AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE GASTROINTESTINAL DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

EFFICACY AND SAFETY OF TYSABRI (NATALIZUMAB) FOR PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

Tuesday, July 31, 2007

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. SACHAR: Good morning. On behalf of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, I welcome you all to our joint meeting to discuss the efficacy and safety of Tysabri (natalizumab) biological license application for patients with moderately to severely active Crohn's disease.

I am David Sachar, Professor of Medicine and Director Emeritus of Gastroenterology at Mount Sinai School of Medicine. I am not, nor ever have been, the Surgeon General, but I do have a particular interest in Crohn's disease.

We will in a few moments go around and ask the members of the panel to introduce themselves. But first, there are some regulatory statements that need to be read and disseminated.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the Advisory Committee members take care that any conversations about today's topic take place in open forum of the meeting and not during breaks or lunch, corridors, elevators, and in passing.

We are also aware that members of the media are eager to speak with the FDA about these proceedings. However, like the Advisory Committee members, FDA will refrain from discussing the details of this meeting with the media until the meeting's conclusion.

For the convenience of the media representatives, I would like to identify the FDA press contact is Ms. Rita Chapelle. Here at this

point, please stand. Good. So that is your point of contact.

Finally, we look forward to an interesting and a productive meeting. Thank you for your participation and cooperation

Just to know who folks are, I have already identified myself as David Sachar from Mount Sinai, Chair of the joint meeting, and let's start in counterclockwise order.

DR. VEGA: Jose Vega from Global Clinical Development at Amgen and I am the Industry Representative.

DR. NEATON: Jim Neaton, Professor of Biostatistics from the University of Minnesota.

DR. LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center, Albany, New York.

DR. COUCH: James Couch, Professor of Neurology, University of Oklahoma Medical School.

DR. CHANG: Lin Chang, gastroenterologist, UCLA.

DR. NELSON: Lewis Nelson, Associate Professor, Emergency Medicine at New York

University School of Medicine and a medical toxicologist.

MS. EICHNER: Marilyn Eichner, Patient Representative.

DR. KRIST: Alex Krist, Associate Professor, Virginia Commonwealth University, Family Medicine.

DR. DAVIS: Terry Davis, LSU Medical Center in Shreveport, Louisiana. I think I am on here because of my expertise in health literacy.

DR. LEVINE: Bob Levine at Upstate Medical University, State University of New York, Professor of Medicine, Division of Gastroenterology.

DR. HENNESSY: Good morning. I am Sean Hennessy. I am an epidemiologist at the University of Pennsylvania, School of Medicine.

DR. FERRETTI-ACETO: Vickie Ferretti-Aceto, Designated Federal Officer.

DR. PLATT: Richard Platt. I am Professor and Chair of the Department of Ambulatory Care and Prevention at Harvard Medical School and Harvard Pilgrim Health Care.

DR GARDNER: Jacqueline Gardner, Professor of Pharmacy, University of Washington. I am a pharmacoepidemiologist.

DR. KOSKI: Carol Lee Koski, retired Professor of Neurology, University of Maryland, currently Medical Director of the GBS/CIDP Foundation.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

MR. LEVIN: Arthur Levin, Director of Center for Medical Consumers in New York, Consumer Advocate.

DR. PASRICHA: Jay Pasricha, Professor of Medicine and gastroenterologist at the University of Texas, Galveston.

DR. KRAMER: Judith Kramer, Associate Professor of Medicine, Duke University, interest in drug safety and effectiveness in practice.

DR. SMITH: Margo Smith, Director of Infectious Disease, local here in Washington Hospital Center.

DR. KORVICK: Joyce Korvick, Deputy

Division Director for Gastroenterology Drug Products, FDA.

DR. BEITZ: Julie Beitz, Director, Office of Drug Evaluation III in CDER/FDA.

DR. DAL PAN: Gerald Dal Pan, Director of Office of Surveillance and Epidemiology, CDER, FDA.

DR. AVIGAN: I am Mark Avigan, Director, Drug Risk Evaluation Division in the Office of Surveillance and Epidemiology at the FDA.

Conflict of Interest Statement

DR. FERRETTI-ACETO: I will be reading the Conflict of Interest Statement.

The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest with the following exceptions.

In accordance with 18 USC 208(b)(3), Dr.

James Neaton has been granted a waiver for his unrelated consulting for a competing firm. Dr. Neaton receives less than $10,001 per year. Dr. Terry Davis has been granted waivers under 18 USC 208(b)(3) and 21 USC 355(n)(4) for her ownership of stock in two competing firms. The stock values are between $5,001 to $25,000 and $25,001 to $50,000.

Dr. Carol Koski has been granted a waiver under 21 USC 355(n)(4) of the Food and Drug Administration Modernization Act for her ownership of stock in a competitor. The stock is valued from $5,001 to $25,000. Because 5 CFR 2640.202(a) de minimis exemption applies, Dr. Koski does not require a waiver under 18 USC 208(b)(3).

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jose Vega has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. Dr. Vega's role at this meeting is to represent industry interests in general, and not any one particular company. Dr. Vega is employed by Amgen.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from the discussions and their exclusion will be noted for the record.

With respect to all other participants, we ask that, in the interest of fairness, they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. SACHAR: Dr. Korvick will now provide an introduction and background for today's meeting.

Introduction/Background

DR. KORVICK: Good morning, Dr. Sachar and members of the Gastrointestinal Advisory Committee and the Drug Advisory Committee for Drug Safety and Risk Management Activities and temporary voting members.

Today, the focus of our discussion will be the treatment of Crohn's disease with natalizumab or Tysabri. Natalizumab is the first of a new class of therapies for the treatment of Crohn's disease. It is a recombinant humanized alpha-4 integrin monoclonal antibody.

Natalizumab returned to the market in June 2006 for the treatment of relapsing forms of multiple sclerosis with a risk-management plan, the TOUCH program, Tysabri Outreach Unified Commitment to Health.

Because this is a joint committee, I will take a few moments to comment on the disease, the risks, the composition of the committee, the need for a thorough and scientific discussion of the benefits and risks of the treatment of Crohn's with natalizumab.

Crohn's disease is a serious and disabling disease whose peak age of onset is between 15 and 25 years. It is estimated that between 10,000 and 47,000 new cases of Crohn's disease are diagnosed annually in the U.S. and is estimated that over 630,000 people in North America have Crohn's. Certainly, many of you have been involved with the diagnosis of Crohn's disease in patients, their ongoing care, or know of friends and family affected by the serious and disabling disease.

As the course of this disease progresses, many patients are managed by gastroenterologists or physicians specializing in this field. Frequent symptoms include abdominal bleeding, fever, malaise, anorexia, weight loss, diarrhea, and rectal bleeding. It is a waxing and waning disease, but its course is chronic leading to strictures, perforations in most patients.

Ultimately, these patients will receive surgery in 70 to 90 percent of cases. Complications include multiple surgeries, short bowel syndrome, anastomotic leaks, sepsis,

infertility, and sexual dysfunction.

It is not unexpected then that these patients, especially the most severely affected, have a higher rate of depression than the general population and an overall increased risk of mortality.

Today, you will hear presentations regarding the clinical spectrum of Crohn's disease, how it is evaluated in clinical practice and in clinical trials, and the risks associated with therapy including immunosuppression and rare cases of PML.

To this end, we have invited participation from both the GI and Drug Safety Advisory Committees, as well as two members from the Neurologic Drugs Committee, Dr. Couch and Dr. Koski, who were in attendance at the previous advisory committee that returned Tysabri to the market.

In addition, we have invited a member of the Anti-Infectives Committee, Dr. Smith, who will discuss PML. We expect that this joint committee

will have the scientific and clinical knowledge to fairly advise the FDA on Tysabri.

You will hear Dr. Sandborn, a well-known Crohn's disease expert, presenting the natural history and other details of Crohn's disease during the sponsor's presentation to the committee.

There are standard treatments for Crohn's disease. Usually, they progress in a stepwise fashion from corticosteroids to immunosuppressants, such as azathioprine, and inhibitors of tumor necrosis factor, such as in infliximab and adalimumab in those failing other therapies.

This strategy moved potentially less toxic to potentially more toxic, but hopefully more effective, therapy. As you will hear during the presentations and discussion today, each therapy has its unique benefits and safety risks.

As more effective therapies are approved for Crohn's disease, clinical practice is evolving including the use of anti-TNF agents in combination with corticosteroids or other immunosuppressants as initial therapy in patients with Crohn's disease.

Dr. Sandborn will also touch on the CDAI score, the Crohn's Activity Index, which is used to define patient eligibility in clinical trials for moderate to severe disease. This criterion has been commonly used in trials. There is much controversy regarding its adequacy and the CDAI score is not usually used to manage patients in clinical practice.

Regarding the safety of natalizumab, you have received in your backgrounders, a summary of the data from the prior neurologic advisory committee, as well as data from the marketing experience of Tysabri since June 2006, captured in the TOUCH program.

The two members of the Neurologic Advisory Committee present will serve as experts for today's committee meeting, also as experts who have used Tysabri to treat patients with multiple sclerosis.

In addition, we have invited Dr. Smith, the infectious disease specialist, to give a brief presentation on PML during the FDA's presentations this morning. Dr. Smith will serve as an expert in

this area, as well.

The charge to Dr. Sachar and the joint committee will be to address the benefit/risk of natalizumab for the treatment of moderately to severe Crohn's disease. While it will be important for the committee to have a basic understandings of the proceedings of the Neurologic Advisory Committee, today's meeting is not meant to be a forum for reevaluating the previous committee's recommendations on MS TOUCH program. However, where informative, comments regarding the differences and similarities of patient population, prior and concomitant therapies will be informative to the FDA.

Again, our focus is Crohn's disease. I would like to thank the sponsor, Elan Pharmaceuticals, for its timely responses to our many data requests and also my colleagues in the Office of Surveillance and Epidemiology and my own division, Gastroenterology Products. They have worked closely together during the preparation and review of this data for today's meeting.

I am sure that Dr. Sachar will aptly lead us through the day and facilitate a full and rigorous scientific discussion of the FDA's questions that you have before you.

Thank you.

Dr. Sachar.

DR. SACHAR: We will start the presentations with sponsor presentations for approximately the next 90 minutes. It will fall into several components and questions will be held until the final presentation on the clinical perspectives so that we will have a seamless series of presentations starting with an introduction by Dr. David Feigal.

Sponsor Presentations

Introduction

DR. FEIGAL: Good morning. My name is David Feigal and it is my privilege to introduce the Elan presentation to you this morning.

[Slide.]

Eleven years ago a novel immune therapy called Tysabri, which was discovered in the

laboratories at Elan Pharmaceuticals, began its first human clinical trials on a development path that would lead to new treatments for serious conditions including multiple sclerosis and Crohn's disease. This morning we welcome the FDA and the joint Advisory Committee's review of the application for Crohn's disease from Elan Pharmaceuticals and its Tysabri collaborator Biogen Idec.

[Slide.]

The first Phase I trials for Tysabri began in 1996 and by 2001, Phase III trials were initiated for both multiple sclerosis and Crohn's disease. The striking effectiveness of Tysabri for the treatment of multiple sclerosis in the first year led to an approval in November of 2004 for relapsing forms of MS.

In February of 2005, the development of progressive multifocal leukoencephalopathy in 3 patients led to a voluntary market withdrawal of Tysabri and clinical trials were put on hold.

Fifteen months later, in June of 2006,

after a comprehensive safety evaluation and a review of the two-year multiple sclerosis clinical trial data, the product was reintroduced into the market with MS with enhanced safety warnings and a risk-management plan known as the TOUCH prescribing program which, through restricted distribution and education, seeks to minimize the risk of PML, as well as better understand that risk.

Today, you are considering an application submitted in December 2006 by Elan and Biogen to add the indication for Crohn's disease.

[Slide.]

What type of patients do we think will benefit from Tysabri? In the briefing book we have included the indication proposed at the time the application was filed. Our clinical trials have demonstrated that Tysabri can induce a sustained clinical response, maintain remission, and reduce or eliminate steroid use in patients with moderately severe to active Crohn's disease who have evidence of inflammation as indicated by an elevated C-reactive protein above the upper limits

of normal.

However, to assure the benefits worth the infrequent but serious risk of PML we feel the drug will best help patients who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies.

[Slide.]

In previous approvals for Crohn's disease, conventional treatment in the product label refer to steroids and immunosuppressant drugs. However, because of the safety concerns and after consultations with gastroenterologists knowledgeable in Crohn's disease, we anticipate that the initial use of Tysabri will be in patients who have also failed anti-TNF therapy during induction or who have lost a response to anti-TNF, or who do not tolerate the anti-TNF therapies.

There are also patients who are unsuitable for anti-TNF who have failed immunosuppressant drugs.

[Slide.]

To further assure benefit, we will

implement a risk-management program as has been successfully introduced for treatment of patients with multiple sclerosis. The risk-management program will seek to both minimize the risk of PML and opportunistic infections, as well as to continue to assess that risk. Distribution will be controlled and pharmacovigilance will continue to be proactive and comprehensive.

The risk-management program for patients with Crohn's disease and their physicians will ensure that they are informed of the risks and the appropriate use conditions. The program will recommend discontinuation of Tysabri at 3 months in the absence of a clinical response to treatment. Tysabri use will be reassessed when steroid tapers are not completed within 6 months.

[Slide.]

We feel that our presentation this morning will demonstrate the Tysabri has a favorable benefit to risk profile to support approval. We have proposed that the RiskMAP for Tysabri developed for multiple sclerosis be expanded and

extended to include Crohn's disease to ensure that appropriate patients are considered for treatment with Tysabri and that physicians and patients are educated and that there is proactive pharmacovigilance

Tysabri is effective for inducing and maintaining a response and remission and is steroid sparing in Crohn's disease. But, because of the potential risk of PML, the target population is likely to be patients that have failed conventional therapies including both immunosuppressants and anti-TNF drugs.

[Slide.]

This morning Professor William Sandborn will present the clinical perspective on Crohn's disease followed by presentations on the effectiveness and safety findings from our clinical trials by Dr. Stephen Jones and Gordon Francis. Dr. Will Maier will present our experience with, and our proposals for, risk-management of Tysabri, and Dr. Sandborn will conclude our presentation with clinical perspectives on benefit and risk.

We look forward to being able to answer your questions, address your concerns, and present to you the evidence that Tysabri can offer people with Crohn's disease a new treatment option when others have failed.

Dr. Sandborn.

Crohn's Disease

[Slide.]

DR. SANDBORN: Dr. Sachar and members of the Committee, I would like to review for the next few minutes, the clinical perspective on Crohn's disease and a brief review of our currently available therapies to help you as you consider Tysabri today.

I can say right off the bat that I share very much Dr. Korvick's view of the natural history of the disease, and we will just go through that briefly for emphasis.

[Slide.]

Crohn's disease is an inflammatory disease of the gastrointestinal tract that may involve any part of the gut. It is characterized by chronic

inflammation of all the layers of the bowel wall.

The pathogenesis is incompletely understood. There are elements of genetic susceptibility, environmental triggers that are as yet not fully understood, and altered immune function.

This altered immune function is characterized by the migration of leukocytes from the vasculature into the gut mucosa, and ultimately the enhanced production of pro-inflammatory mediators.

[Slide.]

On the left you can see a colonoscopy view of a normal bowel and on the right the severe tissue destruction that can occur with moderate to severely active Crohn's disease. You can imagine that serious consequences can occur from uncontrolled inflammation such as you see on the right. In fact, we have come to understand that in the longer term, Crohn's disease is a chronic progressive destructive and ultimately debilitating disease.

As Dr. Korvick said earlier, patients generally present with abdominal pain, diarrhea, and weight loss, and then, as the disease progresses, they will form strictures that lead to bowel obstruction with requirement for operation, and perforation of the intestine with either fistulas or abdominal or pelvic abscesses, which again lead to the need for operation.

[Slide.]

The disease is a lifetime disease. The median time to the first or most common form of complications, the strictures, is about 5 years. The median time in the second sort of form of complications, penetration of the disease with fistulas or abscesses is about 8 years.

The median age of onset is 30. Half the patients have the onset of disease before the age of 30 and most commonly in the 15 to 25 years of age. Patients will have disease often for 40 or 50 years, and so, when you are thinking about the treatment of Crohn's disease you have got to take the long-term view.

Seventy to 90 percent of patients will undergo operation from 20 years from diagnosis, and you can think of a rule of two-thirds. About two-thirds of those patients will come to a second surgery and two thirds of those to a third surgery, and on and on. So, there is a substantial minority of patients who have a large number of surgeries.

You can see extra intestinal manifestations that can affect the eyes, the joints, and the skin. There is an important impact on the patient's quality of life in day to day function. I will come back to that in just a moment.

This is not a benign condition, as Dr. Korvick said. This is a serious condition and it is actually associated with an increase in mortality. One recent study suggested a standardized mortality ratio of 1.5 compared to the general population.

[Slide.]

How do we measure Crohn's disease? I am sure we will come to the discussion of this from

clinical symptoms as the course of the day goes on, but I want to introduce the concept of the Crohn's Disease Activity Index. This is a validated instrument that was developed in an NIH-sponsored trial in the 1970s. It has been really the basis of the clinical trials that have led to our clinical practice and for the drugs that are approved for Crohn's disease, the basis of approval for those treatments.

It is comprised of eight components which include diarrheal stools, abdominal pain, and general well being, and those are the major drivers of the index along with the use of antidiarrheals, the presence or absence of an abdominal mass on physical exam, the presence of anemia on laboratory evaluation, and the presence of weight loss.

[Slide.]

The Crohn's Disease Activity Index can range from a low of about zero to a high score of approximately 600. Patients above 450 are actually exceedingly rare, usually critically ill and often have a variety of comorbidities and would not be

appropriate for clinical trials.

We generally define remission as a score of less than 150, and Dr. Jones will come back to the definitions for clinical trials in a few minutes.

For patients with moderate to severe Crohn's disease, we will typically enroll patients with scores of 220 to 450 points. What do those patients look like for those of you that don't typically think about the CDI score?

[Slide.]

The patient with moderately active Crohn's disease is actually quite ill. They will have moderate or worse pain on most days, 8 or more stools per day. They feel poorly. They often have some interference with their daily function whether they are going to school or trying to work.

The severe outpatient form of Crohn's disease, patients will have severe pain on most days. They may have 12 or more stools per day. They feel terrible and they are often impaired in their ability to work or go to school.

[Slide.]

As I have mentioned earlier, in contrast, patients in remission generally feel well and patients with CDIs of more than 450 are infrequent and usually have comorbidity problems.

[Slide.]

I told you I would come back to the quality-of-life issue and I think the easiest way to think about this is with the generic health-related quality of life that is going to be used to cross the variety of diseases.

In yellow, at the top, you can see the health-related quality of life scores as measured by the SF-36 instrument for the U.S. general population.

In white, in the middle, you can see the scores for multiple sclerosis at baseline in the clinical trials that led to the approval of Tysabri for the treatment of multiple sclerosis, so this is the subset of patients with multiple sclerosis that were deemed appropriate for Tysabri.

In blue, at the bottom, reflecting a

relatively severe impairment in the quality of life across these physical and mental domains, you can see the impact that moderate to severe Crohn's disease has on the patients that entered the trials for Tysabri.

[Slide.]

How do we treat Crohn's disease in 2007? Dr. Korvick talked about the evolution and thought toward a top down strategy where biologics are introduced early. I think what we can say today is in 2007, we are still very much in the step-up progressive strategy.

The clinical trials that will begin to evaluate the so-called top-down strategy with the early intervention with anti-TNF biologics are just beginning. Those trials won't finish for years, and I think we are a number of years away from changing our treatment paradigm in Crohn's disease.

So, in 2007 and for the intermediate term, I think we are still very much in a step-up strategy. As Dr. Korvick mentioned earlier, we began with the least effective drugs. They are not

FDA-approved for this indication. They have minimal efficacy, but they are thought to be quite safe, the 5-amino-salicylate drugs and antibiotics.

We moved there from budesonide, a topical corticosteroid, and then prednisolone or prednisone, the systemic corticosteroids, which have considerable toxicity, I will come back to that.

We move from there to azathioprine and 6-mercaptopurine, the immunosuppressive drugs, and finally to the anti-TNF biologics, infliximab and adalimumab.

[Slide.]

Let's focus on those last three categories, because those are the drugs that are clearly effective for various indications in Crohn's disease.

We can begin with corticosteroids. These are effective as induction agents, but not as maintenance agents. They have a variety of side effects especially to prednisone, prednisolone variations, cataracts, osteoporosis, infection, and

drug-induced diabetes.

Infection is particularly important. There are a couple of investigator-initiated trials which really formed the basis for the use of corticosteroids and for induction treatment in Crohn's disease. In one of those trials, there was about a 2 percent mortality from sepsis that was presumably from steroid use, and in the other trial, about a 1 percent rate of sepsis that wasn't fatal.

There are considerable toxicities with steroids especially with infection.

The immunosuppressive drugs are relatively slow acting. They can take three months or so for a clinical benefit to be seen, so we have predominantly used these as maintenance drugs rather than induction drugs, and that places some limitations around their use.

There are two important forms of toxicity that are seen with these drugs. You can see lymphopenia or leukopenia and infection, both bacterial infection and opportunistic infection

either in the setting of leukopenia or just more generally with immunosuppressive properties of these drugs. More recently we have come to understand that there is about a 4-fold increased risk in non-Hodgkin's lymphoma associated with these patients who are treated with this drug for Crohn's disease.

[Slide.]

Finally, the anti-TNF therapies. Infliximab was approved in 1998, so we are coming up on the 9-year anniversary. This biologic has really revolutionized our clinical practice. It is effective for induction and maintenance, but it doesn't work in all the patients. Both adalimumab and infliximab, about a third of patients will have no response, a primary non-response to that mechanism of action.

Another third of patients will respond. But eventually it will lose response under maintenance therapy. So, very valuable for the patients that benefit. It met a large unmet need, but there is still an important group of patients

who are not sufficiently treated by these agents.

These agents also have important toxicities. The FDA was instrumental in postmarketing surveillance in reporting the reactivation of latent tuberculosis with this agent, the dissemination of histoplasmosis, and more recently, an association of hepatosplenic T-cell lymphoma in young patients, predominantly males, who were treated with a combination of azathioprine and infliximab.

Yet, every day in clinical practice, we make risk-benefit calculations with this drug. We are able to identify the patients whose disease is progressing, who failed the other therapies, and whom the risk of anti-TNF therapy is outweighed by the profound clinical benefits. And yet there are patients that aren't adequately treated.

I would also make the point that the FDA intervention of requiring testing for latent tuberculosis has been very effective in altering the course of that complication. So, now we screen for latent tuberculosis, we are able to cull out

the patients who are at risk, and that has led to an improvement in the safety profile. And I think that risk-management strategy applied to other drugs like Tysabri will be important as you make your deliberations today.

So, finally, I would just like to emphasize the point that there is a big unmet need in Crohn's disease for the most severe outpatients who fail our other therapies, and this is still an important subset of patients. About 30 percent of patients again won't respond to the anti-TNF therapies and some of the patients who do respond eventually lose response.

We need new treatments in 2007 with a different mechanism of action who will treat some fraction of those additional patients.

Thank you.

DR. SACHAR: Thank you, Dr. Sandborn.

Without questions, we will move directly to hear from Dr. Jones about efficacy data.

Efficacy Data

DR. JONES: Hello.

[Slide.]

DR. JONES: My name is Dr. Stephen Jones. I am Director of Clinical Development with Elan Pharmaceuticals and I am going to talk today about the efficacy of natalizumab for the treatment of Crohn's disease.

[Slide.]

Before I go into the efficacy, I am going to just address the novel mechanism of action of natalizumab for the treatment of Crohn's disease. I am also going to talk a little bit about the treatment objectives for Crohn's disease and also talk a little about the trial tools that were utilized to assess whether or not our drug has benefit and meets those objectives.

The bulk of my talk will be based on the Phase III clinical development program, and we will be talking about induction of response, and for that, there are two induction studies we carried out, CD301 and 307.

I will be going into a lot more detail about these in the forthcoming slides. We will

also be talking, of course, about maintenance, as well, maintenance of response.

[Slide.]

We heard from Dr. Sandborn that the pathogenesis of Crohn's disease involves enhanced recruitment of white cells into the gut mucosa from the gut vasculature. The reason this occurs is because the white cell expresses small proteins on the cell surface known as integrins.

These integrins can combine with small adhesion molecules on the inside of the blood vessel wall. This combination allows the white cell then to leave the vasculature into the gut mucosa where it causes inflammation or can enhance the inflammation.

[Slide.]

Natalizumab works by blocking the interaction of these integrins with their corresponding receptor on the vascular wall, and this prevents the white cell entering into the gut mucosa where it would cause inflammation.

This is a novel mechanism of action. This

is different to the biologics that are currently on the market at the moment for Crohn's disease.

[Slide.]

We will now talk about the treatment objectives for Crohn's disease. Initially, what we need to do is we need to treat these patients who have active disease. We refer to this as induction of response and remission, so we are bringing these patients into a clinically acceptable state.

Once we have done that, it is very important, of course, to maintain patients in this quiescent disease state. We call this maintenance of response and remission. This is to prevent flares.

We know that the long-term use of steroids should be avoided because of the complications associated with them, so an important endpoint of any clinical trial, of course, will be to look at reduction of steroid use.

Ultimately, of course, we want to improve a patient's quality of life.

[Slide.]

We heard from Dr. Sandborn that the Crohn's Disease Activity Index is still widely accepted as the best tool for Crohn's disease activity measurements in clinical studies. We know this is primarily based on the patient filling in a diary card, and he or she will record the bowel symptoms, the abdominal pain, the general well-being of the previous 7 days.

There is also a physician's assessment, as well, and the physician will assess for abdominal mass, would be looking for extra intestinal manifestations, would measure hematocrit, weight, and these scores are combined to give you a score range of between zero and 600, 600 being the worst score.

We define moderately severely active Crohn's disease as a score between 220 and 450. I am pointing this out because this is the population we treated in our clinical studies.

A clinical response is defined as a 70 point or greater reduction in CDAI score from the baseline value. We discuss clinical remission, and

clinical remission is a score of 150 or less.

[Slide.]

Other measurements are the tools we use in our clinical studies. The Inflammatory Bowel Disease Questionnaire. Now, this is a disease-specific quality-of-life questionnaire. It is 32 questions and each question ranges from 1 to 7, 7 being the best score. So, the total score can range from 32, which is the worst score, up to 224, which is the best score.

A score of 170 or above equates to a patient who is in clinical remission.

We also use the Short Form 36, which is the general quality-of-life measurement.

Importantly, as I mentioned, we need to look at steroid sparing. To do this, we look at the proportion of patients who were discontinuing steroids at a particular time point.

In addition, and I will talk a little bit more about this, the C-reactive protein. Now, C-reactive protein is produced by liver cells in response to inflammatory mediators. This can serve

for two purposes. It can serve as a marker, an objective marker of inflammation, and we can also use this. We can measure this over time to see whether our drug is reducing down inflammation.

[Slide.]

We now turn our attention to the Phase III Clinical Development Program. Following a successful Phase II program, the first study we conducted was for induction, and this was CD301.

In this study, we saw benefit for natalizumab over placebo, but we demonstrated significant benefit in a large subpopulation that had an objective marker of inflammation, and that was the C-reactive protein.

So, following this induction study, we carried a second induction study out to confirm our findings, and that you will see on the right, CD307. In addition to these two induction studies, we also carried out a maintenance study, and this is CD303.

All these patients were then eligible to go into an open-label study CD351. Now, this was

conducted for safety purposes and Dr. Gordon Francis will talk more in detail about that in his forthcoming talk.

[Slide.]

So, if we talk about CD301, this was the induction of response and remission in patients with moderately to severely active Crohn's disease.

[Slide.]

905 patients were recruited to this study and we used a 4:1 randomization, and this was to allow us to have enough natalizumab responders to enter a maintenance study CD303. So, in total, we had 724 patients randomized to natalizumab and 181 to placebo.

The dosing was carried out in the study at Week zero, which is baseline, Week 4, and Week 8. The primary outcome measure was at Week 10.

[Slide.]

If we look at the patient disposition, we can see of those patients that 78 percent of those placebo patients completed the final visit, which was Week 12; 83 percent of natalizumab patients

completed the final visit, which was Week 12.

The reason the placebo patients, if we look at them first, and continue, we see the lack of efficacy 9 percent. We also see the worsening and we also see CD-related AEs was 4 percent, and Other was 9 percent.

We actually went back and we looked at the 16 patients and evaluated them, and the majority of those patients was voluntary withdrawal that we noted was their reason for discontinuing.

If we look at the natalizumab group, again, here we see a lack of efficacy with 7 percent, and we see that CD related AEs was 6 percent. We are going to be talking more about the safety in the next coming study.

[Slide.]

If we look at the baseline characteristics now for CD301, we can see that they were balanced between the two groups. We see that approximately 40 percent of patients were taking steroids at baseline and roughly about a third of patients were taking immunosuppressants.

Previously, 40 percent of patients had taken anti-TNFs in the past, so this is prior to entry. They weren't allowed to be on concomitant TNF-alpha inhibitors during any of our induction studies.

[Slide.]

Now, if we look at the results for CD301, and this was our primary outcome, and this is Week 10, so what we are looking at is response at Week 10.

Here, we see a trend in favor of natalizumab at all time points, however, we see a slightly higher placebo response rate than one would anticipate in a Crohn's disease study evaluating this patient population.

So, we thought, okay, well, maybe this has possibly to do with the trial design that we used on 41 randomizations, there is a slightly higher expectancy of receiving active drug, maybe to do with the frequent visits. But we also know that many of these patients, although we know they have Crohn's disease, also have coexisting conditions,

such as irritable bowel syndrome. They may have bile salt diarrhea. They may have symptoms that are driven by stricture formation.

So, it is possible that some of these patients, the symptoms were actually driven, and the score was driven by conditions outside the inflammatory process that you get in Crohn's disease.

So, we thought, well, let's go back, let's have a look at those patients who have got an objective marker of inflammation. We know the C-reactive protein serves this purpose.

[Slide.]

So, we looked at this patient population. This is the patient population that had a C-reactive protein above the upper limit of normal, and we referred to that as 2.87. This was a post-hoc analysis but, in this, we see a significant benefit in favor of natalizumab over placebo. However, as I say, this is post hoc. So what we did is we carried out a second induction study to confirm our findings that patients with an

objective marker of inflammation, we can see a significant benefit in Crohn's disease with natalizumab.

[Slide.]

The second study we carried out was CD307. Again, this is induction of response and remission in patients with moderately to severely active Crohn's disease. However, in this study, all patients had to have an elevated C-reactive protein at the baseline.

[Slide.]

In this study, 509 patients were recruited and this time we randomized on a 1:1 basis, so we had 259 patients on natalizumab and 250 patients on placebo.

Again, dosing was carried out at Week zero, Week 4, and Week 8, and this time a prime assessment was at Weeks 8 and 12.

[Slide.]

If we look at the objectives and the endpoints for CD307, we see that the primary endpoint was the response greater than a 70-point

reduction in the CDAI from baseline at Weeks 8 and 12 is mentioned.

The secondary endpoints were remission of less than 150 at Weeks 8 and 12, response at Week 12, and remission at Week 12, so these are primary and secondary endpoints for this study.

[Slide.]

If we look at the disposition in this study, we see that out of the completed the final visit, 83 percent of those patients on placebo completed the final visit, 85 percent on natalizumab completed the final visit.

Of those patients who did not complete, you see that 12 percent on placebo as opposed to 5 percent on natalizumab were due to lack of efficacy or worsening of Crohn's disease. We see slightly more adverse events in this study and, again, Dr. Francis will talk to that in his next presentation.

[Slide.]

If we look at the baseline characteristics, again, you can see these were balanced between the two groups, between placebo

and natalizumab, and actually, they are very similar to those of 301.

In this case, though, we see a slightly higher number of patients who took TNF-alphas in the past.

[Slide.]

We look at results now for CD307. Again, the primary outcome is mentioned as Weeks 8 and 12, and you can see this in the right-hand side of this chart. We actually saw significance at each of the visits, Week 4, Week 8, and 12, as well. We see 48 percent of patients were in response on natalizumab as opposed to 32 percent on placebo.

[Slide.]

If we look at the secondary outcome, and this was remissions. So, when we talk about remissions, this is a score below 150. Again, we are looking at the same visits, Weeks 4, Weeks 8, Weeks 12, and also Weeks 8 and 12, which is our primary outcome. Again, we saw significance at Weeks 8 and 12, and we also saw it at 8 and 12 as well.

[Slide.]

Now, I have talked quite a bit about CRP, and we see that in those patients in the top line, in yellow, those patients were randomized to placebo. But the C-reactive protein didn't change throughout the study. However, those patients who were randomized to natalizumab, we can see that the C-reactive protein roughly halved over the course of the study at Week 12.

[Slide.]

Now, on the left is the ITT population for 307. This is the results I presented in my previous slide. We went back and we did a post-hoc analysis. We applied the same statistical algorithm that we used for a primary analysis of 307 to 301, so now we are looking at 301 patients at time point Weeks 8 and 12 who all had an elevated C-reactive protein, and when we did this--this is post hoc--but we saw that the results were comparable between the two populations or between the two studies.

[Slide.]

Now, I am going to turn our attention actually to the patients who failed other therapies. We see on the left, that is the intention-to-treat population again, and this is just there for reference.

If we now work up the treatment paradigm that Dr. Sandborn addressed in his previous presentation, we look, first of all, at those patients who failed steroids. When we talk about failed steroids, this is failed steroids prior to entrance to the study, or they could be on steroids at baseline, and we deem them as failures by the fact that they have active disease, moderate to severely active disease despite the concurrent use of steroids.

So, if we look at that patient population, we see again the results are relatively consistent with what we found in the ITT population. You can see 45 percent of patients on natalizumab were responsive as opposed to 31 percent on placebo.

We now move to the next level of the pyramid and we look at those patients who failed

immunosuppressants. Again, these patients either failed previously or were on those drugs at baseline. Again, we see figures and we see results that are consistent again with the intention-to-treat population.

Now, they are the patients that have failed conventional therapy, conventional therapy being steroids and immunosuppressants. If we now turn our attention to the right-hand side of this graph, we are now looking at patients, those who failed TNF-alphas.

These have failed in the past because none of these patients could be on TNF-alpha during the study. If we look at that patient population, again we see significant benefit in this hard-to-treat population that had been refractory to other therapies.

[Slide.]

Summary for induction. Natalizumab induced response and remission in patients with objective evidence of inflammation. We induced response and remission, and that seemed to be

consistent across all subgroups who had failed other therapies.

So, in conclusion, we feel that natalizumab is effective for the treatment of patients with moderately to severely active Crohn's disease.

[Slide.]

Now, I am going to turn our attention to the maintenance study, which is CD303, and this was the maintenance of response and remission.

[Slide.]

In CD303, patients who responded in CD301, and what I mean by "response," I mean they had to be in response to greater than 70 point reduction from the baseline score at both Weeks 10 and 12, and had to have a CDAI score below 220 at both those time points.

For these patients who entered into CD303, they were randomized on a 1:1 basis, natalizumab and placebo. Dosing was carried out on a monthly basis, and the duration of the study was for 12 months.

[Slide.]

If we look at the patient disposition here, this is the efficacy population that we are addressing here. These are the patient populations that responded to natalizumab, and this is the patient population I will be talking about in the forthcoming slides.

We see complete to the final visit. But only 30 percent of those patients randomized to placebo actually completed as opposed to 67 percent on placebo. Now, the reason the placebo patients didn't complete, you can see there was worsening of disease, lack of efficacy. This mainly makes up the reasons that they didn't complete.

We also see that non-CD related AEs made up about 7 percent of those patients that didn't complete and Other made up 14.

Now, for both natalizumab and placebo, we went back again, and we looked at the other category, and actually, when we went through the category, we could see that most of those patients that actually withdrew were actually lack of

efficacy.

[Slide.]

So, if we look at the primary outcome for CD303, the primary outcome was a proportion of patients who did not lose response at any assessment through to Month 6. What I mean, "lose response," the patient had to have a score above 220 and an increase above 70 points from the baseline 303 score.

Our contingent primary, there was a proportion of patients maintaining remission, a score below 150 at every assessment through to Month 6. We call it "contingent primary," because if we had our first primary, which was maintenance of response, and a contingent primary becomes elevated to a co-primary.

[Slide.]

Now, if we look at the results for CD303, and this is our primary outcome, the primary outcome being a primary endpoint being at Month 6, we see that those patients who were randomized to natalizumab maintained response at every assessment

through to Month 6, 61 percent of those patients, and those that were randomized to placebo, only 28 percent of those patients maintained response through to Month 6.

Now, just to confirm that, basically, they had to be in response at every single time point up to that assessment. We also see as a secondary endpoint, Month 12, we also see a significant greater proportion of patients on natalizumab were in response as opposed to those randomized to placebo.

[Slide.]

If we look at remission now, which is contingent primary, again, we see a statistically significant greater proportion of patients maintained remission at every assessment through to Month 6 as opposed to those who were randomized to placebo, and we also see that at Month 12, as well.

[Slide.]

We turn our attention now to the Inflammatory Bowel Disease Questionnaire. We can see here those patients who responded to

natalizumab in CD301. There is an elevation in their IBDQ as you would expect from 124 up to 182.

What we are showing in this slide is that those patients who were randomized to natalizumab maintained their inflammatory bowel disease score, questionnaire score above what we consider as being clinical remission, so remember 170 points equates to a patient who is in clinical remission.

We see with natalizumab, those patients maintained a score higher than that level throughout the clinical study, whereas, those patients who were randomized to placebo, we actually see the results going down and down below that level.

[Slide.]

As mentioned, a very important endpoint to any clinical study should be trying to get patients off steroids. We know that long-term steroids are associated with considerable side effects.

So, CD303 was designed to investigate the ability of natalizumab maintenance treatment to eliminate oral steroid usage.

We also looked at the number of patients who were in steroid-free remission. So, subjects followed a protocol-defined steroid withdrawal algorithm, which commenced at Week 10 of our induction study CD301.

[Slide.]

If we look at the results now on the left, this gives us the proportion of patients who we could eliminate steroid usage from, and we can see on the left there, at Month 6, which again this is one of our secondary endpoints, that 58 percent of patients were able to eliminate steroid usage. This is obviously a proportion of the patients that were using steroids at the start of 301 as opposed to 28 percent of those patients randomized to placebo.

We also see at Month 12, and this was actually a tertiary endpoint for this clinical study. But again 49 percent of patients randomized to natalizumab were actually able to eliminate steroid usage as opposed to only 20 percent on placebo.

Importantly, of course, we also want to look at steroid-free remission, so not only are we getting these patients off steroids, we were also keeping these patients in remission, as well.

We can see here on Month 6, that 45 percent of those patients on natalizumab were in steroid-free remission as opposed to 22 percent on placebo. This was also seen at Month 12, we saw 42 percent versus 14 percent on placebo.

[Slide.]

This is really just for reference. This is actually a list of all our secondary outcomes for CD303. There were seven of them. I addressed most of these today.

You see when the p-value actually hits statistical significance in all of these. I have addressed the sustained response through to Month 12 and sustained remission through to Month 12 in my first two slides in 303.

Time to loss of response, again, you can see is significant. We saw it took 86 days. The median time for loss of response to those patients

randomized to placebo as opposed to greater than 12 months, because we couldn't measure the median, because the majority of patients was still in response at the end of the study.

We have also looked at the change from 301 baseline in IBDQ score, and we have now discussed, as well, the patients not taking oral steroids at Month 6, and the proportion of patients in steroid-free remission as well at that time point.

[Slide.]

I am just going to turn our attention now to some of the populations of interest. We know that the long-term use of immunosuppressants, or should I say concomitant use of immunosuppressants, will be avoided now due to the safety concerns.

So, we have also looked at that patient population who were not taking immunosuppressants in this clinical study. Again, we see at Month 6 and Month 12, both response and remission. We saw statistically significant benefit for those patients who were randomized to natalizumab as opposed to those on placebo.

[Slide.]

We have heard that primarily, natalizumab will be utilized initially in those patients who failed the TNF-alpha, so here we are seeing those patients who failed therapy. Again, we see at Month 6 and Month 12, both response and remission, a significantly greater proportion who were randomized to natalizumab still in response and remission as opposed to those on placebo.

[Slide.]

So, in summary, for induction, natalizumab has demonstrated efficacy for response and remission in patients with an objective marker of inflammation.

We have demonstrated efficacy in patients who failed therapy with corticosteroids, immunosuppressants, and also patients who failed therapy with an anti-TNF alpha.

For maintenance, we have demonstrated sustained response and remission. We have also shown a significant quality-of-life improvement was maintained with natalizumab. We have also shown

significant steroid-sparing effects of natalizumab. We have also shown that concomitant immunosuppressants were not required to maintain this long-term efficacy.

So, with that, I am going to it over to Dr. Gordon Francis, who will talk about Safety.

Safety Data

DR. FRANCIS: Thanks, Steve.

[Slide.]

My name is Gordon Francis. I am the head of Clinical Development at Elan Pharmaceuticals. As indicated, I will turn our attention now to the safety profile of natalizumab that was obtained during the clinical development program.

[Slide.]

In terms of the safety profile, we will talk briefly about the exposure of the population, as well as a brief general safety overview, and spend somewhat more time talking about items of interest from the safety, specifically, infections, items of safety concern related to mechanism of action of the drug including hypersensitivity

reactions, and then finally, discussing briefly the post-marketing safety findings that have been achieved since the second launch in June of 2006.

[Slide.]

When we are talking about the safety population, there are two specific components of this, the MS patient population, as well as the CD patient population. As we heard here last year, the natalizumab exposure in the MS clinical trial was 1,617 patients in the placebo-controlled setting with approximately 1,100 placebo patients.

Many of these placebo patients could be re-randomized or enrolled into an open-label study, such that ultimately, 2,321 patients with MS were exposed to drug during the clinical development program with 3,300 patient years of exposure.

Similarly, in the Crohn's indication, as has been already described by Dr. Jones, the natalizumab exposure was approximately 1,180 patients with 506 placebo patients. Again, placebo patients could re-randomize into the open-label study, such that 1,563 patients ultimately were

exposed concomitantly to natalizumab therapy for 1,338 patient years.

Pooling those two populations, we have 3,800 patients who have somewhat over 4,600 years of patient exposure during the clinical development program. We will focus mainly on the CD experience today but call upon the MS experience as needed for items of specific interest.

[Slide.]

In the CD safety group, we will be talking about two types of populations. One is the short-term placebo-controlled studies of active Crohn's disease that Dr. Jones has just described, generally, with three months of dosing with placebo control.

As we have heard, approximately 80 percent of the patients in this safety population are culled from the two induction studies, CD301 and 307, the remainder of patients coming from the Phase II studies.

In addition, we will talk briefly about the short- and long-term dosing in which there was

no placebo-controlled group, but approximately, 1,500 patients had exposure for up to three years.

[Slide.]

In terms of the long-term exposure of natalizumab in the Crohn's program, the CD351 was the open-label extension study into which patients could enroll from the active placebo-controlled studies, and approximately, 1,100 patients enrolled in those studies.

The mean number of infusions during the open-label phase for those patients was 11 with a median of 8. If one includes the natalizumab exposure that those patients received during the earlier study, such as CD301 and 307, the total mean number of monthly infusions for the patients in the Crohn's program was approximately 15 with a median of 12.

[Slide.]

I will talk very briefly about the general safety overview of the product. Some of the more detailed information is in the briefing book.

[Slide.]

Overall, most patients in most clinical trials have adverse events, and the same was true here with somewhat over 85 percent of patients experience adverse events.

The most common adverse event in Crohn's, as it was in MS, was headache seen in approximately 30 percent of patients, about 5 to 6 percent greater than in the placebo-controlled group.

Infections, as you see here, were slightly imbalanced, with slightly more in the natalizumab group than in the placebo group, and this is due mainly to mild viral upper respiratory tract infection, the difference between the two groups.

Importantly, serious adverse events were comparable between the two groups. The largest component of serious adverse events being Crohn's related flares, and thus, when one excludes the Crohn's related adverse events, the non-Crohn's serious adverse events showed a slight imbalance with 10 percent in the natalizumab group and 7.8 percent in the placebo group.

Serious infections were comparable between

the two groups in terms of the proportions of patients affected, and the serious hypersensitivity reactions, something that one might anticipate could have happened with an infused biologic was actually quite an infrequent event.

The malignancies are slightly imbalanced, at 0.6 versus 0.2 percent of patients, and we will come back to that at a later point during the discussion.

[Slide.]

If we turn specifically to the serious adverse events by organ system, excluding Crohn's disease, you can see there again the 10.1 percent versus 7.8 percent, slightly greater for the natalizumab group.

Gastrointestinal is slightly overrepresented and this being a symptom, such as abdominal pain or intestinal stenosis. Infection, as we had already described, is quite balanced. Cardiac events, there were five events in the Crohn's natalizumab group compared to the placebo group, a variety of cardiac complications that, in

the most part, were due to pre-existing cardiac disease.

Also, four events in the hepatobiliary system versus none in the placebo group. This was two episodes of cholecystitis and two of cholelithiasis.

[Slide.]

Looking at events that lead to discontinuation of therapy in the placebo-controlled studies, slightly more patients in placebo group than in the natalizumab discontinued for adverse events, the most common cause being Crohn's disease, as we talked about earlier.

This is approximately double the rate in the placebo group as it is in the natalizumab group.

In terms of the patients who received natalizumab, I would draw your attention to the events, such as urticaria, flushing, pruritus. These are symptoms related to hypersensitivity reactions as I mentioned, something that one would

expect to see with an infused biologic therapy, this being the more common reason for discontinuing in natalizumab than in the placebo group.

[Slide.]

There were 6 deaths in the Crohn's disease program, one that occurred during the placebo-controlled phase and 5 during the open-label extension. On those, I think that the Agency has one of the deaths included in the placebo-controlled database, the patient with the peritonitis. This had occurred during follow-up from the original placebo-controlled study, so the same 6 deaths are reported by both groups.

You will see here the one that occurred during the placebo-controlled phase was an accidental asphyxiation, a work-related accident. Three of the deaths we will come back to later on, the PML, the pulmonary aspergillosis, and the Pneumocystis carinii pneumonia. The other two events listed there are myocardial infarction and peritonitis with renal failure in a patient with a number of postoperative complications.

Overall, looking at the death rate in this particular study in relation to both the general population and the expected rate in the Crohn's population, the rate of death does not exceed that, that would be expected based on age and gender.

[Slide.]

I will now turn our attention to the infections. We will be discussing the serious infections, the risk of infection over time, the risk of infection with concomitant medication use, and then, because of the issue about the mechanism of action of this drug and its ability to potentially limit immune surveillance, there is a risk of viral reactivation syndromes, and we will look at the herpes viral reactivation, and then finally, issues related to the opportunistic infections including PML.

As I had earlier discussed, there is a slight imbalance in the common infections, 40 percent versus 36 percent, and this was due to viral upper-respiratory tract infections as I had mentioned, and otherwise, we will not comment on

the common ones. Again they are listed in the briefing book in detail.

[Slide.]

Turning specifically to the serious infections, as I mentioned earlier, these are quite balanced between the two groups, 2.4 percent in both groups. The most common infectious adverse event, labeled as a serious event, is abscess, and again these are balanced between the two groups. There were two cases of viral meningitis. No organism was cultured, and two episodes of urinary tract infection that were labeled as serious infection in the natalizumab group, not seen in the placebo group.

[Slide.]

Because of the issue about immune surveillance and the risk of infection, one of the concerns is does the rate of infection increase over time as patients receive more infusions in the long-term therapy of this disease. As Dr. Sandborn mentioned, this is a life-long disease.

[Slide.]

As you can see here, looking at the incidence and the rate of infection by 6-month interval of infusion up to 2.5 years of natalizumab dosing, one can see that the incidence of infection does not increase over time, and in fact, decreases slightly, and the rate of infection likewise decreases slightly over time.

If one only examines the 294 patients who actually got to 30 months throughout their time of exposure, a similar pattern is seen of a gradual decrease in the rate and the incidence of infection over time so that there is no data to suggest that there is an increasing risk of infection with increasing numbers of infusions over time. The most common infections again are relatively benign viral infections.

[Slide.]

Therefore, we took a look at the rate of serious infections over time specifically, again looking at the short- and long-term dosing using the same 6-month interval paradigm, and what you can see here is that in common with the general

infections, that the rate of serious infections likewise does not increase over time and may decrease slightly.

[Slide.]

One of the issues that has been asked to the panel, and has been raised frequently in discussions with clinicians, is the issue about washout of concomitant therapy.

As you have heard, many Crohn's patients are on steroids or immunosuppressants, and when we are implementing natalizumab therapy, we are recommending that patients not take those drugs concomitantly on a chronic basis and, therefore, there is some potential for an overlap of the immune suppression or the immune modulation of previous therapy when patients initiate natalizumab therapy.

There is a question of concern. Should there be a washout? Is there an increased risk for these patients during the first weeks or months of their natalizumab therapy while the previous therapy washes out?

I think the statement first principals the drugs that are used generally have very short half-lives in terms of either hours to days. However, the biologic effect may last longer, of course.

However, the best data that we have in terms of whether or not there is functional overlap from discontinuing therapy is to look at the rate of infections in patients who are on concomitant therapy during the first three months of their natalizumab therapy.

What you see here is the incidence of infection with concomitant medication use in the placebo-controlled studies for the first three months. The column in the far left is natalizumab monotherapy alone, and you see that 40 percent of these patients experienced infections during that interval and, regardless of whether the patients are also on immunosuppressants, steroids, or the combination of immunosuppressants and steroids, the rate of infection does not increase.

So, concomitant use for that three-month

interval does not lead to an increase in general infections.

[Slide.]

However, again, we want to look at the more severe infections, and this is looking at patients who have serious infections during that first same three-month interval. And what you will see here is looking at the monotherapy, so either a placebo or natalizumab, in combination with immunosuppressants, with steroids, or both with steroids and immunosuppressants. What you can see here is that there is indeed a slight increase in the rate of the infections, the serious infections, during that first three-month interval, in the range of 1 to 2 percent difference between monotherapy alone.

Thus, physicians will need to be aware that there is a potential for an increase in serious infections although I would also indicate that this is a worst case scenario and that this is, in fact, concomitant therapy, not washing out therapy.

[Slide.]

As I mentioned earlier, we would also like to look at the issue of reactivation of latent viruses. As you will hear later, JCV is a latent virus, herpes is another example of a latent virus that may reactivate based on immune surveillance issues.

So, we have looked at the rate of herpes infection overall, and then we have looked also at the serious herpes infections. What you can see here is that the total proportion of patients with herpes infections is slightly greater for those receiving natalizumab than those on placebo, approximately one-half of 1 percent difference, and the majority of this difference is driven by herpes simplex infections. Otherwise, various herpes infections were not frequent, and the finding was similar in the MS patient population.

[Slide.]

However, there were a number of serious herpes infections, which I have listed here. There are six listed here. There is one that will be

discussed by the agency that is not on this list. It is the same patient, the 36-year-old woman at the top who had an episode of herpes vaginitis with a history of recurrent herpes vaginitis. Her first episode occurred prior to the development of therapy.

She also developed a conjunctivitis 8 months after having received a single dose when she was being seen in the safety follow-up, so that item is not listed here, but is included in the Agency's data.

As I said, there are six items here, two of these actually onset before the patient had received the first dose of natalizumab, the first two, the vaginitis and the herpes zoster. They developed before therapy, but were reported after the initiation of therapy.

The second two cases are CMV infections, CMV colitis and a general CMV infection that occurred after relatively little exposure to natalizumab in patients who had received concomitant immunosuppression.

The next case is a case of varicella pneumonia that occurred in a woman who had a child with active chicken pox at the time, and the last case is a localized herpes zoster in a patient who was receiving concomitant steroids and immunosuppressive therapy. Importantly, none of the herpes infections were disseminated, all of these recovered with either acyclovir or spontaneously.

[Slide.]

I would like to turn to the opportunistic and atypical infections that have occurred in the Crohn's development program.

[Slide.]

There have been five opportunistic infections that have been reported as you will see here. We will talk later about the PML case, the third one there. The other four cases are all pulmonary in origin, a Burkholderia, a cepacia pneumonia, a Mycoplasma avium complex infection pneumonia, pulmonary aspergillosis, and a Pneumocystis carinii pneumonia.

The age and gender is presented there, as well as the number of infusions that the patient had had prior to the onset of the symptoms. As you can see, there is quite a wide range between 3 months up to 34 months of infusions with natalizumab.

The important factors also are the concomitant use of medications in four of these patients including steroids and azathioprine, so that many of these patients were on concomitant immunosuppressants during the time that they were also receiving natalizumab and at the time the opportunistic infection occurred.

It is unclear what role those concomitant medications played in addition to the natalizumab, but this is part of the recommendation that the drug be used as a monotherapy, and not in combination in a chronic basis with steroids or in combination with immunosuppressive medications.

Two patients recovered and three died as a result of their infections.

[Slide.]

In order to be comprehensive, we have also included what might be called atypical infections because there is always the debate about what is an opportunistic infection, what is an atypical, so we have broken them into the two slides here.

The other six, atypical infections, are listed here for you. Some of these we have already discussed in the prior slides including the CMV colitis, the CMV infection, and the varicella pneumonia case.

Again, you will see the age and gender of the patients, the numbers of infusions prior to the onset of the infection, also, the number of months since the last infusion that has occurred.

You will see there the first two cases below the dotted line. Below the dotted line is open label, and above the dotted line is the placebo-controlled phase.

The first two in the open label phase occurred several months after having received only a single natalizumab infusion, and both had concomitant immunosuppressive therapy on board.

The pneumonia we have already talked about, a case of cavitating pneumonia with concomitant immunosuppressive use, and finally, a presumptive diagnosis of tuberculous peritonitis. I say "presumptive" because a biopsy of lesions in the abdomen indicated a caseating granuloma. However, the AFB stain was negative. PCR was negative for tubercle bacilli and the culture was also negative.

All of these patients, as you will notice, have recovered.

[Slide.]

If one looks at the rate of non-PML opportunistic infections in Crohn's disease to try to put this in perspective of what this means in terms of other biologic agents and Crohn's disease in general, for each of the unique opportunistic infections that we have reported here, the rate per 1,000 patient years is approximately 0.6.

If one looks at Crohn's patients with the similar types of opportunistic infections, the rate of those opportunistic infections in patients who

are also receiving conventional therapies or inhibitors of TNF-alpha, the range of these same opportunistic infections is 0.3 to 0.5, so comparable to the 0.6 rate that we see with natalizumab and the concomitant use of these medications.

However, one has to recognize that this is increased compared to the rate of opportunistic infections seen in Crohn's disease patients who are not receiving these therapies concomitantly.

[Slide.]

Now, if we turn our attention to PML, the PML, there have been three cases of PML that have been confirmed in the natalizumab program, two MS patients after receiving 29 and 37 infusions. Both patients had been receiving concomitant interferon beta for over three years at the time of their onset of symptoms.

One Crohn's disease patient had received 8 infusions of natalizumab over 18 months, and we will come back to that case in a little bit more detail shortly.

Two of the cases were fatal. One patient survived following the development of what is called IRIS or the immune reconstitution inflammatory syndrome, and we will talk a little bit about that shortly, as well.

[Slide.]

Now, you are going to be getting a more detailed overview from a representative with the Agency regarding PML, so I will just very briefly touch.

PML, as many of you may know, is a rare progressive infection of the central nervous system, which is frequently fatal within the first several months of clinical onset.

It is caused by a JC virus, which is latent in a large proportion of the population having arrived asymptomatically in most of us. This virus reactivates, enters the central nervous system, infects the oligodendroglia cells, leads to demyelination, and thus creating the neurologic symptoms that are a feature of this disease.

The disease primarily affects

immunocompromised patients and in this day and age, that is generally HIV-infected patients. However, it can occur with hematologic malignancies and in organ transplantation patients.

Unfortunately, at the present time there is no effective therapy for PML. However, a number of patients can stabilize or even improve if the immune system function can be ameliorated, such as in the AIDS patients, if they receive highly active antiretroviral therapy or in PML cases that occur in the transplant patients, if one reduces their immunosuppressive medication, you get this onset of the immune reconstitution syndrome, and the immune system is then able to bring the PML under control and either stabilize or sometimes improve function in the patient.

This similar thing had occurred in one of the MS patients, as I indicated. Two to three months after cessation of natalizumab, this patient developed an IRIS syndrome and subsequently stabilized the disease.

[Slide.]

A 60-year-old male who had had Crohn's for 28 years. He had a long history of azathioprine use, had been on recurrent corticosteroid therapy, and had had previous dosing with infliximab, importantly, with a longstanding Grade 3 lymphopenia, with lymphocyte count below 500.

As I indicated earlier, the patient had had 8 doses of natalizumab, 3 in combination with azathioprine in CD301, 9 with a placebo in CD303, and then 5 doses in CD351.

The patient developed neurologic symptoms in June of 2003, had a pathologic diagnosis of an astrocytoma made based on a CNS biopsy in July of 2003, and subsequently, deteriorated and died in December of 2003.

This case was reevaluated based on the finding of the two PML cases in MS, and retrospective review of the histologic samples indicated that this was, in fact, PML, and not an astrocytoma.

[Slide.]

Following the suspension of dosing within

the clinical trials and in the commercial setting, the sponsors undertook an extensive PML safety evaluation, the objectives of which were to determine whether other patients could have had PML or other opportunistic infections.

Over 3,800 patients in the clinical development program were eligible for the evaluation, and the vital status was confirmed in 99 percent of these patients, and 90 percent of the patients participated in the evaluation, which comprised a general physical examination, neurological examination, MRI, blood testing for JCV in the plasma, and in certain patients, a CSF evaluation.

The bottom line of that extensive evaluation, which has been published subsequently, is that there were no new cases of PML discovered.

[Slide.]

One of the issues that comes up now in patients who are receiving natalizumab therapy, what are the options for predicting who might develop PML and how to pre-symptomatically detect

PML.

One of the issues that had been looked at in the safety evaluation was the utility of JC viral DNA testing in the plasma. During that safety evaluation, over 2,000 patients had plasma tested for JCV, 10 patients actually had JCV detected in the blood, none of whom had either MRI or clinical evidence of PML, nor subsequently developed PML.

Of the three cases who developed PML, two never had any detectable JCV in the plasma up to and including the time of their first symptoms. One patient, the Crohn's patient, was reported to have JCV detected in the serum approximately 6 to 8 weeks prior to the onset of clinical symptoms. But a recent review of the medical records of that patient would suggest that the neurologic symptoms may have onset earlier, and the neurologic symptoms may, in fact, have onset coincident with that positive test that was reported.

Thus, the sensitivity and the predictive value of JCV testing in the blood is low, and at

the present time this cannot be recommended as a screening test either for predicting nor pre-symptomatically detective patients with PML although further studies continue to date.

The second mechanism by which one might screen would be using MRI brain scans, and certainly MRI is sensitive for PML, but it is not specific.

What would be involved would be performing large numbers of scans on large numbers of patients to pre-symptomatically detect a rare event in approximately 1 in 1,000 patients potentially.

Thus, although the MRI is helpful diagnostically at the time patients have no neurologic symptoms, there is no practical screening frequency by which this would be useful as a screening measure for patients on natalizumab.

This leads to the conclusion that clinical vigilance is, in fact, the best method by which one can detect the earliest symptoms of PML. Patients and their caregivers and physicians need to be educated about the risk of PML with this product,

what the symptoms of PML might be, and what to do in the setting of those new neurologic symptoms.

This can be facilitated by the fact that patients are seen monthly by health care professionals during their infusions.

[Slide.]

I would like to turn to other safety events of interest including infusion reactions and malignancy, and then we will finally talk about post-marketing safety.

[Slide.]

Hypersensitivity reactions occurred in 3.5 percent of patients in the two induction studies within the Crohn's clinical patient experience. These hypersensitivity reactions generally occur on the second or third infusion. This rate of 3.5 percent is quite comparable to that seen in the MS indication of 4 percent, and is not unexpected given the infusion of a biological therapy intravenously.

More importantly is that the serious systemic hypersensitivity reactions or the

anaphylaxis was actually quite an infrequent event occurring in 0.1 percent either in the short-term or in the long-term observational studies.

[Slide.]

If we turn to malignancy, I mentioned earlier that the proportion of patients was imbalanced between the two groups with 0.6 percent of patients on the natalizumab versus 0.2 percent of patient in the placebo group having neoplasms, and the neoplasms are listed by organ there, that had occurred during the placebo-controlled study.

Importantly, to note is that the placebo-controlled exposure in these patients is actually relatively brief, in the range of only three months, and that is the biologic plausibility of a relationship between these short duration infusions of natalizumab with the occurrence of neoplasms within the first two to three months is actually quite low.

We have continued to look at this and in the open-label extension phase of the program, including the short-term placebo-controlled

exposure, there have been 23 malignancies detective in 22 patients, 7 of these malignancies are cutaneous in 6 patients all but 1 being basal cell or squamous cell carcinomas.

There have been 13 tumors in solid organs. In this case, many of these are listed here. Ten of those 13 occurred in patients who had received 4 or fewer infusions, and thus again, the link between therapy is unclear.

Importantly, related to the mechanism of action of this drug is the occurrence of hematologic malignancies. There have been 2 lymphomas reported and 1 episode of chronic lymphocytic leukemia in the Crohn's population.

The 2 lymphomas occurred 6 and 20 months following the infusion of natalizumab. Patients had received 6 and 2 infusions respectively. Following the discontinuation of the natalizumab in both of the patients, they had both been on chronic immunosuppressive therapy prior to the onset of the detection of their lymphomas. Both were low grade lymphomas, 1 B cell and 1 nodular sclerosing

lymphoma.

The case of chronic lymphocytic leukemia had received 19 infusions and developed CLL approximately 20 months following discontinuation of natalizumab at a time when she had been on chronic immunosuppressive therapy after discontinuing natalizumab.

Obviously, this is something that continues to be part of the observational program in MS. I would mention that in MS, there was no indication of an increased risk of neoplasm based on the clinical development program data, and I will share with you the post-marketing data shortly.

[Slide.]

So, the summary of the safety in the clinical development program is that common adverse events were comparable between the treatment groups and generally mild apart from the headache, which was slightly more frequent.

The proportion of patients experiencing serious adverse events was comparable.

Infections were slightly more common with natalizumab, approximately 4 percent due to viral upper respiratory tract infections.

There is a low rate of hypersensitivity reactions particularly anaphylaxis. However, there does appear to be a risk of opportunistic infections including PML, and there is a possible signal for malignancy that requires further post-marketing surveillance measures.

[Slide.]

In terms of the post-marketing safety, this is all in MS, of course. 11,500 MS patients worldwide have received natalizumab commercially between June of 2006 and May of 2007, which is the cut point for our safety evaluation.

Serious infections. The reporting rate of the serious infections is 1.2 percent. This is quite comparable to that seen in the clinical trial setting of 2.6 to 3.2 percent. Urinary and pulmonary infections were the most common ones reported. However, there have also been 4 cases of atypical herpes infection.

Two of these occurred during the first launch. These were the herpes encephalitis and herpes meningitis. Two have occurred in the second launch, a multidermatomal zoster and herpes simplex virus type 1 esophagitis, considered as an opportunistic infection, has occurred in the second launch.

It is important to note that serious and all herpes infections are included in the U.S. label for natalizumab.

In addition, serious hepatic dysfunction has been reported in 4 cases who have had marked elevation of liver function tests including an elevation bilirubin in 3 of these 4 cases. There are a number of potential confounding factors including prior illnesses, prior medications, or concurrent medications, and the evaluation of these cases is ongoing.

Importantly, there was no signal seen in the clinical development program regarding hepatic dysfunction including either adverse events, serious adverse events, or liver function test

abnormalities.

[Slide.]

Malignancy, as I had indicated, in the MS clinical development program, which had 2 years of placebo-controlled data, there was no suggestion of the difference between the two groups, natalizumab or placebo. There was a slight imbalance in the Crohn's program, but the question of relationship is still open.

The reporting rate of malignancy in the post-marketing situation now is approximately 6 per 1,000 patient years. Again, this is comparable to what was seen in the clinical trials of 3.8 to 7.3 per 1,000 patient years and the SEER database of approximately 5 per 1,000 database per patient years based on age and agenda adjustments.

One thing that has been detected in the post-marketing surveillance is that the hypersensitivity reactions were occurring more commonly in patients who had previously received therapy during the first launch and had a gap in therapy prior to coming back onto therapy during

the second launch and, because of this, a label change is being implemented to highlight this for physicians; should they interrupt therapy with natalizumab, the patients may be at increased risk for hypersensitivity reactions compared to those starting therapy de novo.

We have already mentioned the herpes cases. Importantly, there have been no other reports of opportunistic infections and no confirmed cases of PML.

Thus, overall, there has been no change in the safety profile of natalizumab in the post-marketing setting compared with the clinical trials.

[Slide.]

In summary, we feel that there is a favorable benefit-to-risk profile for the product based on the efficacy for inducing and maintaining response and remission, and the benefits seen consistently in a broad range of subgroups.

The safety profile remains comparable to that seen in MS indication apart from the potential

increased risk of non-PML opportunistic infections in the Crohn's patients although this was confounded by the use of concomitant immunosuppressives and steroids, something which will be warned against and the indication being not to use these therapies in combination with natalizumab going forward.

Finally, there is a RiskMAP in place for MS that will be adapted for the Crohn's disease indication to further evaluate the long-term safety risk that we have discussed.

At this point I will turn it over to Dr. Maier who will present that information to you.

Risk-Management Plan

DR. MAIER: Hello. I am Will Maier. I am going to be talking about the Tysabri Risk Management Plan. I am a Senior Director of Epidemiology at Elan Pharmaceuticals.

[Slide.]

In my talk today, I am going to give you a description of the current risk-management plan that is in place for MS. As was mentioned earlier,

this is the TOUCH Prescribing Program, which stands for the Tysabri Outreach Unified Commitment to Health.

I will also give you an understanding of how well this program is working and I will describe the kind of changes that we expect to make to this risk-management plan with the addition of the CD indication. I think what you are going to see is that the current plan is working well and that we are confident that it can be adapted to Crohn's disease.

[Slide.]

The Tysabri Risk Management Plan goals and activities were developed in collaboration with the FDA. We have both risk minimization and risk assessment goals.

The risk minimization goals are to promote an informed benefit-risk discussion and decision at the time of therapy, to minimize the risk of PML by reinforcing its use as a monotherapy, and to potentially minimize death and disability due to PML by promoting clinical vigilance of new