they have elevated CRP--that is, they have inflammatory disease. But in the more severe population, in the mix of patients, how many patients actually have relatively fixed fibrostenotic disease which would not respond to anti-inflammatory therapy?

DR. SANDBORN: I think that is a good question. How can patients with Crohn's disease get symptoms? You can have obstructive type symptoms, nausea, vomiting on the severe end, pain, cramping, abdominal distention fairly shortly after eating on

the sort of partial obstruction end. Gastroenterologists are used to using clinical judgment to evaluate that.

Really, if there is any important hint of obstruction, the patient will need some kind of a radiographic study to exclude that, and that was really part of the exclusion criteria for the trial. So, we would typically do either a small bowel fall-through, barium x-ray, or a CT enterography at some centers.

The CRP actually, in my mind, is more about--in the clinical trials--more about identifying patients who are going to have a lower placebo response rate than necessarily an enhanced clinical response rate. But, in the context of trying to get a risk-benefit assessment, I think patients with an elevated CRP are more likely to have biologically active inflammation.

I actually have a fairly low threshold in my clinical practice to do colonoscopy in supplementary clinical trials or radiology studies as I am trying to decide if a patient is

appropriate for any immunosuppressive therapy, and this is frankly true for steroids, for azathioprine, for the anti-TNF agents, and I anticipate it would be true for this agent, as well.

DR. SACHAR: I would reinforce Dr. Sandborn's point by pointing out that in the last 10 or 15 years, since we have become more aware of the clinical distinctions among purely inflammatory fistulizing and stricturing stenotic disease, virtually every clinical trial designed anywhere around the world for medical therapy has deliberately excluded patients with the obstructing fixed strictures of the type that you are describing because they are, of course, not amenable to any medical therapy currently known.

Dr. Couch, you had another question.

DR. COUCH: Yes. Just one other neurologic question. You comment that the Crohn's disease patients typically do not have neurologic deficits.

One of the interesting developments over

the last probably 10 or 15 years, as obesity surgery has become more prominent, are the neurologic risks that are beginning to appear from the obesity surgery, which are mainly gastric.

I am not aware of any long-term studies about neurologic diseases, perhaps copper deficiency, which a great deal of that was done at Mayo, or zinc deficiency, things like that, that may result from chronic intestinal problems relating to neurologic disease.

There is the information on gastric problems from instrumentation. Could you comment about whether there are any long-term studies dealing with neurologic disease related to the intestinal problems?

DR. SANDBORN: I think as you point out probably as a specialty, we also do nutrition within our specialty, and TPN and oral nutrition, and screening for nutritional deficiencies in this patient. So I think that is probably not--unrecognized deficits in that regard are probably not a major issue for us, but we do

interact with neurologists on a fairly frequent basis.

Patients with inflammatory bowel disease have a 2 to 5 times increased risk of venous and arterial thromboembolism, and so there are a variety of CNS events that can occur with that in our patient population that require evaluation by a neurologist.

We see peripheral neuropathy from metronidazole use. We can see demyelination from anti-TNF therapy, and there will be patients where you are uncertain about symptoms that need referral for MRI and neurologic evaluation. So, I think those referral patterns are in place with neurology, and we are used to doing that.

Dr. Levine, I think now I recognize the context of this. Again, as we start to think towards the future about potentially early intervention with biologics, and that, at this point in time, is really focused towards the anti-TNF class before the early intervention trials, which are just being planned and started,

will be completed years away. One approach people have taken to trying to get a hint into what those trials might show is to stratify the outcome of the clinical trials according to how long the patients have had disease.

So you could take patients in an anti-TNF trial and stratify them according to whether they have had a year of disease, two or three years of disease, three to five, or more than five, and it turns out that the absolute rates of response with a couple of anti-TNF agents are higher if the patient has had disease for a year or less than if they have had it for more than five years, and results are in between.

With natalizumab, a similar subgroup analysis was done in some of the trials, and there wasn't a clear difference in outcome between the patients who had had disease for a short period of time and patients who had had the disease longer, you know, subgroup analyses that are clearly exploratory.

There was actually a fairly small number

of patients in the subgroup that had had disease for a short period of time. I wouldn't make too much of that. The definitive experiment would be to do it prospectively, and I think we would be some years away from such an experiment with Tysabri.

DR. SACHAR: Dr. Chang.

DR. CHANG: I just had a question about the CRP, because I guess, you know, in clinical practice, you are not going to be caring about the placebo rate, but I wasn't exactly sure how it is going to be utilized.

In the studies with Tysabri, it wasn't a very high CRP threshold that you used. But, in other IBD trials, it looks like it is using 10, above 10 or below 10. I am just trying to understand and put in perspective what is the meaningfulness of CRP.

DR. FRANCIS: I think I will try to address that. The level that we have picked of 2.87 is using the highly sensitive assay, and that is the upper limit of normal, so it was a fairly

logical cut point of saying you are either abnormal or not for that level of exclusion. Other studies have used different assays; therefore, they are not directly comparable in terms of the information.

I think the point that Dr. Sandborn had actually made was that the CRP is being used, not to select for responsiveness, but rather to select for patients or de-select patients who may not be appropriate for therapy with this drug, partly because they don't have evidence of inflammation and this drug is used as an anti-inflammatory drug and probably because of the safety issues that we want to restrict the drug to the patients who are likely to benefit most, and not use it in patients who are less likely to benefit.

DR. SACHAR: Many of the questions that we are asking with regard to clinical background are really overlapping with questions on efficacy, and I would like to move on to the crux of some questions about efficacy that Dr. Sandborn and/or Dr. Jones or others may want to answer, and I would like to lead that off.

I have actually three questions on this point, and I will just indicate them one at a time.

You have stratified cases in various ways according to concomitant therapy and other things, but I haven't seen in this presentation, although I have seen in the written presentation, some stratification according to disease location.

I would like to hear some comments about specific efficacy data and the therapeutic delta from placebo for the efficacy of Tysabri in colon-only disease versus disease involving the ileum.

To help you, I think if you look in your written material there is some data on that in Table 46.

DR. FRANCIS: I will ask Dr. Jones if he would like to respond to that and, in the interval, we will pull up the table from the briefing book as a slide.

DR. SACHAR: While you are working on that, my second question is also a stratification question. In slides 43 and 56, you showed the

efficacy of the Tysabri specifically in patients who had failed anti-TNF therapy either as primary nonresponders or intolerant or attenuation of response.

The numbers might be getting a little small to try to cut those three categories further, but there may be sufficient data for you to be able to tell us what the therapeutic delta was and if there were any differences among primary nonresponders to anti-TNF, attenuated responders to anti-TNF, and people who could never get the anti-TNF because of intolerance. So I am going to ask you to take a look at that in slides 43 and 56 and tell us if you have any subgroup analysis on that.

While you are working on that, I will just have a final question that has to do with the maintenance of remission. If you would like, I will hold off on that one until you have had a chance to wrestle with the first two.

DR. FRANCIS: I think as you indicated, once one starts getting into the various subgroups,

you are getting smaller and smaller n's. But there is data that we have on the TNF failure groups and its further subcuts, and I turn that over to Dr. Jones.

DR. JONES: I think I will address the TNF failure group actually to start with, and if we can have maybe some of the backup slides, I think it is slide 938 actually, if my colleagues can do that.

We did actually divide those patients into several groups. We looked at those patients who were unresponsive, and we looked at those patients who were intolerant. I will just show you the plots here in CD307.

In 307, we only actually categorized them into those two categories. They could only be categorized as being intolerant or unresponsive.

DR. SACHAR: Right. Unresponsive was both primary nonresponders and secondary nonresponders.

DR. JONES: Both primary and secondary nonresponders. Now, for CD301, we actually captured the data just slightly differently. We actually did divide into those patients who had

nonresponse to initial therapy. That's a small group and I can show you that data. I think that is slide 995. Well, I will just show you this data. This is the intolerant versus the unresponsive in CD307. You can see for this we did actually see benefit in both those patient groups.

DR. SACHAR: That is very helpful. Off the top of your head, are you able to tell us if -- it seems to be equally favorable in primary nonresponders as attentuators.

DR. JONES: Absolutely. When we look for CD301, we actually had 13 patients who had elevated CRP. We had 13 patients randomized to placebo and we had 55 patients who were randomized to natalizumab. This is the primary nonresponder patient population.

What we actually saw--could we have 996, please.

Here we go now, I have the data in front of me.

This is patients, as I say, read with caution because this is actually how it is captured

in CVCRF. These are patients who had no response to initial therapy to TNF, so these you could equate to primary nonresponse. We haven't got p-values here, the numbers are very small. Actually, at Week 12, we actually did have a p-value.

DR. SACHAR: That answers the question very helpfully. Thank you, Dr. Jones.

I am very concerned about this question of anatomic location, because as I interpreted Table 46 in the written submission, the evidence for therapeutic delta from placebo seemed to apply only to those who had colonic involvement only. I may be misinterpreting the data in that table, but I couldn't see therapeutic benefit in patients who had ileal involvement.

DR. JONES: If it's CD307, you are absolutely right, we didn't actually see benefit in the population that didn't have ileal involvement, and that was approximately 25 percent of the population that was actually recruited to that study.

In CD301, this again is post-hoc analysis for this population, but we did actually start seeing some benefit in that group. We saw this population; it is quite small numbers. We actually had 30 patients randomized to placebo in 301 and 135 patients to natalizumab.

In that study, in the earlier time points, we did actually see some benefit. In fact, we saw statistically significant benefit at Week 6. But, at Week 10 and Week 12, we didn't, and that is probably to do with a few patients that were in the placebo group actually did develop a spontaneous response. We haven't seen clear benefit in that patient population.

DR. SACHAR: That is 307, and what about 301, is it, the induction?

DR. JONES: Could we just go back to that previous slide, please, and I will show you the data for 301. This is for the elevated C-reactive protein population from 301.

This is the response in the patients with disease confined purely to the ileum. You see, we

saw some response earlier on in the stud. But there were 4 patients in the placebo group that then went into response, and that is now canceled out, and you can see the placebo rates go up quite considerably.

I mean we see the natalizumab group that stays constant between 6 and 12/. But again we didn't see statistical significance in this, on Week 6.

DR. SACHAR: Given the fact that the great preponderance of patients with Crohn's disease have disease not necessarily confined to the ileum, the plurality do. But the majority have disease involving the ileum. But are you concerned about our ability to extrapolate your overall efficacy data to the groups of patients who have primarily ileal disease?

DR. JONES: Well, actually, the patients who had ileal colonic disease, which made up approximately half of the patient population, actually, we did see a response and quite good response. I am just seeing if there is a slide

there for that. This is for 303. I need it for the induction studies, please. But we did actually see a response in that patient population, the ileal colonic disease.

DR. SACHAR: In 301, but not so much in 307 again, I think.

DR. JONES: Yeah, in 307, but we were still seeing benefit.

DR. SANDBORN: David, I think you know probably better than anyone we have learned a little bit about doing clinical trials even in the last few years with all the trials that have been done in Crohn's disease.

I think one of the things we have learned is that the optimal length of an induction trial, in retrospect now, is probably 4 to 6 weeks, and a 12-week trial, the 10 to 12 week mark is the point at which you are most likely to see a placebo response. And then if you go on beyond that, the placebo response tends to wane again.

So, what we actually saw there was a nice separation between drug and placebo in the early

point before the placebo rate went up. The absolute response rates for ileal disease looked just like ileocolitis and colitis, but the placebo response made the delta small, and I personally think that, you know, you have got to be careful when you get into these multiple, multiple, multiple subgroup analyses. Things will happen by chance.

I think that that is probably an artifact of clinical trial design and that it is not real. I would actually be focused more on the fact that the absolute response rate in the natalizumab group looks like the absolute response rate in the other anatomic subgroups.

DR. SACHAR: I am quite satisfied with that and I think we have to take your points into account when we select the time points for our primary endpoints.

My last question has to do with the maintenance of remission. You have shown strong evidence that continuation of Tysabri will maintain a Tysabri-induced remission where Tysabri has

already been a success.

Do you have any data at all? I doubt it because of the trial design. There probably are no data on the effectiveness for maintaining a remission that was induced by agents other than Tysabri itself.

In other words, if we have used cyclosporin or steroids as a bridge, I doubt that there has been any work at all on the ability of maintaining that remission by the introduction of Tysabri.

If that is the case, could we interpret your request for approval for maintenance of remission to be limited to maintenance of Tysabri-induced remission, or are you seeking further approval for an indication for which there are yet no data?

DR. FRANCIS: No, I think you are quite correct. We don't have data on whether or not one could maintain a remission that was induced by another agent as all of the studies were enrolling patients who were active despite therapy with those

prior agents, and the indication is directed at the natalizumab patients who had a response or remission induced. and for maintaining that response and remission. There is no data to argue for other.

DR. SACHAR: Then, possibly, we might want to slightly clarify the language of the application to make it clear that we are speaking of maintenance of natalizumab-induced remission.

DR. FRANCIS: Certainly, we are open to those discussions.

DR. PLATT: Could I just follow up your question? I am looking at slides 49 and 50. The question is maintenance of remission. Did you give us figures on the proportion of people who remain in remission? Forty-nine and 50 make it look like about half or fewer are continuously in remission. Is that the right number?

DR. FRANCIS: Yes, that is correct. Are you asking about the proportion at a time point specifically?

DR. PLATT: Well, it is going to come back

when we think about the management plan. But is the assertion that half of patients remain in remission, or is it that it is a larger fraction and that you don't have to be in remission at every single point?

DR. FRANCIS: If you look at the data that has been presented by Dr. Johns, the patients who were in remission at every assessment, if you looked specifically at the 6-month time point of the proportion of patients at that time who were actually in remission or in response, the figures are actually slightly higher as is shown here on the screen.

So, this is the point in time analysis, somewhat more traditional analyses that are used with other studies of IBD, and you can see here that you have got a higher proportion of patients who are in response and remission at Month 6 and at Month 12.

So, we have got Month 12 here. The primary time point was at Month 6, and the proportion of patients who are in response is 67

percent versus 55 percent for remission.

DR. SACHAR: Is the glass half full or half empty? The patients who responded to Tysabri, about half of them are still in remission a year later on maintenance therapy and half of them aren't.

DR. PLATT: So, this gets at the question of what will be the criteria for discontinuation. This may not be the right point to discuss that, but it would be an important part of the riskMAP it seems to me.

DR. FRANCIS: I think Dr. Sandborn had indicated that, certainly for the patients who initially are exposed to therapy, that, within three months, if there has not been a clinical response, that the recommendation is that they discontinue therapy at that time point, if that is your question. If the question is if the patients who have responded, whether they then relapse is what the management plan would be at that point.

DR. AVIGAN: I just wanted to follow that question up because I think it is going to be quite

important when we talk about risk management and maintenance, is that the patients on Tysabri, if they have a flare or have a worsening, from what I understand, in your protocol and also in your inferred risk-management plan, that it would be permissible to modify dosaging of other agents to which Tysabri is added on to.

So, the question is the management of flares while on Tysabri therapy. Did you actually encounter such patients and how were they managed in your clinical trials?

DR. FRANCIS: Yes. Patients who had failed, well, these are essentially treatment failures, if they went on to use steroids for the management of the Crohn symptomatology, so patients who at that point were deemed failures in terms of their response or remission endpoint, but patients did receive corticosteroid therapy for flares.

DR. SACHAR: I am aware at this point that we are going overtime on the allotted schedule. I should point out that the allotted schedule allowed only 20 minutes for questions to the sponsors,

whereas, in fact, that is the most important part of the entire meeting are our questions toward the sponsors on the data that they have presented.

We are going to take our break now with the understanding that the later part of the program, which are questions and answers, may, and, in fact, I am certain will, come back to many more questions for the sponsors because I can't think of any more useful spot.

We are going to take--it says in the program a 15-minute break, that usually takes half an hour--we will actually take a 5-minute break. That takes 10 minutes.

[Break.]

DR. SACHAR: This is the point we would like to hear from the FDA staff, which has put I am sure as much time and thought and energy into analyzing the sponsors' presentation as the sponsors have in compiling it.

With that, we will start with Dr. Margo Smith, who brings us an infectious disease perspective.

FDA Presentations

Progressive Multifocal Leukoencephalopathy

DR. SMITH: Good morning, everyone. I am going to go ahead and get started. Hopefully, I will try to skip over the part that I think is redundant, and then we will take questions at the end.

[Slide.]

In my CME capacity, it is always better to start off with a case, and this is from a case series where--the majority of the work I do is involved in HIV and AIDS--and this is a case from a lecture I give talking about the neurological complications of HIV and AIDS. It happened to be the Case 5.

This is a 43-year-old man with AIDS who presents with a 4-week history of ataxia. He has progressive right hand weakness and a tremor. On his exam, he is indeed ataxic and weak on the right when compared to the left side. He is afebrile.

His CD4 count is 56 and a serum toxoplasmosis titer was performed, and that

antibody test was negative. He is on trimethoprim sulfamethoxazole, and as the question goes on, you order an MRI scan, and the MRI shows that there is a 2 x 4 cm lesion in the left cerebellar hemisphere on the T2-weighted image.

There is no enhancement when gadolinium is given and there is no mass effect.

[Slide.]

This is what the MRI scan appears to look like.

[Slide.]

So, the most likely diagnosis. This is PML.

[Slide.]

Just to give background information, some of this has already been given, and I am not going to belabor the point, but I think what I want to emphasize is that this virus is indeed a DNA virus, and it was first reported in 1958 and, as has already been mentioned, it has particular effects on the oligodendrocytes.

It has an interesting receptor that I am

sure somebody is going to speak about who knows more about it than I do, where perhaps the JC virus binds to this receptor the 5-H2A to actually cause disease. It causes a demyelinating disease of the brain.

Interestingly enough, although it causes this problem in the cerebral, cerebellum, and the brain stem, it does not invade the eye and the spinal cord, which is rather interesting.

[Slide.]

There is some debate when you read various reports whether it's primarily a asymmetrical, but it can be presented as asymmetrical disease. But primarily it can really affect all parts of the brain except the spinal cord and the eye, and when you look particularly at the HIV AIDS population, there is more brain stem involvement than anyplace else. In HIV and AIDS, it has a very rapid progression to death.

[Slide.]

Some of the basics of the immunology has already been talked about prior to the HIV AIDS

epidemic, the disease was seen in older individuals and people who had leukemia/lymphoma. Again, it can present in subacute fashion with no clear markings that makes a clinician recognize that it is indeed PML.

So, it can present as simply as personality changes or cognitive changes, or in the case that we had, motor weakness, and it can present as a nuance of seizures.

[Slide.]

Classically, prior to the HIV epidemic, the kind of patients that we saw it involved with were those leukemia and lymphoma patients primarily in B cell diseases. There were also case reports of individuals who had more advanced AIDS and again with some of the other autoimmune diseases like rheumatoid arthritis and some of the dermatomyositis type diseases.

Also, seen in transplantation primarily in renal disease, that is, renal transplantation, because that is where the majority of patients over time have been studied and evaluated.

[Slide.]

PML. There is some interesting information about its relationship to other viruses or in the family of other viruses. BK. For those of you who don't know, BK virus is a very important virus in transplantation and causes hemorrhagic cystitis in transplant patients.

The big question is, is how does one acquire it. It is clear that the general population, if you look serologically, there is a high rate of positivity. The current theory is that it is acquired as a respiratory infection and where it hides or where it has its latency period is up for question.

Many people who have been researching the disease believe there is a latent virus that stays within the kidney. Others believe perhaps there is more in the bone marrow than we appreciated, and there is lots more argument whether or not there is a latency virus in the CNS.

There appear to be two different strains, one that primarily infects or affects the brain,

and then one that primarily is seen in the kidney.

[Slide.]

When we look specifically at HIV and AIDS, this is a disease that affects 2 to 5 percent of the population.

If you look across the board, in those individuals who don't actually have manifestations of PML disease, and you look for the virus, in roughly 50 percent of the HIV AIDS population, if you check for leukocytes, you can find circulating virus.

PML as a disease is an AIDS-defining illness and, as a general rule, you see the vast majority of cases in those individuals who have CD4 counts that are less than 100, although you can see them with better immune systems and case reports are out there looking at patients who have C4D4s in the 200 to 300 range. But, by far, 90 percent of the disease occurs in the very immune suppressed HiV-infected individual.

The diagnosis in HIV, like in other cases, is made by MRI where you have a non-enhancing

lesion and it's suspect, and then to go on to do the CSF-PCR where you look for DNA virus, the JC virus.

When you read the statistics about how sensitive or specific the PCR assay is, you can see ranges from 75 to 92 percent. I used 80 because it is sort of in the middle.

[Slide.]

In HIV and AIDS it has already been discussed that the primary treatment is to treat the underlying disease, and when one looks at the literature at treating with highly active antiretroviral therapy in this group of individuals, it is a mixed bag. Most of these are case reports, maybe very small case series, looking at the response of highly active antiretroviral therapy, and it's a 50-50 response where 50 percent of the people stabilize--and I want to emphasize stabilize. They don't get better. The disease does not go away, and 50 percent rapidly progress.

We have already had some discussion about the immune reconstitution syndrome, which primarily

has been described in individuals who are HIV infected and start on antiviral therapy and have a wonderful response, and either they have a subclinical opportunistic infection that is only brought out because we are now restoring their immune systems and they manifest disease where, when this first occurred, we often thought that they had an unusual reaction to their antiviral therapy or that they were relapsing from their underlying disease, and as it turned out, it's actual, their T-cell immune response responding to the infection.

[Slide.]

Rather interestingly enough, we can see this immune reconstitution response in many cult infections and, later on in the talk, we will talk about some of the other diseases, subclinical opportunistic infections we have seen it in.

When you look at PML in individuals that are not HIV infected, T-cell immunity is probably the most important underlying disease that you see the individuals in again. It's the transplant

population that primarily the disease has been seen, and in those who have chronic granulomatous disease and those who have other lymphoproliferative disorders.

The rate of disease in individuals that are not HIV infected, in a hematologic malignancy group, the rate is extremely low, 0.07 percent. As we have learned already in this particular monoclonal, it appears that it is 1 in 1,000.

When you look in the non-HIV population and you look at the ratio of the incidence of disease in men versus women, it is 3 to 2 more men than women.

The disease, again in the non-HIV population, peaks in older ages, in the 60s.

[Slide.]

Comparing sort of survival of PML, traditionally, the disease prior to antiviral therapy was weeks to months in those who had AIDS. When we look in the non-HIV population prior to the monoclonal antibodies that we are speaking of, these individuals lived from months to perhaps as

long as 18 months.

Looking at individual literature of are there therapies out there that we can actually use to treat individuals that have the disease, they were all case reports, there are no case series, and there are no long-term case-controlled studies.

There are individual case reports of people who have responded, presumably to the therapies that have introduced. These are looking at the various interleukins, cytarabine and cidofovir. Cidofovir is rather interesting because it's a drug that has been looked at and treating people who have severe BK virus disease and hemorrhagic cystitis and transplantation with some success.

There is one case report that talks about using a rather interesting way of blocking the receptor 5-H2A, which is a serotonin antagonizer, looking at a particular antidepressant drug and whether or not it may have some impact on the disease.

[Slide.]

So, here is the dilemma. Can one predict who is at risk for the development of PML?

[Slide.]

From the evidence that I have read and some of the other literature that people have actually done quite an investigation, there really is no premorbid serological test that is available. As one looks at serology, the longer you live, the more likely you are to have positive serology, positive antibody for the JC virus.

There is no premorbid CNS screening test available, so doing things like MRIs or doing lumbar punctures, looking for virus, is not very helpful, and it is not clear if there is a particular subgroup of individuals when you are looking at pre-exposure to other immune suppressive agents if that clearly is a risk factor as opposed to those that have never been exposed to those drugs.

How helpful is looking at urine for JC virus DNA? The literature that I have reviewed and what most people have said, it is hit or miss, it

is not predictive.

[Slide.]

So, in my mind, from what I have read and what I know from taking care of my population with HIV, there are really many more questions, and really no clear answers, and all I see are more and more questions, and does prior immune suppression really increase risk?

I don't know what the answer is. And, if one believes that it does put people at risk, is there a particular time at which someone is immunosuppressed that puts them at greater risk for disease? I don't know what the answer is.

Is there a role at some point looking at monitoring antigens that are specific since there is some evidence to suggest that those individuals who have a better CD-8 response, is that perhaps a predictive indicator of how one will respond either in developing disease or having a better outcome if they have PML disease.

I guess the question to all of us is do we think at this point, given the information and the

current knowledge that we have, is there 1 in 1,000 chance of reasonable risk for individuals.

Clinical Review

DR. RAJPAL: Good morning.

[Slide.]

My name is Anil Rajpal. I am a clinical reviewer in the Division of Gastroenterology Products. I am going to talk to you about the efficacy of natalizumab for Crohn's disease and the safety of natalizumab.

[Slide.]

The sponsor has provided much of the background information regarding the efficacy and safety. We thought it would be most helpful to the committee if we gave you our review of the efficacy and safety data and filled in some information where appropriate.

[Slide.]

First, I am going to speak briefly about the original review for the MS indication, the discovery of PML and the considerations that went into the decision for the return to market.

Then, I will discuss the basic design and main efficacy results of the induction studies and the maintenance study.

I will discuss exploratory subgroup analyses.

Finally, I will discuss our review of the major safety concerns.

My goal is to allow you to consider natalizumab's risk-benefit profile more fully as you consider the questions that we have posed to you.

[Slide.]

First, background.

[Slide.]

In the original review for the MS indication, the treatment effect was described as unprecedented in the MS field. There were two pivotal MS studies. The first was a monotherapy study. The second was an add-on study for relapsers on Avonex or interferon beta, and the treatment effect. I have here the absolute reduction in relapse rate was 49 percent for the

monotherapy study and 42 percent for the add-on study.

Approval was under the Accelerated Approval regulations based on 1-year data, and attesting to the magnitude of the treatment effect.

[Slide.]

At the time of the original approval, there was no suggestion of increased risks compared to other MS therapies. Infections were ordinary and uncomplicated, anaphylactoid reactions were less than 1 percent. There were small increased trends in depression in both the monotherapy study and the add-on therapy study. There was a higher incidence of menstrual disorders.

[Slide.]

Then, a few months after marketing, cases of PML were seen. You have already heard the discussion of these PML cases from the sponsor and the discussion of PML from Dr. Smith. It is worth noting that each of the MS patients that had PML were on concurrent Avonex and were exposed to natalizumab for approximately 2.5 to 3 years.

The Crohn's patient, although technically on monotherapy for the last five months, had a long history of immunosuppressant use, as well as a history of bone marrow suppression.

With the discovery of PML cases, marketing was suspended and dosing was suspended in ongoing trials including the Crohn studies.

[Slide.]

There was an extensive retrospective safety review in those suspended trials to identify more PML cases and to estimate the risk of PML. The analysis of possible cases of PML from clinical trials included more than 3,000 patients, approximately one-third of those were Crohn's patients. No additional cases were identified.

So, the conclusion was that the risk of PML was approximately 1 in 1,000 patients treated for a mean of approximately a year and a half, and the risk of longer treatment wasn't known.

[Slide.]

In March 2006, an advisory committee was convened largely to assess the benefit to risk

ratio in MS and to consider whether or not natalizumab should be returned to the market.

The advisory committee concluded that PML risk wasn't limited to concomitant therapy, but they recommended that natalizumab should not be taken with immune modulators and that a washout period was needed if switching from immune modulators to natalizumab.

They were split on whether natalizumab should be allowed as first line therapy for MS, and they did not believe additional studies were needed.

Their conclusions were facilitated by a high treatment effect in each study, a prospective MS monotherapy study, and no clear benefit of add-on therapy over monotherapy.

[Slide.]

Prior FDA review by Neurology was completed in June 2006. The reviewers concluded that the magnitude of the treatment effect made the risk of PML acceptable for some patients, generally for those who didn't tolerate or respond to

alternate MS therapies.

They concluded that natalizumab should be approved as monotherapy because of the concern of higher risk with concomitant therapy.

Again, monotherapy had been studied prospectively. The reviewers acknowledged that there was limited data to conclude that the risk of PML is reduced with monotherapy.

They concluded that short courses of steroids were reasonable and they decided that natalizumab should be returned to market under the TOUCH program, which discourages concomitant steroid and immunosuppressant use.

Dr. Karwoski will discuss the TOUCH program after this presentation.

The FDA reviewed decision on return to market was again facilitated by a high treatment effect, a prospective MS monotherapy study, and no clear benefit of add-on over monotherapy.

[Slide.]

Now, the current Crohn's disease application. The proposed indication is for

induction of response and remission, for maintenance of response and remission, and for eliminating steroid use. The proposed indicated population is moderately to severely active Crohn's disease with inflammation as evidenced by elevated CRP or another marker.

I will discuss each of the efficacy claims and the rationale for the use of elevated CRP with the discussion of each of the studies. The bigger point, though, will be the overall risk-benefit profile with regard to PML, other opportunistic infections, or other risks.

There is a possible higher risk with concomitant therapies and, compared to the MS patients, Crohn's patients are more likely to require long-term therapy with steroids and/or immunosuppressants. The question will be if there is a more severe or refractory Crohn's population that would make the risks acceptable.

[Slide.]

The second half of the indication statement states the risk of PML, but doesn't

specify if natalizumab should be used as monotherapy. It says "generally recommended for patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies" where conventional Crohn's disease therapies include mesalamines, steroids, and immunosuppressants. But the proposed indication does not mention that patients should have also had an inadequate response to or have been unable to tolerate biologics, such as anti-TNF agents.

[Slide.]

The sponsor has provided a detailed presentation of efficacy. I will repeat some of the main points, but I will try to highlight the key issues that we believe are relevant to the committee's considerations.

[Slide.]

There are three placebo-controlled Phase III studies. These were two induction studies CD301 and CD307 and one maintenance study CD303.

The first induction study did not select

patients based on CRP, but in a post-hoc analysis, the elevated CRP population had a higher treatment effect.

Thus, the second induction study 307 was designed to prospectively study the high CRP population.

The maintenance study 303 studied responders from study 301.

It is worth noting that each of these studies was designed prior to the concern of PML, so considerations for monitoring or for restrictions on concomitant or prior therapies were not part of the design of any of these studies.

[Slide.]

All the studies had these features; concomitant use of anti-TNF's was prohibited and there was a washout period of three months before entry. Continuation of azathioprine, 6-MP, methotrexate, steroids, and mesalamines were allowed if they had a stable prior dose. So, this can be thought of as an add-on study to a number of ongoing background treatments in contrast to the MS

add-on study, which was to Avonex only.

New Crohn's treatments were allowed for rescue therapy only.

[Slide.]

First, I will discuss the two induction studies.

[Slide.]

The first study 301 was randomized 4:1 natalizumab to placebo, and enrolled 905 patients.

The second study enrolled 509 patients and was randomized 1:1.

The first induction study used a 4:1 randomization, so that there would be more patients for the continuation maintenance study. The dose was 300 mg Q 4 weeks x 3 in both studies.

The primary endpoint in the first study was clinical response at Week 10 and in the second study was clinical response at Weeks 8 and 12.

Dr. Sandborn has already described the CDAI scale. It has both objective and subjective components. The scale goes up to 600 and the population studied was 220 to 450, moderately to

severely active Crohn's.

Clinical response was defined as CDAI decrease of 70 or more. From a regulatory standpoint the primary endpoint of response has been accepted previously.

The main secondary endpoint in the first study was clinical remission at Week 10 and in the second study it was clinical remission at Weeks 8 and 12. Clinical remission was defined as CDAI less than 140.

The first study did not select patients based on CRP. But a post-hoc analysis in the 75 percent of the patients that had elevated CRP showed a higher treatment effect.

The second study prospectively selected patients based on elevated CRP. Because the first study had both a high and low CRP population, but the second study only enrolled a high CRP population, further determination of the utility of CRP in predicting clinical response was not possible.

[Slide.]

This slide shows the proportions of patients in each study with prior use of medications for Crohn's disease. These were patients that reported any prior use of these medications. In each study, hardly any patients were treatment naive. CD307 had a lower proportion of patients with prior use of mesalamines, steroids, and immunosuppressants, but a slightly proportion of patients with prior anti-TNF use.

Across the studies we see that there was a high proportion who had used steroids and past use of immunosuppressants and anti-TNF agents was pretty common.

[Slide.]

This slide shows the proportion of patients in each study by medication use at the time that they entered the study. These were patients who were on a stable prior use and were allowed to continue these medications throughout the study.

The proportions of baseline medications were similar for the two studies. Anti-TNF agents

were not allowed as a concomitant medication.

Although the slide doesn't show it, about a third of patients were on monotherapy meaning not immunosuppressants or steroids, and 7 percent of less were on no Crohn's medications at all.

[Slide.]

Here are the results for clinical response, which is a 70-point drop in CDAI score. For the first induction study 301, shown on the top, the treatment effect, meaning the difference in proportion of responders, is under 8 percent, and the p-value is borderline/nonsignificant.

An analysis of the subgroup of subjects with elevated CRP showed a statistically significant treatment effect of almost 13 percent, shown in the middle. This analysis wasn't prespecified and is considered exploratory, but it was used to generate the hypotheses that natalizumab is effective in subjects with increased inflammatory involvement as measured by CRP.

This hypothesis was tested in the second study 307, shown on the bottom, which prospectively

confirmed the finding of efficacy in that subgroup with a treatment effect of 15.5 percent.

The remainder of my discussion of efficacy in the induction studies will focus on the increased CRP subjects. I should note that the second study 307 failed to provide more information about the low CRP population to definitively show the utility of CRP.

I should also note that the treatment effects are relatively modest in both the studies ranging from approximately 8 to 15.5 percent.

[Slide.]

The results for the secondary endpoint of clinical remission paralleled the results for clinical response. Remission is a CDAI score under 150. For the first study, the results for this endpoint in the overall population were pretty weak with a treatment effect of 6.5 percent, but an analysis of the subgroup of subjects with elevated CRP showed a modest but statistically significant treatment effect of 12 percent.

The second study prospectively confirmed

the finding in the elevated CRP subgroup for a treatment effect of 10 percent. Again, none of these effects were particularly large.

[Slide.]

Next, I will discuss subgroup analyses of the induction studies.

[Slide.]

Because of our concern surrounding the safety profile, particularly PML, we decided to do exploratory analyses of subgroups to see if we could identify a group of subjects for whom natalizumab might be especially effective and also to try to investigate whether there might be a loss of efficacy if use is restricted to some subpopulation based on medical need or in an attempt to reduce risk.

So, possible surrogates for higher severity and for a more refractory population were higher CDAI score at baseline with a limitation of using CDAI score at baseline was that CDAI may vary with disease activity, so we may not necessarily be identifying patients with more severe disease in

the chronic sense.

Prior medication, those with prior immunosuppressant use for those with prior anti-TNF use are generally more severe. Patients that have been tried on more and stronger agents is one way to capture severity, but this makes assumptions about patterns of use.

Failures of prior medications, this may represent a population with greater medical need. A limitation of this was that there were no rigorous criteria used to identify these patients. In particular, there was no requirement for a highest dose or duration of prior therapy and identification of failures was based on the physician's report.

The next objective was to determine if similar efficacy was found in monotherapy versus with concomitant immunosuppressants or steroids. This objective is related to therapeutic recommendations to see if it is feasible to give as monotherapy.

We are limited by the fact again that

there was no prospective monotherapy study that showed similar efficacy to add-on therapy as was done in the MS indication, but a subgroup analysis may give some tentative information.

At the outset, we recognized that there are underlying limitations of these exploratory subgroup analyses.

[Slide.]

As I will show you in the next few slides, the treatment effect in each subgroup was generally similar to the overall treatment effect. We cannot identify a subgroup for which natalizumab had a clearly more remarkable effect, nor did we find any subgroup would clearly be expected to have a substantially reduced efficacy.

Because the subgroups are much smaller than the overall population, and thus will have more variability, and because there are a large number of subgroups that we are looking at and because all these analyses are done post hoc, any apparent differences I showed need to be interpreted with caution.

[Slide.]

Here, we show treatment effect by quartiles of baseline CDAI score where milder cases are on the top and more severe on the bottom of the table with the overall in green.

In the first induction study, there were some variations in the two more severe categories, but there was no clear trend overall.

[Slide.]

In the second induction study, there appears to be, if anything, a trend toward higher treatment effect for patients with more severe disease shown on the bottom, but none of these analyses are adjusted for multiple looks at the data.

Our conclusion based on both of these studies is that there is no obvious difference across subgroups based on entry CDAI scores.

[Slide.]

Here, we are looking at prior medication use, which may be a sort of surrogate for disease severity more chronically. Each of the prior

medication groups are not mutually exclusive categories as a patient could have been treated with one or more of these agents.

Numerically, the highest treatment effect was in the prior anti-TNF group, and the lowest was in the prior immunosuppressant group. Bu,t again, these apparent differences must be interpreted with caution.

[Slide.]

For the second study we see a little different result from the first study. Numerically, the treatment effect in each of the groups are minimally higher than that of the overall group, and they are all fairly similar to each other.

Our conclusion then based on both studies is that there is no obvious difference across subgroups based on categories of prior medication use.

[Slide.]

Next, we have subgroups of the inadequate responders to prior medications, which can be

viewed as a reflection of how refractory the disease is. These were as reported by the investigator, but without rigorous criteria for their definitions.

Across subgroups, the treatment effect appeared to be retained, but is modest, which is between 10 to 12 percent in each subgroup. There was no clear difference between groups or from the overall group.

[Slide.]

In the second induction study, the results appeared to show a trend of higher treatment effect in the anti-TNF group than overall. But the results are not consistent with the previous slide, which was from the first study, and none of these analyses are adjusted.

There is further the limitation that the identification of the inadequate responders is not based on rigorous criteria, so any interpretation requires caution.

So, our conclusion based on both studies is that there is no obvious difference in treatment

effect across the subgroups based on categories of inadequate response to prior medications.

[Slide.]

Our last subgroup analysis looks at the effect of concomitant medication use with particular attention to feasibility of using monotherapy.

In the first induction study, the monotherapy group appeared to have a lower treatment effect and the concomitant immunosuppressant group appeared to have a higher treatment effect.

Recall that there was no concomitant anti-TNF because they were not allowed as concomitant medications.

[Slide.]

In contrast, in the second induction study, the monotherapy group appeared to have a higher treatment effect, and the concomitant immunosuppressant group appeared to have a lower treatment effect.

So, on balance, based on both of these

studies, there is no obvious difference across subgroups based on categories of concomitant medication use.

[Slide.]

I will now discuss the maintenance study.

[Slide.]

The long-term maintenance study enrolled from the first induction study, study 301, patients had mildly active disease or were in remission based on CDAI scores at Week 12, 428 patients were enrolled and re-randomized 1:1, natalizumab or placebo. The dose was 300 every four weeks x 12, the same as the induction dose.

The analysis population for the primary endpoint was only the population that received natalizumab in study 301. The primary endpoint was maintenance over response through Month 9, which was six months after randomization into the maintenance study. This meant that CDAI stayed below 220 and did not increase 70 or more from the start of the maintenance study.

The contingent primary endpoint was

maintenance of remission, and this meant that CDAI stayed below 150.

The secondary endpoints included withdrawal of steroids after six months using a protocol-defined steroid taper algorithm, but there were a number of other secondary endpoints, as well, which the sponsor has described.

CRP was not part of the entry criteria for this study as it was a continuation of the first induction study. Post-hoc analyses were done in the high CRP population.

[Slide.]

Here, I have the concomitant medication proportions at the start of the maintenance study. These were similar to the overall population of CD301 responders, and 1 percent, which was three patients, were on concomitant anti-TNF's in violation of the protocol. but these subjects were all in the placebo group and shouldn't bias the results in favor of the treatment group.

Prior medication use proportions were similar to those for the preceding induction study,

so I won't show those here.

[Slide.]

Here are the main efficacy results. The primary endpoint, maintenance of clinical response, which was based on CDAI below 220 and not increasing 70 or more from the start of the maintenance study.

On the top is shown the ITT population and on the bottom is shown the high baseline CRP population. The treatment effect appeared to be similar in each, suggesting that there is efficacy in maintenance of response regardless of CRP before induction.

Although the response rates fall somewhat from Month 9 to Month 15, where this corresponds to Month 6 and 12 from the start of the maintenance study, the treatment effects were similar, suggesting that maintenance of response continues to Month 15.

[Slide.]

The results for maintenance of clinical remission parallel the results for response. The

treatment effect appeared to be similar for the ITT and CRP population, and as for response, the effect on remission appears to continue to the Month 15.

[Slide.]

Now, I will discuss some subgroup analyses of the maintenance study.

[Slide.]

We looked at the same kinds of subgroup analyses as described for induction. Subgroup analyses will be shown for the overall population, as well as the high CRP population had very similar results.

Our conclusion again is that the treatment effect is generally similar for each of these subgroups to that of the overall group.

[Slide.]

Looking at Baseline CDAI, there is no clear trend based on CDAI score quartiles, but here the range is smaller than that for the induction studies because patients were required to have had a response on entry into the study.

[Slide.]

For prior medication subgroups, there was a trend of anti-TNF having a higher response than immunosuppressants, which in turn was higher than steroids. But these are post-hoc subset analyses, so it is hard to interpret the differences, but at least these data suggest that patients whose disease required anti-TNF agents in the past are getting a response to natalizumab.

[Slide.]

Subgroups of inadequate responders to prior medications appeared to show a slight trend of higher treatment effect in the anti-TNF and immunosuppressant groups. But none of these analyses are adjusted for multiple looks at the data, and we should still note the lack of rigorous criteria used to identify inadequate responders.

These data don't suggest that an inadequate response to prior medications has adverse implications for the possibility of responding to natalizumab. But it is important to keep in mind the exploratory nature of these analyses.

[Slide.]

Subgroups of concomitant medications appeared to show a slight trend of higher treatment effect in the immunosuppressant group. But the effects are fairly similar and we conclude that no obvious difference was found across subgroups based on categories of concomitant medication use.

[Slide.]

Summary of Efficacy.

[Slide.]

In the first induction study 301, a retrospective subgroup analysis of elevated CRP showed a statistically significant treatment effect on clinical response of 13 percent. The treatment effect for the entire study was just under 8 percent.

Study 307 was consistent with the finding in the subgroup analysis of Study 301. A treatment effect of 15.5 percent was found in the prospectively selected high CRP population.

There was no confirmation, however, that high CRP predicts clinical response because the low

CRP population was not included in that study for comparison.

[Slide.]

In the maintenance study, efficacy was demonstrated in the overall population of induction responders with a treatment effect of 33 percent through Month 9, which is six months from the start of the study.

The subset with high CRP at baseline had a similar response to that of the overall population suggesting that there is efficacy in maintenance regardless of CRP at baseline.

This leaves a question regarding whether the population should be restricted to elevated CRP as it did not seem to matter in the maintenance study.

Secondary endpoints were not adjusted for multiple comparisons and the steroid withdrawal secondary endpoint is listed as one of several secondary endpoints. While the results seemed to show an effect, interpretation is complicated and the appropriate statistical approach is still being

considered.

[Slide.]

For the subgroup analyses, the treatment effect was generally similar across subgroups, but any conclusions from these analyses were guarded because the analyses were exploratory and were not statistically rigorous.

Our conclusions were that there is no definitive impact on treatment effect. There is no obviously higher treatment effect in any one group, but also no clear loss of effect across the range of CDAI levels, across the categories of prior medication use, and across the categories of inadequate response to prior medications.

Use of monotherapy had no clear impact on treatment effect, but there was no prospective evaluation of use of monotherapy as there was for MS.

[Slide.]

The sponsors provided much of the details regarding safety data. I will give you our review of the data and emphasize the main points that are