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AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

55TH MEETING

Thursday, December 18, 1997

8:40 a.m.

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NDA SUPPLEMENT 16-295/S-029 DROXIA
(hydroxyurea capsules USP)
Bristol-Myers Squibb

Janice J. Dutcher, M.D., Chairperson
LT Jannette O'Neill-Gonzalez, MHS, Executive Secretary

MEMBERS
E. Carolyn Beaman, M.H.S. (Consumer Rep)
James Krook, M.D.
David H. Johnson, M.D.
Kim A. Margolin, M.D.
Derek Raghavan, M.D., Ph.D.
Victor M. Santana, M.D.
Richard M. Simon, D.Sc.
Sandra Swain, M.D.

CONSULTANT:
Lawrence S. Lessin, M.D.

GUEST EXPERT
Albert Lin, M.D.

PATIENT REPRESENTATIVE
Joan Wise

FDA
Paul Andrews, Ph.D.
Robert DeLap, M.D., Ph.D.
John Johnson, M.D.
Robert Justice, M.D.
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NDA 20-798 DepoCyt
(cytarabine lipid-particle injection)
DepoTech Corporation

Janice J. Dutcher, M.D., Chairperson
LT Jannette O'Neill-Gonzalez, MHS, Executive Secretary

MEMBERS

E. Carolyn Beaman, M.H.S. (Consumer Rep)
James Krook, M.D.
David H. Johnson, M.D.
Kim A. Margolin, M.D.
Robert Ozols, M.D.
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Sandra Swain, M.D

PATIENT REPRESENTATIVE
Kenneth Giddes

FDA
Robert DeLap, M.D., Ph.D.
Steve Hirschfeld, M.D., Ph.D.
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P R O C E E D I N G S

Opening Remarks

DR. DUTCHER: Good morning and welcome to the advisory committee meeting. Before we start, LT O'Neill Gonzalez will read the conflict of interest statement.

Conflict of Interest Statement

LT O'NEILL GONZALEZ: Good morning, everyone.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions. In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Drs. Sandra Swain, Derek Raghavan, Kim Margolin, Victor Santana, and Mr. Ken Giddes.

A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, located in Room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the

record that Dr. Robert Ozols' employer, the Fox Chase Cancer Center, has interests in Pharmacia & Upjohn, sponsors of competing products to DepoCyt, which do not constitute financial interests in the particular matter within the meaning of 18 U.S.C. 208. Notwithstanding these interests, it has been determined that it is in the Agency's best interest to have Dr. Ozols participate fully in all matters concerning DepoTech's DepoCyt. Further, because Dr. Ozols and his employer have extensive unrelated financial interests in Bristol-Myers Squibb, Dr. Ozols will be excluded from participating in the committee's discussions and deliberations concerning Bristol-Myers Squibb's Droxia.

Lastly, we would like to disclose that Dr. Larry Lessin in the past served as a member of the National Institutes of Health, National Heart, Lung and Blood Institute's Data Safety Monitoring Board for the Droxia trial in Sickle cell disease. This past involvement will not preclude Dr. Lessin from participating fully in the committee's discussions and deliberations concerning Bristol-Myers Squibb's Droxia.

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 such involvement and their exclusion will be noted for the record.

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

Thank you.

DR. DUTCHER: I would like to now go around the table and introduce the panel. Dr. Johnson.

DR. JOHN JOHNSON: John R. Johnson, Clinical Team Leader, FDA.

DR. ANDREWS: Paul Andrews. Pharmacology Team Leader, FDA.

DR. LIN: Albert Lin, Medical Reviewer.

MS. WISE: Joan Wise, Patient Representative.

MS. BEAMAN: Carolyn Beaman, Consumer Rep.

DR. RAGHAVAN: Derek Raghavan, Medical Oncologist, USC.

DR. DAVID JOHNSON: David Johnson, Medical Oncology, Vanderbilt.

DR. KROOK: Jim Krook, Hematologist-Oncologist, Duluth Clinic.

LT O'NEILL-GONZALEZ: Jannette Gonzalez, Executive Secretary.

DR. DUTCHER: Janice Dutcher, Albert Einstein Cancer Center, New York.

DR. MARGOLIN: Kim Margolin, Hematology and Oncology, City of Hope.

DR. SANTANA: Victor Santana, Pediatric Hematologist/Oncology, St. Jude Children's Research Hospital, Memphis.

DR. LESSIN: Larry Lessin, Medical Director, Washington Cancer Institute.

DR. SWAIN: Sandra Swain, Medical Oncologist, Washington, D.C.

DR. SIMON: I am Richard Simon. I am the head of the Biometric Research Branch at the National Cancer Institute.

DR. DeLAP: Bob DeLap, Oncology Drugs Division Director, FDA.

DR. DUTCHER: Thank you.

Open Public Hearing

DR. DUTCHER: As I understand it, no one has requested to talk at the open public hearing other than the patient representatives that are speaking on behalf of the sponsor.

Is there anyone in the audience that wish to make a statement other than those people?

[No response.]

DR. DUTCHER: Then, we will proceed with the applicant's presentation, and I believe you wanted to have the patient representatives speak first, is that correct?

DR. SMYTH: I will just introduce them.

DR. DUTCHER: Dr. Smyth.

NDA SUPPLEMENT 16-295/S-029 DROXIA

(hydroxyurea capsules USP)

Bristol-Myers Squibb

Applicant's Presentation

Patients' Presentation

DR. SMYTH: Good morning. I am Collier Smyth from Bristol-Myers Squibb. Before we begin our formal presentation, we have invited two patients who are actually patients locally at the Howard University Center for Sickle Cell Disease. They are Delphine Bassey and Ronald Mixon.

We are aware that many of the physicians on the ODAC Committee don't regularly see patients currently with sickle cell disease, so we thought it would be worthwhile to hear from a couple patients firsthand for their spontaneous comments.

Delphine, would you like to come up first, please.

MS. BASSEY: Good morning, ladies and gentlemen.

My name is Delphine Bassey. I am a married working mother of two, and I am 33 years old.

I have been on hydroxyurea since July of 1996 after being hospitalized for the second time with sickle cell chest syndrome. Initially, I wasn't on the drug because my doctor didn't feel that I was per se sick enough to be in the initial study of hydroxyurea.

After my second hospitalization last year, after, say, from 1993 until the present time, when I was in a crisis, I initially always had the sickle cell chest syndrome, and my doctor feared that with me having continuous bouts with the chest syndrome, there would be a tendency for scarring of my lung tissue, and that's when I started taking it.

I have to admit I was reluctant to take the drug at first because of the side effects and also having to do regular blood tests every two weeks, but I was also willing to give it a try because I was tired of having a crisis every year.

Considering what I have gone through with my illness, hydroxyurea has been a blessing. When I tell people that I have sickle cell disease, they are surprised and they compliment me on well I am and they compliment on just going along with my regular activities as a person

without an illness.

I give hydroxyurea high praises and as far as having to go to the hospital for the regular blood tests, I just consider it part of my daily routine in staying well.

Thank you.

DR. DUTCHER: Thank you very much.

DR. SMYTH: Ron.

MR. MIXON: Good morning. I am Ron Mixon. I am married, I have three kids, and it means a lot to me. Prior to taking hydroxyurea, I must say I was having sickle cell crisis at least four to five times a year, which caused me to be off from work for two months. Each crisis I encountered it was two months, sometimes three months.

When I talked to my doctor, and he mentioned something to me about hydroxyurea, getting onto the study, and which I did, and unfortunately, I was doing well. I went several years without having one crisis and prior to that, I got depressed and stopped taking hydroxyurea. When I did stop, I was having sickle cell chest syndromes, one behind another. I would be hospitalized, I would come out for two weeks, and end up going back in the third week.

Once I got back on hydroxyurea, it has been almost three and a half to four years, and no sickle cell crisis, no pain. I was able to gain weight from 140 pounds up to

185 pounds, and I also would like to mention, too, I have other people in other states, parents, that do have kids that have sickle cell and teenagers, and it is a shame, when I mentioned that you should talk to your doctor about getting on hydroxyurea, and the feedback I get days later is that the doctors don't recommend that for their patient. I am a living example that it does work, and right now I consider myself being healthy.

I just want to say thank you and keep up the work.

DR. DUTCHER: Thank you very much.

Introduction

[Slide.]

DR. SMITH: I am Collier Smyth, Vice President of Medical Affairs with Bristol-Myers Squibb.

[Slide.]

We are pleased to present the essential details of our supplemental application to ODAC and to the FDA. The application is for Droxia or hydroxyurea for the treatment of sickle cell anemia in adult patients to prevent painful crises and to reduce the need for blood transfusions.

Currently, there is no FDA approved treatment for sickle cell anemia.

[Slide.]

Hydrea has got a few miles under it. It was first

synthesized back in 1869. In 1928, it was noted to cause leukopenia and anemia in animal models. In 1958, antitumor activity in mammalian tumor systems was found, and in 1960, clinical trials for cancer treatment were initiated. Hydroxyurea was initially approved by the FDA for treatment of various cancers in 1967.

[Slide.]

The mechanism of action of hydroxyurea is as a ribonucleotide reductase inhibitor. The end effects that seem most pertinent for sickle cell are the increase in hemoglobin F, the increase in the mean corpuscular volume of the red cells, and a decrease in the neutrophils.

[Slide.]

Currently, hydroxyurea is generally used in myeloproliferative diseases, specifically chronic granulocytic leukemia, polycythemia vera, and essential thrombocythemia. It is also used in psoriasis, hypereosinophilic syndrome, sickle cell anemia, and other hemoglobinopathies.

[Slide.]

An orphan designation was given for sickle cell anemia, for hydroxyurea, in October 1990.

The results of an open-label, dose-ranging trial was published by Sam Charache in 1992, and this showed that

there is an increase in hemoglobin F and an increase in the mean corpuscular volume of the red cells that was directly related to the dose of hydroxyurea.

A subsequent double-blind placebo-controlled Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) was initiated in 1992.

[Slide.]

[Slide description not recorded because of audio malfunction.]

[Slide.]

MSH trial was stopped in January 1995 before the planned termination of the study. It was done on the recommendation of the Data and Safety Monitoring Board and the Steering Committee for the trial concurred with that recommendation. The trial was stopped because of the marked beneficial effects of hydroxyurea.

That same month, January 1995, the National Heart, Lung and Blood Institute issued a clinical alert to clinicians treating patients with sickle cell disease on the benefits of hydroxyurea.

The SNDA for this indication was filed on August 21, 1997.

[Slide.]

Our presenters today. Initially, Dr. Martin

Steinberg, Professor of Medicine at the University of Mississippi at Jackson, will discuss some general background about sickle cell disease. Dr. Steinberg has a long-standing interest in the molecular and clinical aspects of sickle cell disease.

Next, the Multicenter Study itself will be presented by the study chair, Dr. Samuel Charache. Dr. Charache is Emeritus Professor of Medicine and Pathology at Johns Hopkins. He has had a very distinguished career in experimental therapy.

There is a follow-up study to that multicenter trial, which is being chaired by Dr. Steinberg, and he will present the at least current findings in that trial.

Then, we will summarize the presentation.

[Slide.]

Also, in attendance today are Dr. Michael Terrin from the Maryland Medical Research Institute and Franka Barton, who is the statistician from the Maryland Medical Research Institute. Duane Bonds is also attending, who is leader of the Sickle Cell Disease Scientific Research Group at the National Heart, Lung and Blood Institute.

Dr. Steinberg.

Disease

[Slide.]

DR. STEINBERG: Thank you, Collier, and good morning. My purpose this morning is to tell you a little bit about sickle cell disease and the rationale for the use of hydroxyurea in this disorder.

Sickle cell disease is a genetic disorder of the hemoglobin molecule, specifically the beta subunit of the hemoglobin molecule. It is present in about 1 in 350 African-Americans, that is, 1 in 350 have some type of clinically significant form of sickle cell disease, however, about 1 in 600 are homozygous for the sickle gene and have sickle cell anemia.

Sickle cell anemia is a morbid disease with a curtailed life span. The median age of death at the present time, when it was last studied in this country, is in the 5th decade of life.

The characteristics of sickle cell anemia are painful crises, acute chest syndrome, and other vaso-occlusive complications which I will discuss momentarily, however, the frequency of painful crises, and frequency of acute chest syndrome, and the level of fetal hemoglobin are risk factors for premature death in this disorder.

[Slide.]

This slide summarizes the pathophysiology of

sickle cell disease. The mutation, the GAG to GTG in the codon for the 6 amino acid of the betaglobin chain specifies a change from glutamic acid to valine. This is the only genetic change in sickle hemoglobin.

This change changes the physical properties of the hemoglobin molecule under certain conditions. When sickle hemoglobin is oxygenated, it remains in solution like normal hemoglobin. When sickle hemoglobin is deoxygenated, it forms polymers within the cell, and it is this polymerization of sickle hemoglobin that is ultimately responsible for the pathophysiologic consequences of the disease.

Now, what happens as the hemoglobin polymerizes is that the sickle cell, here shown in the oxygenated form, changes in a very large number of ways. The cell with sickle hemoglobin polymer may have the normal shape, but it doesn't mean that it is a normal cell. Typically, the cell forms these bizarre abnormal shapes which gives the disease its name.

These sickle cells have a variety of abnormalities affecting the cell membrane. The cell membrane becomes leaky, the cells become dehydrated, certain adhesive ligands on the surface of the cell are exposed, and the cell has abnormal flow properties.

These cells are also short-lived, so that the patients have a hemolytic anemia, which by itself is only modest, however, the problem is that these cells cause vaso-occlusive disease. Sickle cells interact with other cells in the circulation and with the endothelial cells of the vasculature, and cause the vaso-occlusive disease which is the major problem in sickle cell anemia.

[Slide.]

I will now discuss some of the vaso-occlusive complications of the disease, and my discussion will be limited because vaso-occlusive complications can strike virtually any portion of the body, in any organ system.

Painful episodes are by far the most frequent vaso-occlusive complication. These occur in patients sometimes repetitively, many times a year. Sometimes patients skip years between vaso-occlusive episodes.

The pain is described as excruciatingly severe pain, worse than the pain of fracture, worse than postoperative pain, and sometimes the painful episodes requires prodigious amounts of narcotic for relief.

[Slide.]

This slide shows the survival probability by crisis frequency in sickle cell anemia in the study from the cooperative study of sickle cell disease published a number

of years ago.

These two curves similarly show the survival probability of patients who have less than three painful episodes a year. This curve is the survival probability of patients who have three or more painful episodes a year, and it is this group of patients that we chose to study in the multicenter study of hydroxyurea.

[Slide.]

Other vaso-occlusive episodes include the acute chest syndrome, which you already heard about this morning. This is a very dangerous complication of the disease. It strikes children more frequently. When it strikes adults, it is more severe in adults, and it is associated with significant mortality and morbidity.

Cerebrovascular accidents are the scourge of childhood. About 10 percent of children have overt strokes, a larger number of people have subclinical strokes, which ends up producing cognitive impairment.

Osteonecrosis affects most commonly the heads of the femur, the heads of the humerus, but can affect other bones. It can be a crippling disorder, inhibiting almost totally the mobility of patients, and is also chronically painful.

[Slide.]

Leg ulcers develop in about 10 percent of patients. They can range from small, almost insignificant ulcers, to total denudement of the skin of the lower leg. One characteristic of leg ulcers is that they are terribly painful.

Retinopathy is a complication mainly of hemoglobin SC disease, one of the other types of sickle cell disease, but does occur in sickle cell anemia. It can go through a series of stages leading to retinal detachment and blindness.

Priapism affects about 10 or 15 percent of men with sickle cell anemia. Sometimes the priapism is mild, often it is recurrent. When a major episode of priapism occurs, impotence is the usual results.

Splenic sequestration occurs commonly in childhood, and this is a disease where due to hypoxic damage of the spleen, suddenly the blood supply flows to the spleen, patients become rapidly profoundly anemic, and this is probably the second most common cause of death in childhood.

[Slide.]

Now, in addition to the vaso-occlusive complications of the disease, one could view disease complications in terms of hemolysis. If this was all

patients with sickle cell anemia had, they would be pretty well. They have anemia, which is usually only moderate in degree. As a result of hemolysis and turnover of bile pigments, they have cholelithiasis, which affects at least 50 percent of adults and sometimes occurs at very, very young ages.

Because of the rapid turnover of the bone marrow, they are very susceptible to disorders that temporarily interfere with erythropoiesis, and the B-19 parvovirus is the usual cause of acute aplastic episodes which, like splenic sequestration, could lead to a dramatic and rapid fall in the hemoglobin level.

Linking the hemolytic and the vaso-occlusive complications may be the presence of the reticulocytosis that is a feature of all individuals with hemolysis, because these reticulocytes are not normal reticulocytes, they also have special adhesive molecules on their surface, and they be very important in initiating the vaso-occlusive complications of the disease.

[Slide.]

Now, years of chronic vaso-occlusion take their toll on most of the organs in the body, so that with slowly progressive renal failure, it is commonly seen in adult patients now, ending in severe anemia, sometimes requiring

dialysis or even renal transplantation.

Subclinical cortical damage, which I already mentioned, leads to cognitive impairment in many of these patients.

We have heard that chronic lung disease can develop from multiple episodes of the acute chest syndrome, and cor pulmonale is also a feature of chronic lung disease in some of these patients.

Because of sickling in the placenta, miscarriage is a common feature of women who are pregnant with sickle cell disease, and the splenic fibrosis from repeated sickling in the spleen leads to very early loss of a functional spleen, a little bit later loss of the presence of a spleen at all, and high susceptibility to infection with encapsulated organisms especially the pneumococcus.

[Slide.]

The treatment of sickle cell disease has lagged behind our understanding of the pathophysiology, and this slide summarizes the current state of treatment. We use analgesics in large amounts, narcotic analgesics for the treatment of painful episodes, and patients often take oral narcotic analgesics at home when they have pain episodes that they feel aren't severe enough to bring them to the hospital.

We use antibiotics to treat the infectious complications, which are common. Hydration is used to prevent hemoconcentration, which we think makes vaso-occlusion worse.

Transfusions have been a mainstay of treatment, not so much for the anemia, which as I mentioned is only moderate, but mainly for some of the vaso-occlusive events like severe acute chest syndrome, like early severe priapism, and it is also used prophylactically to prevent recurrence of stroke in children.

Transplantation is currently being studied as a possible means of curing the disorder. Of course, in the studies so far, there is about a 10 percent mortality rate in transplantation and a very small percentage of patients with sickle cell anemia have a donor for transplantation.

[Slide.]

Now, it has been almost 50 years since clinicians and scientists have recognized the role of fetal hemoglobin in sickle cell anemia. The first observations were made in New York, and these observations shows that newborns with sickle cell anemia are asymptomatic, and the presumed reason for this was that newborns have upwards of 50 percent of their hemoglobin is fetal hemoglobin.

In addition, adults who have the combined

heterozygous disorder, sickle cell hereditary persistence of fetal hemoglobin, an additional mutation in the betaglobin gene complex which allows the fetal hemoglobin genes to be continually expressed during life, so these individuals have 20 to 30 percent fetal hemoglobin with sickle hemoglobin, are clinically well. They have none of the crises I talked about and they are not anemic.

When these observations were taken to the laboratory, it was shown that fetal hemoglobin increases the concentration of sickle hemoglobin needed to gell in the test tube, and further worked showed that the reason that fetal hemoglobin inhibits polymerization is that the gamma globin chain, that globin chain which characterizes fetal hemoglobin specifically interferes with the polymerization of sickle hemoglobin.

[Slide.]

The importance of fetal hemoglobin is further demonstrated in this slide taken from another cooperative study of sickle cell disease paper, which showed that individuals who have fetal hemoglobin levels at the 75th percentile have a longer survival than individuals who have lower fetal hemoglobin levels, but any level, the fetal hemoglobin survival is increased.

[Slide.]

Finally, I want to show you some of the potential effects of hydroxyurea in sickle cell disease. What I have shown here is bone marrow, blood, and vasculature. We think that hydroxyurea has effects on all of these compartments, so that in the bone marrow, the hydroxyurea reduces marrow cellularity, and a large part of painful episodes is probably due to necrosis and swelling within the bone marrow.

Most importantly perhaps, hydroxyurea increases the clones of erythroid precursors that retain the program for synthesizing large amount of fetal hemoglobin, so that more hemoglobin-F containing red cells escape the marrow because of the selective action of hydroxyurea on erythroid progenitors.

In the blood shown before treatment and during treatment, a number of things happen. Fetal hemoglobin is increased, the cells become large because they become better hydrated cells. There is a reduction in the sickle forms in the blood shown before treatment and after treatment.

The reticulocytes shown here are reduced by hydroxyurea treatment, and there are fewer granulocytes that are present during treatment with hydroxyurea.

Finally, the vasculature is probably changed before and during treatment. Before treatment, there is

interaction of sickle cells, neutrophils, platelets with vascular endothelial cells leading to vaso-occlusive disease.

During treatment, a number of things happen. There is less interaction among the formed elements of blood. There is reduce adherence of sickle cells to endothelial cells, and there is probably improved function of the endothelium itself.

I would like now to introduce Dr. Sam Charache, who was Chairman of the Multicenter Study of hydroxyurea.

Thank you.

Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH)

[Slide.]

DR. CHARACHE: The main study question in the Multicenter Study of hydroxyurea was whether treatment with hydroxyurea could substantially reduce the rate of acute vaso-occlusive crises in patients with sickle cell anemia.

[Slide.]

The organization of the study is shown on this slide. At Johns Hopkins University, we had the central office which took care of administrative affairs, the core laboratories which analyzed blood samples sent to us from the 21 participating clinics, the treatments distribution

center which sent out the treatments on a regular basis and monitored blood counts in addition to the monitoring done by the Maryland Medical Research Institute.

Finally, we had a central caller. This was a blinded woman who called each patient in the study once a month to determine whether the patient had had any illness in the preceding month, if the patient was taking his pills, and if anything else had happened. This turned out to be a very useful way of keeping track of the patients.

The Crisis Review Committee was appointed by the central office. These were blinded physicians, hematologists and internists, who decided whether or not a given clinical event represented a sickle cell crisis, and we can go into that later if you wish.

The Maryland Medical Research Institute was the data coordinating center. They kept track of the numbers, they devised the scheme by which patients who received placebo had simulated abnormal blood counts and could, in principle -- well, appeared to develop toxicity since the physicians in the peripheral clinics had no access to blood counts if we stopped treatment because of toxicity, they probably believed it.

Finally, there was the National Heart, Lung and Blood Institute, which appointed the Data and Safety

Monitoring Board, which oversaw the subject, and was run by the Sickle Cell Disease Research Group. The study was funded by NHLBI.

We did get the drug powder from Bristol-Myers, and we got a small financial grant which paid for some of the things that NIH would not pay for.

[Slide.]

The study design is shown here. In each of the clinics, first, patients were screened for eligibility, and I will show you what the eligibility requirements were. Those who were eligible were then randomized. We started out with 152 patients on hydroxyurea and 147 on placebo, and then each of these two groups had drug dose titration and follow-up.

[Slide.]

Inclusion criteria were a Core Laboratory diagnosis of sickle cell anemia or sickle beta-0 thalassemia by electrophoresis. Three or more acute vaso-occlusive crises in the year prior to enrollment. Patients had to be 18 years of age or older. They had to give informed consent. They were instructed in techniques on contraception and had to agree before we started that they would use contraceptive techniques.

Exclusion criteria were the use of more than 30

oxycodone capsules or their equivalent per month. Recent transfusion. Active liver disease. An elevated creatinine, since the drug is primarily excreted through the kidney. Contraindication to immunosuppressive therapy. We thought at the beginning of the study that hydroxyurea might be immunosuppressive. Finally, B-12, iron or folate deficiency. If these conditions were discovered and treated the patient could subsequently enter the study.

[Slide.]

Other exclusion criteria were previous hydroxyurea therapy because of the worry about a washout effect. Pregnancy of breastfeeding at the time of starting the study. Sickle-beta-plus thalassemia. The use of an anti-sickling agent or purported anti-sickling agent A stroke within four years because such patients would probably be being transfused. And finally, congestive heart failure.

[Slide.]

Now, the dose titration scheme is shown in the next two slides. All patients started at 15 mg/kg/day. This dose was increased by 5 mg/kg/day every 12 weeks unless the patient was toxic, and I will show you what I mean by that on the next slide. It meant blood count depression. If toxicity occurred, treatment was stopped until blood

counts recovered and then was resumed at 2.5 mg/kg/day lower than the dose being taken. The dose was adjusted by 2.5 mg/kg every 12 weeks until we thought we had reached the maximum tolerated dose, that is, the dose at which the patient was just below toxicity. The patient had to tolerate that dose for 24 weeks before we declared it to be MTD.

If the patient was pre-toxic -- and I will show you what that is -- the dose was not increased, but was continued at the same level.

[Slide.]

Here are the criteria for pre-toxicity and toxicity. Neutrophils had to be less 2,500 to be pre-toxic, at less than 2,000 to be toxic. Reticulocytes, platelets, the hemoglobin criterion was less than 4.5 grams. The reticulocyte count, that is, the criterion for the reticulocyte count depended on what the hemoglobin level was because if the patient's hemoglobin rose, we would have expected the reticulocyte count to fall just because he was less anemic.

[Slide.]

The highest dose which did not cause toxicity in 24 weeks was considered to be the maximum tolerated dose, however, no patient was given more than 35 mg/kg/day.

[Slide.]

If for some reason blood could not be obtained or was not obtained when the patient came to clinic, the patient was given no drug for the next two-week period. If we did not receive a blood sample from a patient at the central office, that clinic was called and told to tell the patient to stop treatment. In situations in which we needed action to be done quickly, the central caller would sometimes call the patient directly and say stop your treatment. Now, this could be for real toxicity or simulated toxicity.

[Slide.]

Now, the goal of the study was to reduce the frequency of acute vaso-occlusive crises, which meant we had to define what a crisis was. The definition we used a visit to a medical facility of 4 or more hours duration. Because of the pain of sickle cell disease in which the patient was treated for pain and included, in addition to pain in any part of the body, chest syndrome hepatic sequestration, and priapism.

[Slide.]

The Crisis Review Committee reviewed reports of these medical contacts. There were discharge summaries, xerox copies of emergency room records, and so on. As I

stated, the Crisis Review Committee were independent hematologists and internists who were blinded and were not part of any clinical center.

They used classification rules which are developed a priori to decide if a given episode was a painful crisis. Two members of the committee had to agree before a medical contact was considered a crisis. If those two could not agree, the case was given to a third member of the committee. If no two of those three could agree, then, the committee chairman broke the impasse.

[Slide.]

To classify events, we had documentation of medical contact as I described. These were reviewed by the Crisis Review Committee using the study definition of an acute vaso-occlusive crisis, and two reviewers had to agree.

[Slide.]

Patients could be unblinded during the study, and patients receiving placebo could be unblinded for the same reasons, which included pregnancy, accidental ingestion of the drug or a deliberate overdose, infection or bleeding with low blood counts, and any other situation in which information as to what drug the patient was receiving, placebo or hydroxyurea, was critical for patient management.

[Slide.]

The baseline characteristics of the patients in the study are shown on this slide. Here, we have 152 on hydroxyurea, 147 on placebo, and you can see that the frequency of chest syndrome, ankle ulcers, aseptic necrosis, and the number of crises in the prior year is remarkably similar in the two groups.

I would point out that this distribution of crises is very, very different from the distribution of crises in the general population of patients with sickle cell anemia. Most patients with sickle cell anemia have many less crises than these.

[Slide.]

This is what blood smears looked like at the beginning of the study and at the end. You can see that there are numerous irreversibly sickled cells on the lefthand side. On the righthand side, with a little bit of imagination, maybe the cells look a little bit bigger, but there are few, or no, irreversibly sickled cells present.

[Slide.]

This shows you what blood counts were like in the two treatment groups before and after. At baseline, white cell counts, neutrophils, hemoglobin levels, reticulocyte counts, and fetal hemoglobin levels were identical in the two groups.

At the end of the study, in the placebo group, blood counts were not really different from what they had been at the beginning. In the hydroxyurea group, however, the white count was somewhat lower, although I would point out not at a level that anyone would consider life-threatening. Neutrophil counts were lower, hemoglobin was a little bit higher, reticulocyte counts were a bit lower, and hemoglobin concentrations were somewhat higher, although not a great -- patients were not rendered normal by treatment.

[Slide.]

The primary endpoint was the acute crisis rate, and here you can see comparing median crisis rates in the hydroxyurea group with that in the placebo group, that there was a very statistically significant difference between the two groups.

Now, this is all crises. These are hospitalized vaso-occlusive crises. That is, hospitalizations in which the patient had, or during which the patient had, a crisis, and again you will see that the median crisis rate is distinctly lower in the hydroxyurea group than it is in the placebo group.

[Slide.]

The time to development of crises also differed in

the two treatment groups. Here we have the time to the first crisis after starting treatment, the second crisis, and the third crisis. Here are the times for the hydroxyurea group, here are the placebo patients, and you can see that in each group, the crisis, be it first, second, or third, occurs later than it does in the placebo group.

[Slide.]

Here we have broken down the two study populations by three-month intervals, by quarters, and we have plotted out the crisis rates during the entire two-year follow-up treatment. Placebo patients are yellow, hydroxyurea patients are red.

There are two points to make from the slide. The first is that in the first three months' block of time, the two groups already differed; and secondly, that that difference persisted during the study.

[Slide.]

Here we show death, stroke, and chest syndrome. There were a few deaths, there were a few strokes, and there were a few episodes of hepatic sequestration. There were too few instances of any of those complications to make a difference, however, the difference between chest syndrome in the hydroxyurea group, 56 versus 101, was significant. As you have heard, chest syndrome is a life-threatening

condition.

[Slide.]

The transfusions were different in the two groups, as well. The number of patients who were transfused, 55 versus 79, and the number of units transfused, 423 versus 670, were both different.

[Slide.]

Here is the distribution of the last dose of hydroxyurea at the time the study ended. In yellow, we have patients whose last dose had not been declared to be the maximum tolerated dose, those in red were considered to be maximum tolerated doses.

Several points to be made. It is more or less a bell-shaped curve which centers at about the starting dose, 15 mg/kg. There are a group of patients who are at the highest dose that we would give anyone regardless of their blood counts, and about half the patients ended up on doses of hydroxyurea which were less than the starting dose of 15 mg/kg.

Indeed, there were a few patients who could not tolerate hydroxyurea at all, who presumably bone marrows that were so scarred by previous vaso-occlusive events that there just weren't enough marrow precursors there to tolerate the dose.

[Slide.]

There were a number of permanent treatment stops, 19 in the hydroxyurea group, 13 in the placebo group. A few were for long-term transfusion therapy, acute renal failure, fulminant hepatitis, myelotoxicity at the lowest dose of hydroxyurea -- there were 3 patients in the hydroxyurea group -- and we had to adjust the simulated toxicity schemes because if some patients were stopped altogether when they really had marrow toxicity at the lowest dose, there had to be some placebo patients who also were stopped. So, we had 2 simulated myelotoxicities at the lowest dose.

Two patients overdosed in the hydroxyurea group. There were 16 pregnancies, 10 in hydroxyurea, 6 in the placebo. I will show you more about them. there was 1 patient who got elevated liver function tests, and 1 patient in the placebo group, the personal physician decided to take the patient off the study.

[Slide.]

Pregnancies are shown here. Now, these results are at the end of the study. We have more data on these patients, which you will see later. Among the patients, there was 1 normal full-term delivery in the hydroxyurea group, 2 in the placebo group. There were 4 elective terminations in the hydroxyurea group, 1 in the placebo.

Partners of patients, that is, women whose male partners were receiving hydroxyurea, there were 4 normal full-term deliveries versus 3, and one spontaneous abortion versus none.

[Slide.]

Now, these are known side effects of hydroxyurea which were reported by the patient at some time during the study. This could have happened one or it could have happened 15 times for any given patient.

We have got hair loss, skin rash, fever, and GI disturbance. Those of you who have used hydroxyurea yourselves realize that these frequencies are very, very high for anyone getting hydroxyurea. There is no claim made that these were due to hydroxyurea. This is what the patients told us. You will notice that the patients in the placebo group told us the same thing.

I can tell you that, for instances, many of the GI disturbances were some kind of flu. The hair loss in many cases was due to the use of the hair straighteners. The skins rashes and fever could have been due to anything. But the take-home message is that the two groups did not differ.

[Slide.]

There were some things we did not observe. We did not see any neoplasms in either of the treatment groups.

There were no birth defects observed in children born to the patients, and there were not deaths due to hydroxyurea.

[Slide.]

If hydroxyurea is to be used safely, careful monitoring of blood counts is required, and this mean, on a regular basis, blood counts must be done and physicians must review those blood counts to be sure they are okay.

We also reviewed biochemical tests to be sure that nothing went wrong, and there has to be at least some attempt to be maintain contraception for reasons which we can to into later.

[Slide.]

We think hydroxyurea was efficacious because it caused a reduction in annual crisis rate, it caused a reduction in the frequency of chest syndrome, and it caused a reduction in the frequency of transfusions.

Now, it must be obvious to you that in a study in which patients were only treated for two years, that that is not a long enough follow-up to look for long-term effects of therapy, and because of that, with sponsorship from the NHLBI, a follow-study was started.

Dr. Steinberg is in charge of that study, and he will describe the results of it.

MSH Follow-up Study

DR. STEINBERG: Thank you, Sam.

As Dr. Charache mentioned, part of the suggestions by the NHLBI Advisory Council prior to starting the trial that he just described was to continue to follow these patients for a more prolonged period of time.

[Slide.]

So the MSH patients' follow-up study was started. Now, this is an observational study. Its initial phase is for five years, and the purpose is to evaluate the mortality, morbidity, and general health status of patients who were originally enrolled in the clinical trial.

We are going to look at the outcomes related to hydroxyurea by the original randomization of patients, as well as the total amount of hydroxyurea patients have taken since the inception of the study.

[Slide.]

Now, the study plan is as follows. Patients will have annual follow-up visits at which time they will have a medical review, physical examination, and laboratory testing, which includes blood counts, blood chemistries, chest x-ray, electrocardiogram.

Importantly, we are attempting to get some idea of the actual amount of hydroxyurea patients have used since the beginning of the trial and into the follow-up phase.

The other important aspect of the follow-up study is to review the development of offspring born to patients taking hydroxyurea and fathered by patients taking hydroxyurea.

Events we are especially interested in are death, stroke, cancer, organ failure, serious infection, and events surrounding reproduction.

[Slide.]

Now, at the present time, there are 35 patients who were originally randomized who have died; 139 patients are alive, who have been enrolled already and completed the first annual visit of the follow-up study. There are 125 patients who have yet to complete their first annual visit, which should be done by early next year.

[Slide.]

This slide shows events that have occurred up until the present in patients initially randomized to hydroxyurea and initially randomized to placebo. Single patients may have more than a single event.

These are the deaths in hydroxyurea and placebo arm. These are strokes, renal failure, hepatic failure, cancer, sepsis, live births, and other reproductive outcomes which I will discuss momentarily.

[Slide.]

This is a life table analysis of cumulative mortality in patients originally enrolled in the MSH. This is the end of the randomized control portion of the study that Dr. Charache just described.

These are the events that have happened up until the present, the mortality in the placebo arm of the study, and the mortality in patients originally randomized to receive hydroxyurea.

[Slide.]

This is the cause of specific mortality in these patients shown by the cause of death here and in the hydroxyurea, and in the placebo arm, and the all-cause mortality on the bottom.

There are no statistically significant differences at the present time in the cause of death between patients originally randomized to receive hydroxyurea and those originally randomized to receive placebo.

[Slide.]

These are reproductive events up until the present in patients who bore children, women who bore children, and males who fathered children, showing the live births, elective termination, miscarriage, fetal death in both pregnant women and in men who fathered children.

[Slide.]

Now, there have been certain events. This shows live offspring, birth status and development, again in the male and female group, 5 live offspring in each group. These are in patients who had never taken hydroxyurea.

So this is a little bit different. This slide isn't by the original randomization. This is patients who, after the control portion of the study was finished, may have elected to go on hydroxyurea.

One patient who was originally assigned to placebo subsequently took hydroxyurea for six months. She then stopped hydroxyurea for several months, became pregnant, and delivered twins at 35 weeks of pregnancy. One twin was stillborn, the other twin has microcephaly and blindness.

One male patient, originally assigned to hydroxyurea, fathered a child born with polydactyly and a mucocele of the lip. Polydactyly is a common congenital anomaly present in about 10 percent of the African-American population.

[Slide.]

To summarize, there is no evidence at the present time that hydroxyurea is associated with excess mortality or is protective with respect to mortality in sickle cell anemia. We have not observed any patient who has developed while on the study cancer or leukemia.

There are no adverse events that can be attributed to hydroxyurea. However, many more patient years of follow-up will be needed to detect any uncommon events in this population.

Thank you.

Summary

[Slide.]

DR. SMYTH: In summary, hydroxyurea is a compound that now has about 30 years of real world clinical use since it was first approved in 1967.

We feel that the benefits of Droxia therapy for adult patients with sickle cell anemia outweigh the potential risks.

With regard to this multicenter study itself, we want to point out that there were no deaths attributable to hydroxyurea, no patient developed neoplasia. In patients experiencing myelosuppression, recovery was usually complete within two weeks. Other toxicities were comparable to placebo. With regard to long-term risks, I think specifically for patients with sickle cell disease who are treated with hydroxyurea, we can say in this multicenter study that at least in the two years on average the patients were treated during the study, and now more than three years since the completion of the study, that patients have been

followed on the follow-up study for a total of more than five years of treatment, we really haven't noted any alarming developments indicating carcinogenic or teratogenic effect that we have been able to document and establish.

[Slide.]

Thus, the indication we are requesting is the administration of Droxia represents a safe and effective option for the treatment of sickle cell anemia in adult patients, reducing the incidence of painful crises, and reducing the need for blood transfusions.

Chairman Dutcher, that completes our formal presentation. We are ready for questions.

DR. DUTCHER: Thank you very much.

Committee Questions to Applicant

DR. DUTCHER: Members of the committee, questions for the sponsor.

Dr. Lessin.

DR. LESSIN: In the follow-up study, at anytime during the study per se, were there any looks at the development of chromosomal abnormalities or other genetic abnormalities, oncogenes, or other genetic mutations?

DR. STEINBERG: Larry, that is planned in the follow-up studies. You know, in the initial study of Dr. Charache before the MSH, chromosomes were looked at before

and in the course of treatment, and there were no differences in the groups.

It is our plan in the follow-up study to get at least on a subset of patients chromosomal analysis, some who have never been on hydroxyurea, others who have been on hydroxyurea.

We are also considering looking for mutations in certain genes in these patients, however, this hasn't been entirely worked out at the present time because of the difficulty in storing samples for DNA analysis.

DR. LESSIN: In situations where the hydroxyurea is stopped, what is the rate of fall of the hemoglobin F levels or the F per F cell levels over time, in other words, how long will a sustained effect be maintained after the drug is stopped, either for brief periods or longer periods?

DR. STEINBERG: Sam, do you have any data on that at all?

DR. CHARACHE: I have no data on that. I would guess it would be the life span of those red cells, which would be somewhere, a month or so, but I don't know.

DR. DAVID JOHNSON: I have several questions based on having been one of the primary reviewers.

The patients were required to, as an entry criterion, to have had three or more painful crises in the

year prior to study entry. It wasn't clear to me from reading the manuscript, the article, or your presentation, how those specific crises were defined with respect to time.

During the study, a crisis was defined as lasting a minimum of four hours. Was that the same criterion applied to the year prior to?

DR. CHARACHE: The criterion for entry into the study was not rigidly defined. Patients or their physicians were required to state that there had been three crises in the preceding year. When we made site visits, we checked on many of those patients, found no discrepancies between what had been reported and what we found, but we did not check all patients and all charts.

DR. DAVID JOHNSON: Is it conceivable in your mind, as an expert in this area, that there could have been a bias then in terms of randomization of patients, meaning that a patient who had a 30-minute painful crisis, all those patients ended in the HU group and everyone who had prolonged crises ended up in the placebo group?

DR. CHARACHE: It is conceivable, but I think it pretty improbable that that sort of thing would happen.

DR. DAVID JOHNSON: I am surprised that no quality of life data were presented. It is mentioned in the briefing book and as I reviewed the data on page 74 of your

submission, it wasn't clear that there was any improvement in the quality of life parameters that were presented.

DR. CHARACHE: Ms. Barton will present those data. Franka Barton the statistician from the Maryland Medical Research Institute.

DR. BARTON: Good morning.

[Slide.]

We collected information from the patients on various parameters. The novelty in the study was probably the collection of daily pain according to the patient's subjective measurement, and this was analyzed according to the change from their own baseline levels, because we realized that what might be a pain of zero for one patient might be a pain of one for the other patient, zero being no pain, and 10 being the worse possible imaginable pain on a scale that was basically a 10-digit scale.

So we measured the change in the pain from baseline, and uniformly, the patients in the hydroxyurea group experienced reported drops of about a half a point on the scale. The nominal p value was 0.0055, and this was considered a secondary analysis for which criteria for significance were essentially secondary endpoints in the study are considered observational in nature. It would require an enormous p value, an enormously small p value to

have the force of significant difference at a clinical level.

[Slide.]

The four-week pain recall came from the short form 36. In addition to there not being a very large magnitude of difference in the patients in the two arms, either between the two arms of the study or across time, there may have been a little imbalance at baseline in this measure, but four-week pain recall indicated only minor differences between the two treatment groups at a p level of 0.048.

[Slide.]

The ladder of life is a subjective measure of rate your life from 1, which is the worst possible life, to 10, which is the best possible life. For patients who have a serious chronic disease, an average level of 7 on the scale is actually not that bad, but again, there aren't that many differences across time or between patient, the two groups.

[Slide.]

Those are the results of the main areas that were analyzed. These results are not assessed by our colleagues as yet. In the literature, we are in the process of working these results for publication.

DR. KROOK: One of the things that I either read or I heard was that the effect was really seen in the first

three months, and yet, on the other scale, there were several people who got up to the 35 mg/kg.

Did you see a further effect as the dose went up or was it with the lower dose, because there will be a dosage issue here, that if I look at your escalation scale, it was really no escalated in the first three months to that 35. It took a while if I am right.

DR. CHARACHE: You are right, and, in fact, in half the patients, the dose was reduced in the first few months, so that some of the patients were really at their maximum tolerated dose from the very beginning of the study or were toxic at that level, so that we think that one of the major reasons why there is an effect visible so early on is that those patients were already making as much fetal hemoglobin as they were going to make under the conditions of the study.

DR. KROOK: In the oncology side of the world, we talk about dose response. Do we see a response here with increased dose of the hydroxyurea? I am recalling back in the other half of my life and saying that those issues are going to be something the FDA is going to have to deal with here eventually. I mean can we see the same effect at 15?

DR. CHARACHE: Can I have the first slide in Set I. I hope that is it.

[Slide.]

These are data from our open-label study in which we have got dose level across the bottom and percent fetal hemoglobin across the side. As you can see, there is a fairly linear relationship between the two.

In the double-blind placebo-controlled study we got no data that specifically contradicted this, but as you know, we did have problems with compliance, and so the data are much noisier.

You can get virtually the same curve if, instead of hemoglobin F, you plot F cells and indeed you can get a very similar curve if you plot MCV, the higher the dose, the bigger the MCV.

I don't know if that answers your question.

DR. KROOK: How about compliance? I mean how many people -- whenever we do oral pills in the oncology world, it is always the question of compliance, and it is equally here. I remember my days when I was involved with people with this disease, it was always a problem.

Again, you might see, and I guess as people come off for a period of time, do we see a rebound or a decrease in hemoglobin F? How permanent is the change?

DR. BARTON: I hear two questions. I will describe the compliance data first.

[Slide.]

We took three major measures of compliance, first of all, how often the patients came back for these nuisance two-week visits that involved a needle-stick. Ninety percent in each group completed. The average completion rate was 90 percent in both groups.

We did nominal capsule counts, counting the capsules returned in the bottle, but not watching every patient put every capsule in their mouth. The averages were about balanced and ranged from 77 to 80 percent of the capsules being taken.

We also had random assays of hydroxyurea in the serum. They were taken every eight weeks. The patient did not know when this would happen. The clinics did not know.

Thirty-one percent of the patients had positive hydroxyurea assays in the hydroxyurea assigned group, and two patients, less than 1 percent, had it in the placebo group.

The question of what happens to the fetal hemoglobin after you stop taking hydroxyurea is an analysis that we don't actually have data to show you right now directly. We certainly have the data, but we haven't analyzed it that way yet.

DR. CHARACHE: I can try to describe some of the

other data that we have got. We broke the patients into quartiles on the basis of their final fetal hemoglobin levels, and then plotted out mean fetal hemoglobin levels for each of those quartiles during the course of the study.

You could see the patients who had the highest final F levels went up and stayed up. Those in the lowest quartile went up a little bit and came down to virtually where they started, and the other two groups were sort of in between.

[Slide.]

Here we have the four quartiles and you can see the differences in their fetal hemoglobin levels and some of the indices of compliance, and you can see that those who had the highest fetal hemoglobin levels were toxic more often, they had more positive hydroxyurea levels in their plasma, so that we think that this is reflecting compliance, but it is only an indirect measure.

DR. SIMON: Could you just clarify for me why the hemoglobin assays are so low, why you only get, say, on the slide you showed, 31 percent of the patients has positive assays?

DR. BARTON: Right. The clearance time is an issue here, and we measured the amount of time that patients said that they took their pill from the time that they came

at the clinic visit, at which time the blood was drawn for the serum assay.

The distribution, which I do not have the data here to show you, the Data and Safety Monitoring Committee looked at it several times, showed that was a clear relationship between the amount of time that had elapsed since the patient had taken hydroxyurea and whether the hydroxyurea showed up in the patient's blood.

In general, the amount of time that had elapsed was consistent with this 37 percent rate of patients who showed up positive in the hydroxyurea assay.

DR. DUTCHER: Dr. Lessin.

DR. LESSIN: One of the clinical toxicities of hydroxyurea when used to treat myeloproliferative disorders are leg ulcers. One of the clinical manifestations of sickle cell disease are leg ulcers.

Anecdotally, patients report improvement of leg ulcers in sickle cell disease, whereas, we see them occurring in patients with myeloproliferative disorders on long-term hydroxyurea.

Any comments on that?

DR. CHARACHE: A very interesting observation. I have no data. We have anecdotal reports of patients in the study whose ankle ulcers healed while taking hydroxyurea.

There were no instances in which ankle ulcers got worse. But I cannot explain this anomaly.

DR. SANTANA: As a follow-up to the question regarding quality of life, do you have any data either on reported use of analgesics in both groups?

DR. BARTON: We measured analgesia use in two areas. The first one was at-home oral analgesia use. This is either narcotic or non-narcotic, patient-directed, of course in conjunction with their doctor, but there is no control over what they do.

We converted all of the different dosages and forms into a single total morphine-equivalent in milligrams over the two years of observation that were available for every patient. Again, this is from self-reporting at the two-week visits of how much they estimated to have taken.

Basically, the distribution of the total dose that was taken does not differ between the two treatment groups. This may not be a reflection of the patient's management of pain as it is a question of the patient's relationship with their analgesia.

We have data on the total amount of analgesia taken during medical contacts. That is slide 102, please.

[Slide.]

This is the same technique summing the total

amount of analgesia taken, recorded during all the medical contacts, may they have been hospitalized or not, and here we see about halving in the median amount of parenteral and analgesia that was given over the two-year periods between the two groups.

A lot of that may have to do with the reduction in the frequency of the medical contacts as opposed to the total amount at each medical contact.

DR. DUTCHER: Dr. Johnson.

DR. DAVID JOHNSON: The data that were just shown, I am going to have to digest that for a minute, because those data are very confusing and actually disappointing, and I am not sure I accept your explanation that there is some other, quote "difference." There was an inference that there was some patient relationship with their pain medication. I am not sure I know what that means exactly. We can come back to that, but I have a couple of questions I wanted to follow up on regarding dosing.

It is unclear to me what dose would be recommended, number one. Number two, it is not clear to me from your data how one should or would titrate the dose and what one would use as a titration index, what specifically should you use as the endpoint, are you measuring hemoglobin F, and I am not even sure that that is the thing that is

making difference based on your report.

If, in fact, hemoglobin F is the important parameter and you showed that there is a dose relationship, why would you artificially cut off at a maximum dose of 35 per kg for that reason, why not keep going.

Lastly, as a corollary to that, you mentioned that it is renally excreted, however, should those patients who have renal insufficiency be excluded from treatment with this drug, can't you adjust accordingly, and how about liver dysfunction?

DR. CHARACHE: I hope I can remember all of those.

DR. DAVID JOHNSON: I can remind you.

DR. CHARACHE: Our first goal in designing the study was to be safe. We didn't want to do anyone any harm, and as a result, I think we bent over too far in the interest of safety.

Now, one of your first questions was where would you start, what dose would you start with. We started with 15 mg/kg because that was the median dose in our open-label study, and that is what it ended up to be in our double-blind study, and I would start with 15 mg/kg. If alternate dosage for encapsulations are permitted, you could get closer to 15 mg/kg than we were able to do.

How often should you check blood counts? Again,

because safety was our primary interest, we checked blood counts every two weeks. In other clinics, it is has been done at intervals of a month and there have been no untoward effects.

I can only speak to say that what we did worked. There is no reason to think that if one really were compulsive, you could stretch out that interval between blood counts.

Now, we don't know how hydroxyurea works, so that we can't measure some magic thing and say if this goes up, then, the patient will get better, or if this goes down, the patient will get worse. Fetal hemoglobin certainly has something to do with it, but it is hard to measure fetal hemoglobin, there is variability in the measurement, and it is expensive, so that we looked for a surrogate for measuring fetal hemoglobin, and MCV is probably as good as you can get.

I mean you can get it right while the patient is there in clinic, it is cheap, and it works pretty well. It is not perfect. At the same time, you can see what is happening to the white count, and if you are in a place where they automated reticulocyte counts, you can get that back in a hurry, too, so that those things give you some indication of where you stand.

What were the rest of the questions?

DR. DAVID JOHNSON: I want to know about those patients who have renal or nephrotic dysfunction.

DR. CHARACHE: We excluded patients who had flamboyant elevations of creatinine, but there is no real reason that you would have to do that if you were really, really careful. I mean certainly somebody who, let's say, had a creatinine of 1.5, I would want to watch his blood count very closely, but it doesn't mean that you couldn't give it to him, but for a general population of physicians and patients, you are taking a chance if you do that I think, but you could.

DR. SMYTH: David, you asked one question about the 35 mg cut-off.

DR. DAVID JOHNSON: I was asking about the maximum dosage, and I think what has been said actually addresses that for my satisfaction.

The only other issue that I had asked regarding this was unless you had a different dosing capsule, it comes in one size, right, hydroxyurea capsules, so does one size fit all? Is all of this really sort of irrelevant?

DR. CHARACHE: In the study, we made our own capsules, so we had two dosage forms, and we rounded off to the next lower number of capsules. If you let us do what we

want, we will have different dosage forms this time, too, and we could do it even better, if that answers your question.

DR. DAVID JOHNSON: But unfortunately, what we have commercially available, if I am not mistaken, is one dose.

DR. SMYTH: With the Droxia, the plan is to have a 200, 300, and 400 mg capsule, because literally, the doses were adjusted in 2.5 mg/kg levels, which is a little more than 100 mg at a time, so hopefully, that will allow you to use the same size capsule x number of times a day and get to a more precise dose.

DR. CHARACHE: To amplify on that, from my own experience in treating patients off the study and knowing what other people do, it is this business of odd days you take an odd number of pills even, and that adds risk. Patients can get confused and that is why we really want to keep it the same every day.

MS. WISE: If stress brings on the crisis, sickle cell patient, whether stress due to emotional stress, whether it is infection, or everything like that, were both groups monitored due to the same amount of stress or what?

DR. CHARACHE: We think that there is going to eventually, out of these quality of life studies, that there

will be some information on that question, but I can answer it in a somewhat different way by pointing out that the patients who got placebo, some of them thought that they were improved by placebo, and we think that that was in large part due to things like the central caller calling them every month, how are you feeling, the expression of interest in the patient, the fact that the investigators in each clinic were paying more attention to the patients.

Now, that is not eliminating problems at home, but it is certainly making problems at the hospital a lot easier for patients, so that I agree that that is an important part of this.

DR. MARGOLIN: I think, like Dr. Johnson, most of the rest of us think like oncologists, and we are not too concerned about this teratogenicity, but I am bothered by even the small amount of data that was presented with these birth defects.

More importantly, I think when this is used more, as it probably already is now, it is going to be used for less sick patients because it seems to work so well, increase the quality of life, and the question is in terms of the potential that more of these individuals will be feeling better, will think this is not such a bad disease after all, maybe we should have some children.

So, I just really have a general question about how that is going to be monitored in the postmarketing or in the current studies, and what kind of recommendations are going to be made.

My second question is whether there are going to be plans to study this drug in children, because if it really has an effect long term, at least with continued use in changing the natural history of this disease, it would seem that the children need to be treated, as well, or at least considered.

DR. CHARACHE: Slide tray G.

[Slide.]

First, the question of teratogenicity. The drug is teratogenic in animals. This is 50 mg per hamster, not per kg, and given on day 8 to hamsters can produce central axis deformity, cranioschisis, and spina bifida. In rats, now these doses are mg/kg. Depending on what point in pregnancy you give the drug, you can produce exencephaly, cleft palate, limb deformity, or encephalocele and micrognathia.

It is not limited to hamsters and rats. It has been shown in rabbits, dogs, cats, and rhesus monkeys. It is not clear that the effects of hydroxyurea are solely due to the effect on DNA synthesis. It may have something to do

with blood flow, and it certainly has to do with the area under the curve of blood levels.

That is, if you compare one animal with another, some animals seem to be almost immune, but they handle the drug differently from the others.

[Slide.]

Here are the data that we have been able to get in patients so far. Over here we have essential thrombocythemia, 9 patients with chronic myelocytic leukemia, 1 with chronic lymphocytic leukemia, and 2 here and 2 here with acute leukemia. These were doses, daily doses that were somewhat higher than we were using in these three groups. The patients with acute leukemia were getting combination chemotherapy and really for my money are uninterpretable. However, in the essential thrombocythemia patient, the one who was treated, treatment was stopped at six weeks and the child was normal.

In the 9 patients with CML, 8 were normal and 1 was a stillbirth. Follow-up was 5 to 32 months. This is a very important criterion because in rats, an apparently normal rat can show impaired maze learning some months after delivery, and they can show to have, they have little brains when you look at them. So, unless there is a prolonged period of follow-up, you can't be sure.

This one stillbirth, the mother was eclamptic, and that is harder to explain.

Here, this normal child and a woman with CLL, treatment was stopped at the third month, and not reinstituted until after the time of delivery, and as I said, you can't make very much out of this.

This child, whose mother got combination chemotherapy for acute leukemia, was in the fifth percentile for height and weight some months afterward, but follow-up periods are very variable.

I think the bottom line here is that pregnancy should be vigorously discouraged. That is about all you can do. You can make sure, as we tried to do, to teach the patients how not to get pregnant, but that's about all that you can do.

Now, to talk about pediatrics, can I have tray H.

[Slide.]

Hydroxyurea is being given to children with sickle cell disease all over the world. Scott is in the United States, de Montalembert is in France. There are two studies DeCheese reported, one, her own patients, and one, patients from all over the country. Fersters in Belgium, Vichinsky is in California, Rogers is in Texas, Jayabose is in Valhalla, New York, and the Hug Kids study is a multicenter

cooperative study very much like our MSH Study, that is just beginning to wind down and there aren't too many data.

The ages of these kids vary from the youngest, 2 to 10. The doses are similar to the doses we used. Two groups are deliberately trying to go to maximum tolerated doses, and the follow-up periods have been variable, but none of them really is long enough that one could draw any firm conclusions.

Now, what do we know about them so far? Of these kids, one child in this group, of de Montalembert, developed secondary amenorrhea. One of the children in this group, that is also from France, developed acute lymphocytic leukemia about two months after starting treatment. Hydroxyurea had actually been started because of bone pain, and when the child was treated for acute leukemia, the bone pain went away. This probably is not -- I mean it takes five years or longer to get a leukemogenic effect on polycythemia.

This one, no linear growth in 5 of 15 patients. After the slide was made, I got a communication from Dr. Rogers and she said that is a mistake, even though she said it in her original paper, that her children are growing perfectly normally, so that there have been no developmental delays observed yet. That is all I can say.

DR. SMYTH: Would you like Dr. Steinberg to comment on the follow-up study? Part of that question had to do with what we are going to do in the follow-up study to monitor the results of pregnancy.

DR. STEINBERG: Well, as I mentioned, this is a major goal of the follow-up study, is to try to track the outcome of all babies born to participants in the study, so that there are forms for monitoring the development of these babies, and the babies will also be followed at the visits of the patients to the clinic.

DR. DUTCHER: We can do two more questions.

Dr. Lessin.

DR. LESSIN: Actually, I will have two questions, but I will ask one. Drug interactions, what is known about the effects of other agents on area under the curve? Clearly, anything that will alter renal function will have an effect. What other areas are known?

DR. KAUL: My name is Sanjeev Kaul. I am senior principal scientist in the Department of Metabolism and Pharmacokinetics at Bristol-Myers Squibb.

We have no information on drug interactions with hydroxyurea.

DR. DUTCHER: Dr. Swain.

DR. SWAIN: I just had a question about the dose

and getting back to some of the things Dr. Johnson asked. Are you planning to recommend life-long treatment and, if so, what kind of dose especially those patients who have dose escalated up to the 35?

DR. CHARACHE: We really don't have data to answer your question specifically, but it would seem to me that if you got to a dose that was not depressing blood counts unduly, and the patient had gotten a beneficial effect, and the patient was willing to continue to be followed, and the physician was willing to continue following the patient, I would continue indefinitely.

But if any of those criteria were not met, particularly if the patient didn't show a good response, there would be no -- one of the questions that comes up is, well, how do you long do you wait for a good response. Well, based on our data, a few months ought to tell you something. It wouldn't tell you whether the patient had gotten as good as he could get, but if he were getting better, I would be encouraged to continue, and if nothing had happened, I would be encouraged to discontinue.

But as far as keeping it up, I have always told patients if you don't take it, it won't continue to work, and you will have to take it forever.

DR. DUTCHER: Thank you. I think we will take a

break now for 15 minutes and then we will get back to the FDA presentation.

[Recess.]

DR. DUTCHER: The FDA presentation.

Dr. Albert Lin.

FDA Presentation

DR. LIN: Good morning. I will be presenting our medical review of this supplemental New Drug Application, NDA No. 16-295-SE1-029.

Right after my presentation, Dr. Paul Andrews will give this presentation regarding the regulatory issues related to carcinogenicity of hydrea. We both will be available for answering questions afterwards.

[Slide.]

The drug in this application is Droxia, which is hydrea or hydroxyurea.

[Slide.]

First, I would like to acknowledge just who were involved in this NDA as reviewer or consultants. Their names and expertise are shown on this slide. Without their support and cooperation I wouldn't be able to stand here to give this presentation.

[Slide.]

The proposed indication, as you heard earlier, is

for the treatment of sickle cell anemia in adult patients to prevent painful crises and to reduce the need for blood transfusions.

[Slide.]

My presentation will include introductory remarks followed by discussion of multicenter study of hydroxyurea in sickle cell anemia, MSH clinical trial, patient populations, and results. I will then conclude with a summary.

[Slide.]

A brief regulatory history of hydrea is shown on this slide. Hydrea was first approved in 1967. In 1990, an orphan drug designation was granted to the applicant for treatment of sickle cell anemia.

In 1995, the National Heart, Lung and Blood Institute from NIH issued a Clinical Alert regarding the treatment of sickle cell anemia with hydrea based on the MSH Study.

In response to the Agency's request, the applicant submitted current supplemental NDA in May of this year. The initial ODAC meeting was scheduled in September, however, per the applicant's request, it was postponed to today.

[Slide.]

This slide provided by the applicant shows the

pharmacokinetic parameters for hydroxyurea following the administration of a 2-gram oral dose. I would like to bring your attention to the AUC, the area under the curve. Notice that the difference in AUC between the hydrea use for MSH's study and hydrea is about 2-fold. It may be due to different formulations used in these two studies.

We were informed that hydroxyurea, which is going to be marketed by the applicant for the treatment of sickle cell anemia has a different formulation from the hydrea used in the MSH Study.

[Slide.]

I will highlight some of the important points from the MSH Study in the new few slides.

The primary objective, as you heard earlier, was to determine if the treatment with hydrea will reduce about 50 percent of frequency of acute vaso-occlusive crises.

[Slide.]

Acute vaso-occlusive crises is defined as an acute painful event that requires visiting a health care facility lasting more than 4 hours, and the treatment was initiated with either narcotics or parental non-steroidal anti-inflammatory drugs. Chest syndrome and hepatic sequestration are also considered as acute vaso-occlusive crises. The intervals between events are required to be

greater than 24 hours, otherwise, both events will be considered as one single event or crisis.

[Slide.]

The secondary objectives were to establish the relationship of fetal hemoglobin levels and other patient or treatment characteristics to the occurrence of vaso-occlusive crises, and to evaluate the effect of treatment on the quality of patients' lives.

[Slide.

You have heard earlier the treatment administered and dose adjustment -- I am going to skip the next two slides -- let's look at the patient population.

357 patients were screened for potential eligibility. 58 patients were excluded due to incomplete run-in period or violation in eligibility. After randomization, 152 were assigned to hydrea and 147 to a placebo arm, with a total of 299 patients.

[Slide.]

Patients were enrolled at 21 study centers or clinics in the U.S. and Canada. This and the next slide show the number of patients enrolled at each center, in this column, and the breakdown of the number of hydrea patients versus number of the placebo patients.

[Slide.]

Both numbers are evenly distributed throughout each study center.

[Slide.]

Regarding baseline characteristics of study patients, both hydrea patients and placebo patients assigned to the study have a well-balanced distribution in terms of demographics including age, sex, ethnic background, annual crisis rate, and other characteristics, such as medical conditions, concurrent medications at entry, and laboratory profiles.

[Slide.]

Let's look at the study results. We discussed annual crisis rate, time-to-event analysis, and crisis rate and age.

[Slide.]

Since the original records were not available to us, our analysis was mainly based on the data set submitted to us. We used the following algorithm per protocols definition and identified crisis as pain, and duration more than 4 hours, and requiring treatment with parental narcotics or oral narcotics where parental narcotics was not administered, or parental non-steroidal anti-inflammatory drugs.

[Slide.]

We found the median annual crisis rates were 2.3 and 4.5 for the hydrea-assigned and placebo-assigned patients respectively. Both rates were very close to applicant's result shown in the second and the third columns of the table. In both analyses, the differences between the hydrea group and placebo group was statistically significant.

The annual crisis rate was reduced by 46 percent according to the applicant's crisis rate, and 49 percent according to our crisis rate.

This and the next two slides shown Kaplan-Meier curves of duration from initiation of treatment to first, second, and the third crisis. First, the time to the first event. Shown here, the hydrea group is in green, and the placebo group is pink.

[Slide.]

The median duration with time to the first event for the hydrea patient was 2.9 months, and 1.5 months for the placebo patients. The difference was statistically significant.

[Slide.]

The median duration of time to the second event for the hydrea patient was 8 months, and 4.3 months for the placebo patient.

[Slide.]

We also observed a significant difference regarding the duration of time to the third event between the hydrea patients and placebo patients.

[Slide.]

We looked at these three events using the applicant's crisis rate. The results were similar. The differences between both arms was significant in 0.003 events

[Slide.]

We compared the annual crisis rates between before and after treatment, and we found not only the hydrea-assigned patients had improvement in crisis rate, but a placebo-assigned patient also experienced reduced crisis rate. Both hydrea and placebo patients have the same median baseline crisis rate of 6 per year.

After treatment, the median crisis rate dropped to 2.5 per year for the hydrea group and 4.6 per year for the placebo group.

[Slide.]

We took one step further to look at the annual crisis rate by age group. The rates before treatment are shown in red, after treatment in white. The data for the hydrea-assigned patient is shown on your left, and placebo

patients on your right.

Most reduction was observed in the younger patient population or less than 20, and older patient population or age greater than 40 in the hydrea-assigned patients.

[Slide.]

Regarding the safety review, I would present to you our analysis on adverse events, discontinuation of medication, mortality, transfusion, pregnancy, and drug-related malignancy.

[Slide.]

This slide shows hematologic toxicities profile in hydrea patients and placebo patients. As expected, when compared with placebo patients, hydrea patients experienced a significantly severe myelotoxicity defined as the parameter shown at the bottom of the table.

Myelotoxicity occurred in these patients was mainly due to neutropenia and low reticulocyte counts or reticulocytopenia.

[Slide.]

Clinical toxicity regarding symptoms observed during the study are tabulated in this slide. The second and the third columns list the number of the patients and events in hydrea-assigned patients, and the third and fourth for the placebo-assigned patients.

The difference is number of patients between the two groups was not significant, however, 4 hydrea patients experienced febrile neutropenia. None of the placebo patients had febrile neutropenia during the study.

[Slide.]

Regarding signs of clinical toxicities, no significant difference was observed between these two treatment groups.

[Slide.]

This slide summarizes the result of hematologic lab tests. There was no difference from the baseline measurements between hydrea and placebo groups, shown in the second and third columns. However, two years into the study, significant differences were observed in neutrophils, hemoglobin, and MCV, and reticulocyte counts, shown in the last three columns.

[Slide.]

The only difference between these two groups in chemistry is the bilirubin level. After treatment, hydrea patients had a significantly lower mean bilirubin level than that of the placebo patients.

[Slide.]

Twenty hydrea patients and 19 placebo patients discontinued their medications permanently due to various

reasons shown in this slide. The most common reason is due to pregnancy, either in patients or their partners.

[Slide.]

118 out of 152 hydrea patients experienced 532 events of hematologic toxicity requiring two-week delay of treatment as expected. These numbers are higher than the placebo patients shown in this slide.

[Slide.]

Two hydrea patients and 6 placebo patients died during the study. This table summarizes the causes of death among these patients.

[Slide.]

You heard earlier about the follow-up study. At this point, there were 139 patients enrolled in the follow-up study and 35 deaths were reported, and 125 patients are yet to be enrolled into the follow-up study. It appears to us the vital status is all in clear information, other information is yet to be gathered, so the follow-up is incomplete as far as we are concerned.

[Slide.]

As of November 1997, there have been 15 deaths in the hydrea group and 20 deaths in the placebo group. The most common cause of death for both groups was pulmonary events.

[Slide.]

The applicant also provided us the results of Kaplan-Meier analysis on mortality shown here earlier. The difference between these two groups was not statistically significant. Again, the follow-up is on the mortality.

[Slide.]

In terms of blood transfusion, 55 patients required 423 units of blood transfusion. Both numbers were significantly lower than those of placebo patients.

[Slide.]

Sixteen patients or their partners had deliveries, 10 in hydrea group, 6 in the placebo group.

[Slide.]

As of November 1997, the number of deliveries increased to a total of 28, 16 live births were reported, 8 in each group. Keep in mind the follow-up is incomplete at this point.

[Slide.]

Among 16 live births, two events of birth defects were reported. One had microcephaly and blindness, another had polydactyly and mucocele, as you have heard earlier. Their parents were on hydrea at one point of the study. No birth defects were reported in the placebo group.

[Slide.]

Cancer was not reported either during the study or in the follow-up study.

[Slide.]

Despite cancer was not observed so far, it is still of concern. This and the next two slides show the incidence of acute leukemia in patients treated with hydrea for polycythemia vera and essential thrombocythemia published in the literature.

[Slide.]

I apologize. The slide looks a little bit busy, however, I have only one point to make. Let me quickly take you through. The first column shows the author and the year the article was published. The middle column summarizes each study. I would like you to pay attention to the last column here. The incidence of acute leukemia in patients treated with hydrea alone, very strong, 2 percent to 14.9 percent with a 5 to 10 years of median follow-up.

[Slide.]

To examine the risk of leukemia after the treatment of hydroxyurea, the P. vera study group published their experience from two different protocols, PVSG-08 and 01. One group was treated with hydroxyurea and another received phlebotomy alone to serve as the baseline, since patients with P. vera have increased the baseline risk of

leukemia.

The differences in the risk of leukemia during both on-study and on-and-off-study periods were not statistically significant, however, patients on hydrea had a greater incidence of leukemia. The on-study rate was 5.9 and on-and-off study rates or the cumulative rate was 9.8.

[Slide.]

In the last few minutes I will present to you an analysis we looked at.

[Slide.]

First, we asked the question if the reduction in crisis rates and hydrea-assigned patients can be translated into improvement in quality of life.

[Slide.]

Our statistical reviewer, Dr. Takeuchi, applied the longitudinal analysis using a growth curve model to investigate the treatment effect over time and the correlation of the repeated measurements.

[Slide.]

The results from this analysis shown in this slide, the horizontal axis here, shown time by time, and the vertical axis is changes of the pains scores, going upward from zero to 9 representing increasing pain scores, going downwards from zero to minus 9 representing decreasing pain

scores or improvement of the pain score.

Notice that the upper line here, the flat line, that is from the placebo group. No time trend was observed in this placebo group. Hydrea-assigned patients, the lower line here, shown in red. They experienced some pain reduction in the first 10 months, however, the reduction of the pain score was about 0.5 unit at most.

[Slide.]

When we examined the correlation between the crisis rate and the last dose, we found: first, a two-year crisis rate correlated with the baseline crisis rate; second, the two-year crisis rate also correlated with last dose.

The next two slices are important slides, will be further discussed later on by the committee member.

[Slide.]

These slides are done by Dr. Qing Liu, our statistician. He did a subset analysis based on the baseline crisis rate. This slide shows a median two-year crisis rate in both hydrea patients and the placebo patients with a number of patients next to the crisis rate and divided by the severity of the baseline crisis rate.

Notice that almost half of the patients, either in the hydrea group or the placebo group, had a baseline rate

between 3 to 5, and the differences in crisis rate was not different. The data suggest that this subset of patients having crisis rate, baseline crisis rate between 3 to 5, did not benefit from treatment.

[Slide.]

I would reiterate the point I made earlier about the correlation between the last dose and the median crisis rate. A question was asked about the dose-response curve. What one sees here is increasing last dose, there is a greater mean and median crisis rate.

This makes us wonder what the optimal dose should be in treating these patients, and this will be discussed further.

[Slide.]

In terms of the blinding, before the disclosure of patients' treatment assignment, patients and investigators were asked to guess what kind of treatment patients received or what kind of treatment his or her patients were treated. Interestingly, in the hydrea group, more than half of the patients and more than half of the investigators, they were able to guess that their patients or the patients themselves definitely or probably were on hydrea.

In the placebo group, more than half of the investigators were able to guess their patients were

definitely or probably on placebo. Only those patients on placebo were not sure what kind of treatment they received.

[Slide.]

You saw a similar slide earlier about compliance. To evaluate compliance, patients were supposed to have blood tests four times a year to check the blood level of hydrea. We found 15.3 percent of hydrea patients had non-detectable hydrea blood levels throughout the follow-up.

The lower part here shows the number of hydrea blood tests. 1,247 hydrea tests on the hydrea group, only one-third of the tests were positive. We questioned the sensitivity of the tests, and clearly, compliance was not established.

[Slide.]

In summary, the basis of this submission is the MSH Study. MSH is a double-blind, randomized controlled study designed to determine if hydrea can reduce the frequency of acute vaso-occlusive crisis by approximately 50 percent.

299 patients, older than 18 years, with documented sickle cell anemia and at least three crises per year were enrolled in the study between January 1992 to April 1993. 152 were randomly assigned to receive hydrea, and 147 placebo.

[Slide.]

Patients receiving hydrea experienced 46 to 49 percent less crises than those treated with placebo. Hydroxyurea significantly delayed the median duration of time to crisis. Hydrea reduced the number of patients requiring blood transfusion and the number of units of blood transfused.

[Slide.]

However, taking hydrea is not without risk. 79 percent of hydrea patients versus 39 percent of placebo patients were diagnosed with myelotoxicity, most notably neutropenia and leukocytopenia. Febrile neutropenia as observed in 4 patients on hydrea, none was observed in the placebo patients.

[Slide.]

In addition, we are uncertain about the following issues: optimal dose, carcinogenicity, teratogenicity, mutagenicity, blinding, compliance.

After all, hydrea is not a cure for sickle cell anemia. Using hydrea as a long-term treatment for sickle cell anemia, caution must be exercised to ensure that the short-term benefits outweigh the risk of receiving hydrea and uncertainties in the long-term complications.

Thank you for your attention.

Now I would like to introduce Dr. Paul Andrews.

DR. ANDREWS: Thank you.

[Slide.]

Committee members, FDA colleagues, representatives of Bristol-Myers Squibb, and guests: Good morning. The Division believes the consideration of the carcinogenic potential of Droxia should be an important factor in deciding whether or not this drug should be approved for sickle cell anemia and the conditions of such an approval.

I will be presenting the regulatory considerations regarding the carcinogenicity of hydroxyurea, the active ingredient in Droxia.

My aims are to review the preclinical data which address the risk of developing cancer as a result of Droxia exposure, to explain the regulatory background for carcinogenicity testing of chronically administered drugs, and to convey our perspective on this issue for Droxia as indicated for sickle cell disease.

[Slide.]

A mutagen is an agent that causes a heritable change in the nucleotide sequence, that is, the genetic code of DNA. Many studies in the biomedical literature show that hydroxyurea is clearly mutagenic. It is mutagenic to a variety of organisms from bacteria to mammalian cells. In

mammalian cells, mutations can be detected in several different target genes.

[Slide.]

A clastogen causes structural changes in chromosomes, usually detectable by light microscopy. Numerous studies in the literature have documented that hydroxyurea is a clastogen. The structural alterations detected after exposure of cells in culture to hydroxyurea include chromosome aberrations, such as gaps, deletions, rearrangements, chromosome losses, chromosome breaks, and sister chromatidic exchanges.

Chromosome breaks have been detected in both rodent and human cells in culture. Hydroxyurea is also a clastogen when administered to mice. In this standardized test, polychromatic erythrocytes in bone marrow are examined. Chromatid and chromosome fragments induced by clastogens are left behind in anaphase and included in the daughter cells.

These form structures in the cytoplasm called micronuclei that persist after the nucleus is extruded by the mature erythrocyte. A single 1.2 gram/per meter-squared dose of hydroxyurea, which is nearly identical to the 30 mg/kg dose in humans normalized to body surface area, markedly increase the incidence of micronuclei in mouse

erythrocytes.

[Slide.]

Neoplastic transformation is a multi-step process that includes morphologic transformation, acquisition of immortality, acquisition of tumorigenicity, that is, the ability to form tumors in animals, and malignant progression, that is, the ability to invade adjacent tissue and metastasize to distant sites.

Isolated Syrian hamster embryo cells can model this process, and a standard assay has been developed which determines the ability of an agent to induce the first step morphological alteration.

This Syrian hamster embryo cell or SHE cell assay correlates with carcinogenicity in animals with an 80 to 85 percent predictive accuracy. Hydroxyurea has been reported to be positive in this assay, however, no hydroxyurea data was actually presented in the paper which presented this finding.

Hydroxyurea has also been reported to increase the frequency of transformation in virally infected mouse embryo cells. In this case, transformation included detection of immortalization and tumorigenicity in addition to the first step of morphologic alteration.

[Slide.]

Other evidence exists that hydroxyurea is genotoxic. Hydroxyurea is known to inhibit repair of damaged DNA and therefore may enhance the genetic toxicity of endogenous or environmental insults to DNA integrity.

Hydroxyurea can also promote gene amplification which could endow cells with key growth and survival properties important in the promotion and progression of tumor development.

[Slide.]

In addition to the convincing data showing that hydroxyurea is genotoxic in conventional preclinical tests, it also possesses a structural alert. As shown here, the molecule is very similar to other compounds known to be carcinogens in mammals. Urethane in particular is a well-known carcinogen that might be familiar to many of you. Structural alerts indicate that there is an increased risk for concern prior to obtaining actual evidence.

[Slide.]

At least four papers in the literature examine the appearance of tumors in animals after hydroxyurea exposure, and these were reviewed for their ability to address the carcinogenic potential of hydroxyurea.

Although no clear signal was present that hydroxyurea increased the incidence of any tumor, all four

studies had major design flaws. For well over 10 years, a standardized bioassay for assessing carcinogenicity in rodents has been accepted by industry and regulatory agencies around the world.

A few key aspects of the assay are: that dosing is daily for up to two years, 50 animals per set per dose group should be used to have adequate survival and statistical power to detect a tumor signal. For a genotoxic like hydroxyurea, the high dose group should be based on a maximally tolerated dose, the MTD, to assure a sufficient test of the carcinogenic potential. All the animals and tissues must be examined for malignant and benign tumors. In order to have confidence in negative finds, a reasonable number of animals must survive close to the end of the study. One benchmark is that roughly 50 percent of the animals should survive 80 to 90 weeks of the 104-week study.

The four papers examined failed to meet these design criteria on multiple counts.

[Slide.]

With this preclinical data in hand, we can now examine the regulatory background. The U.S., European, and Japanese regulatory agencies and the pharmaceutical industry collaborated in recent years to harmonize the regulatory requirements needed to register drugs in the three regions.

One of the earliest guidances to be produced by this efforts was Guidance S1A entitled, "The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals."

That guidance states that, "Unequivocally, genotoxic compounds in the absence of other data are presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be subjected to long-term carcinogenicity studies."

Under the spirit of that guidance, we allowed the NDA for Droxia to be filed without regulatorily acceptable carcinogenicity studies, since the available data demonstrate that the active ingredient is unequivocally genotoxic.

Such an approach, however, leaves uncertain what risk Droxia exposure might actually pose.

[Slide.]

In addition to the multitude of evidence of the genotoxic properties of hydroxyurea in a variety of preclinical tests, we also considered the evidence in humans since this drug has been marketed since 1967 for the treatment of cancer.

Hydroxyurea has been reported to be clastogenic when administered to humans. Chromosome breaks and major

aberrations, such as translocated dicentric and fragmented chromosomes were detected in peripheral blood leukocytes of lung cancer patients treated with hydroxyurea.

There are also reports of leukemia and polycythemia vera patients and reports of skin cancers in patients with myeloproliferative disorders after treatment with hydroxyurea. Whether the incidences of these malignancies were directly associated with hydroxyurea exposure cannot, however, be definitively established based on the current data.

[Slide.]

In conclusion, hydroxyurea is positive in all in vitro and in vivo genotoxicity tests. Hydroxyurea is positive in embryo transformation assays including the SHE cell assay which predicts rodent carcinogens. Hydroxyurea is structurally similar to known carcinogens, such as urethane. There is evidence that hydroxyurea is clastogenic and possibly carcinogenic in humans.

Hydroxyurea is thus unequivocally genotoxic and a presumed trans-species carcinogen, which implies a carcinogenic risk to humans.

[Slide.]

The Division of Oncology Drug Products' perspective is thus:

1. If approved, the label should include a warning stating the evidence that Droxia poses a carcinogenic risk to humans. The physician and patient must very carefully consider the potential benefits of Droxia relative to the undefined risk of developing secondary malignancies.

2. An animal study to unequivocally define the carcinogenic potential of hydroxyurea may be valuable. The study should preferably use an alternative assay, such as the P-53 hemizygous mouse which has been used to assess the carcinogenicity of genotoxic compounds. Results from such a study would be quickly available since animals are dosed for only six months instead of two years.

We believe it is appropriate to request such a study under the International S1A guidance, which I mentioned, which states immediately following the previous quote, "However, if such an unequivocally genotoxic drug is intended to be administered chronically to humans, a chronic toxicity study up to one year may be necessary to detect early tumorigenic effects."

In prior correspondence, Bristol-Myers Squibb agreed to conduct such a study post-approval.

Thank you for your attention and I hope this information will be useful as you consider the

risk-to-benefit ratio for Droxia and sickle cell disease.

DR. DUTCHER: Thank you very much.

Committee Questions to FDA

DR. DUTCHER: Questions for the FDA? Sandra.

DR. SWAIN: Dr. Lin, was there any evidence that the patients that only had the three to five crises since you did the subgroup analysis were the patients who were non-compliant?

DR. LIN: That is a good question. I haven't looked at or linked those two files together, so I don't have an answer for you.

DR. DUTCHER: Given the problems with hydroxyurea levels in terms of the assay, could you also look at mean corpuscular volume and/or hemoglobin F levels to assess compliance or was that looked at to assess drug exposure basically? Do you know or does someone from the study know?

You can answer it.

DR. CHARACHE: We did look at that in the paper in Medicine, and by and large, there is a relationship, but there are some glaring discrepancies. In other words, there were some patients who had positive, repeatedly positive blood levels, who did not show a rise in MCV and vice versa, so that over a broad population, you can make some conclusions, but for an individual patient it is very hard.

DR. DUTCHER: Dr. Krook.

DR. KROOK: One of the issues, Dr. Lin, that I still have problems with is the quality of life. You brought up the no great change in pain score. I think you said 0.5. Did you look at the quality of life to -- I guess what I am trying to say is could you see, in the people who were on the hydrea, an increase in the quality of life, or we heard from the people who are here, who have sickle cell disease, that they had improved lifestyle, but I don't think the pain score changed that much, nor other things.

Did we look closer at that at all?

DR. LIN: Well, I agree with you the pain score doesn't change a lot, as you heard earlier, about the ladder of life analysis I included in my report. The study collected a lot of information, and we looked at different angles, different analysis, and nothing can be concluded in terms of quality of life issue.

DR. KROOK: Was there any attempt to count pain pills? I mean we heard from the sponsor that there was, but it seems like the major goal of the study was to decrease the amount of venous occlusive events and yet we don't see a change in the pain score. I mean to me they seem kind of opposite.

DR. LIN: I have trouble with that, too.

DR. KROOK: I mean the pain score stays the same, and yet the events go down.

DR. LIN: That is our finding.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I have a couple of questions. I liked your summary, Dr. Lin, but I wondered again looking at the same issue, which I think many of us on the committee are struggling with, do you think that it may have something to do with the selection bias introduced in the original randomization that relates to, as I recall, patients with a consumption of more than 30 oxycodone tablets a month were excluded from entry?

So, does this suggest that the investigators may have been selecting inadvertently for a particular type of patient, i.e., patients who were having crises, but not using analgesics? Were you able to look at the data with that in mind, and do you have any insights?

DR. LIN: The data sets submitted by the applicant does not answer that question.

DR. RAGHAVAN: I have a question for Dr. Andrews, and that is, I understand the cautionary notes that you have sounded. Can you tell us a little bit more about false positive rates and false negative rates in the SAG assays, how strongly confident are you of the level of risk of

hydrea in that context?

DR. ANDREWS: Well, one problem right off is that the data for hydroxyurea in that assay is very poor. As I mentioned, there is no data, and the paper, as just mentioned as passing in the results, the focus was on another drug studied Ara-C.

We would have to take the authors at their word that it was positive. Certainly, it is not 100 percent predictive accuracy, but it is one of the most accurate preclinical tests out there for carcinogenicity.

Is that a sufficient answer?

DR. RAGHAVAN: Yes and no. I mean you can't make up data that aren't there. I guess I always worry with any drug the guilt by association worries me, and if you don't have some finite data that suggests that this is potentially carcinogenic, I guess if the drug is approved, that potentially is going to create some trauma among the patient population without hard data to back it up.

On the other hand, you would hate to be in a situation where 10 years after the event, you had missed warning a population that the risk was there. So, I guess, as you said, a study needs to be done.

DR. ANDREWS: That is exactly our thinking and why we would really like an animal study to be done to provide

that data.

DR. RAGHAVAN: My final question to the team, the investigating team, if I read Dr. Lin's slide correctly, there were no patients recruited from Hopkins, yet Hopkins was running the study. Why was that?

DR. CHARACHE: I am afraid I was the entire sickle cell study group at Johns Hopkins, and I couldn't do everything.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I am sorry, but I just wanted to get back for a second to the pain score and the report from Dr. Barton about what appeared to be on quick look a lack of significant difference in the total morphine-equivalent usage over the two years in the patients, and the exclusion of patients who were taking more than what turns out to be just one oxycodone per day.

It really turns into a question I guess for Dr. Charache or others who treat these patients.

Is it conceivable that what we really need to do is throw out those aspects of the study because patients with sickle cell anemia most of the time are not having baseline pain, and not taking a lot of drugs in between their crises, and what we are really trying to ask this drug to do is to reduce the number of crises, but we are really

not asking it to do anything in between?

DR. CHARACHE: I think if you talk to most patients, that they will tell you that they always have aches and pains all the time, but that these are punctuated by much more severe episodes as you describe.

That may be the answer to the problem, in other words, the daily aches and pains continue, I mean some of the aches and pains are due to long-standing joint damage that isn't going to go away. You can't fix a joint with hydroxyurea.

I don't know the answer to the question.

DR. DUTCHER: Dr. Simon.

DR. SIMON: A question for Dr. Andrews.

Could you clarify the carcinogenicity test that the company has agreed to do if the product were approved, and what would be the implication if that test showed that the drug were clearly carcinogenic?

DR. ANDREWS: No specific test was agreed to. The company agreed to work with the Division on designing an assay and picking the best model to use for that, and short-term alternatives were suggested. There was no focus on any one particular assay at the time.

The implications are interesting. Of course, if we had the data that showed it was a clear carcinogen in a

rodent, it would go on the label and there would be a stronger warning than just based on the in vitro tests alone.

What might be more interesting is if there was a negative result. Then, potentially more patients would use this for treatment. It is primarily to get the best data available, so that patients can be properly informed of the potential risk.

DR. MARGOLIN: Does anybody have the text of the Clinical Alert that was generated as a result of the first interim analysis of the study?

DR. SMYTH: It is in the briefing document, in one of the early sections.

DR. DUTCHER: We have it. Thank you.

Dr. Lessin.

DR. LESSIN: Regarding mortality, the theory of the pathophysiology of sickle cell disease and data from the mortality study, the CSSCD that was published in The New England Journal indicate that the frequency of vaso-occlusive crisis is associated with mortality.

One would then postulate that cumulative organ damage that occurs as a consequence of repeated crisis is perhaps the mechanism whereby that mortality is seen. Do we have any early hints from either your review of the data or

the investigator's review of the data, that, in fact, cardiovascular or pulmonary mortality is, in fact, reduced?

I noticed on one of the slides in the follow-up study, deaths from cardiovascular and pulmonary events were decreased in the treated group relative to the placebo group. Am I correct on that, and is there any data on which we might begin to predict that mortality would be benefitted overall by reduction of these crises?

The other point I would make is that -- and I think Dr. Charache made this initially, but it needs to be emphasized -- that if you run a clinic with over 100 sickle cell patients, as I once did, you find that a minority of your patients really fall into this category of three or more crises per year. It is maybe 20 or 25 such patients that are the ones that demand most of your clinical time.

So, one of the concerns is that if this drug becomes utilized generally, that the treating physicians and the public realize who those patients are, who the patients are who really should receive the drug. They tend to be the same patients who require the more frequent transfusions, and so on, but I think that is a clear definition that will be necessary.

So, two questions: mortality and mechanisms of defining who the at-risk population are.

DR. LIN: In terms of mortality, I think it is kind of too early to tell at this point the number of the patients, really small, and the rest I would ask maybe the investigators can answer those questions.

DR. STEINBERG: As you observed, Larry, there were more deaths from pulmonary disease in the placebo arm, but as is also true, there is no statistically significant difference. Of course, all of our hopes is that this drug is going to reduce mortality.

Now, the patients that were selected for the MSH are probably the worst group of patients to make that determination, because they were older patients and they were sick patients, and the hope is that as our pediatric colleagues develop their study, and include in their study measurements of organ damage, and start to enroll their patients in longer term studies, then we will ultimately know whether there is an effect on mortality.

DR. DAVID JOHNSON: I would tend to agree with your assessment about the long-term mortality issues, and that may show up with later follow-up data, and that seems to me to be very important.

The study was designed, as I understand the study, to look at reduction in the incidence of crises, not some of these other points that we have been talking about, and it

showed that very effectively.

The only counter to your question -- and I have found these data interesting -- were the sponsor's graph using the Kaplan-Meier plot of the cumulative mortality, which if what you said, in fact, is true, I would have thought that the curves would have separated over time.

In fact, what happens is they separate immediately. That is sort of an interesting phenomenon. I didn't bring that up because I didn't know how to explain that or I didn't know if there was an issue, and I didn't want to confuse it even further, but that strikes me as odd.

If you look at D5, at the sponsor's presentation, the curves precisely track one another after the first three or four months, and that is the interval of time that, in their application, they state that the hemoglobin F changes, and thereafter there are no differences that take place after that. So, there is sort of some interesting data there, and obviously, we are starting to subset even further the data analysis, but this is interesting. This is the curve I am speaking of right here.

DR. SANTANA: Was that age adjusted because, you know, if the other issue is the age, and obviously older patients have more premorbidity when they go into the study versus the younger patients, I think if that is age

adjusted, it may give you a better definition of what the difference is.

DR. DAVID JOHNSON: The ages were balanced going in, so I would assume so, but I don't know that. Maybe the sponsors, if Jan would be willing to let them respond to that issue.

DR. SMYTH: You know where that blue line is there, where the study was closed out? At that point, many, many of the placebo patients went on hydrea, they didn't stay on placebo, so these curves are bound to come together over time. Virtually most of the patients end up on hydrea.

DR. DAVID JOHNSON: That may well be true, but then it doesn't explain the first part of this, it curves. And in follow-up to that, Dr. Smyth, do you, in fact, have data how many of those people, in fact, did go on to hydrea, and so on, and so forth? Those are all the other issues. But you do have the separation, which is sort of a curious one. I don't why it is there.

DR. SMYTH: Dr. Steinberg is chairing that study.

DR. STEINBERG: We are collecting that data.

DR. SMYTH: I am talking about the first part of the curve. I understand you are collecting the other --

DR. STEINBERG: Hydroxyurea has very early effects on different components of the blood. The neutrophil counts

drop within a very short time after treatment. So do the reticulocyte count and the platelet count. Hemoglobin goes up a little bit. So, all of these changes occur.

It may be, as I hinted in earlier slides, that the beneficial effects of drug extend beyond that in fetal hemoglobin and are related to changes in other formed elements of the blood and probably changes in the vascular system. Other than that, I can't give an explanation for why these curves immediately begin to appear different. However, this is no statistical difference at any point. The curves look pretty here, but they don't differ by statistical analysis.

DR. DUTCHER: Ms. Wise.

MS. WISE: I have a problem with the fact, because there is no comprehensive clinic for sickle cell patients, so a lot of patients go HMO and are seen by primary care doctors. By being an advocate already and meeting people who are on hydroxyurea, and even people who are not on hydroxyurea, but doctors are trying to get them on hydroxyurea, they are not being carefully monitored.

So, wouldn't that be a problem if this is given out where they are not carefully monitored, because of the lack of information?

DR. DUTCHER: Well, I think it is a problem, but

one of the things that certainly can be done in a labeling type of situation is the criteria under which the drug can be used, and then that information would be better publicized for both patients and physicians.

I mean you heard the people presenting suggest that patients needed to be very carefully monitored, and we would all agree with that, but that would be one of the stipulations if the drug were formally approved for sickle cell, and then it is the obligation of the physicians to monitor the patients, and also the information be available to patients to insist upon it, and it would be covered by whatever health care organization is being utilized.

MS. WISE: It is very expensive. I do know that much also. So would the cost price be different?

DR. LESSIN: I think you have brought up a good point, but in terms of relative cost, if you can avoid a hospitalization, you have already saved a lot of money or a transfusion, for that matter.

DR. DUTCHER: Unless you don't have a prescription plan.

MS. WISE: Yes.

DR. DUTCHER: These are actually very important issues, and I think that some of the things in the approval of the drug that make it something that is approved for a

specific disease, helps us in arguing with health care financing that patients should be covered for these particular items.

Any comments from the sponsor on that?

DR. CHARACHE: To amplify Dr. Lessin's remarks, we took all the data from the study and calculated how much money was not spent because of the number of crises, and we saved more money than the entire cost of the study, which was in the millions.

We also sat down and figured out how much you would save comparing the cost of hospitalizations and medical care against the cost of the pills, and you still come out ahead. I couldn't agree more. I would like it if they gave the pills away, but the real problem is going to be to convince the people who pay that they are getting a bargain. That is not so easy.

DR. DUTCHER: Any other questions for the FDA?

Thank you very much.

Any other comments by members of the committee before we start to address the questions, any issues that they wanted to bring up that we didn't cover?

Dr. Simon.

DR. SIMON: One question. This is again I guess for Dr. Andrews. For drugs like hydroxyurea, assuming if it

were a carcinogen, is there experience over what time frame those drugs would cause acute leukemia, if that is what you would be expecting?

DR. ANDREWS: That is one factor that is looked at when the animal data is statistically analyzed is how soon tumors appear. How that would factor into how this was labeled, it probably wouldn't have a very big factor at all.

Was that your question?

DR. SIMON: No, I was thinking clinically, for some kinds of drugs that are used in oncology, which it is known that etoposide may take a certain period of time to cause it, alkylating agents take longer, so I was wondering for drugs in this class, what would the time frame be.

DR. ANDREWS: It is very difficult, even if we had the data in animals to extrapolate what the time frame would be in humans. We already have some data for the sickle cell patients out to five years now where we have no incidence in the 150 patients that were treated.

DR. DAVID JOHNSON: But you do have human data in the P. vera experience, and what is the interval between the initiation of that therapy and the onset of secondary leukemias, putting aside whether we think they are caused by that or not, what --

DR. ANDREWS: I don't know off the top of my head

how many years later that was. Do you, Albert?

AUDIENCE: About four years.

DR. LIN: The slides I showed you earlier from the P. vera study experience, the follow-up time varies from five years to 10 years, and you just heard, probably four or five years for the median follow-up time to observe leukemia.

DR. SIMON: What is the age range for polycythemia vera patients?

DR. LIN: P. vera occurs in older, elderly populations.

DR. DAVID JOHNSON: Would we consider this experience in P. vera substantially different in terms of a risk than, say, the risk in Hodgkin's disease for a second malignancy, leukemic malignancy?

DR. DUTCHER: Yes.

DR. DAVID JOHNSON: Jan is saying yes. Do you consider it a lot higher?

DR. DUTCHER: I think that anytime you are dealing with a primary marrow disease --

DR. DAVID JOHNSON: I understand that. Now you are talking to someone who just thinks simply. Is it 10 times worse, five times worse, about the same?

DR. DUTCHER: Well, the incidence in Hodgkin's

disease is considerably lower than what is predicted. It is well below 5 percent. It is about 2 to 3 percent, and it is directly related to the duration of treatment, so we don't give the regimens that are leukemogenic very much anymore, or it is in people that have had multiple treatments, so I don't think you can compare that to the P. vera data or the ET data where you are giving the drug chronically to people that have a primary marrow disorder.

DR. DAVID JOHNSON: Yet, people give hydrea for P. vera, and we worry about the instance of some leukemias, but it doesn't preclude us from giving hydrea to those patients, correct?

DR. DUTCHER: Correct.

DR. DAVID JOHNSON: In your estimation -- I am sorry I jumped into Hodgkin's, I should never have done that -- in your estimation, then, would you guess it to be similar in this type of patient who doesn't have the same kind of marrow injury to begin with?

DR. DUTCHER: Would I guess this was comparable to the P. vera?

DR. DAVID JOHNSON: Yes.

DR. DUTCHER: No, I would guess it would be much less.

DR. DAVID JOHNSON: Okay.

DR. DUTCHER: That would be a guess. Do the other hematology people want to comment?

DR. MARGOLIN: Not as a hematology person, but I think also you have to look at the dose effect, and the doses that we use routinely to control the counts in myeloproliferative disorders are probably two or three times higher than these doses in the sickle cell patients, so if there is any interaction between the dose and the duration and the disease, that has to be taken into account, as well.

DR. LESSIN: The data that we have seen expressed is given in terms of statistical significance and p values. Has anyone attempted a relative risk analysis?

We saw in some cases a multifold increase in the incidence, for example, in the polycythemia vera study group, even though the p values were not significant, it looked as though the incidence was two or three times greater in the hydrea group versus the phlebotomy alone group.

DR. BRINKER: Would you repeat your question, please?

DR. LESSIN: The question I guess is a statistical one, and that is, has anyone looked at these data in terms of a relative risk analysis, or is the data sufficient to permit one to do that?

DR. BRINKER: Allen Brinker, FDA.

The relative risk based on the PSVG-08, which compares hydrea versus the historic controls, suggests a relative risk of 2.6 with a confidence interval 0.8 to 8.7.

DR. DUTCHER: Other comments? Do you want to go on to the questions?

Committee Questions

DR. DUTCHER: In the MSH Study, Droxia appears to decrease the median annual sickle cell crisis rate by 46 percent, to decrease the number of patients transfused by approximately 30 percent, and to decrease the number of transfusions by approximately 37 percent.

Although patients with 3 or more crises per year at baseline were eligible, most of the benefit in crisis reduction was restricted to the subgroups with 6 or more crises per year at baseline.

Considering the proposed patient population,

1. Does Droxia have a favorable risk/benefit ratio for the two year observation period in the MSH Study?

Dr. Krook.

DR. KROOK: After review of the data and the information that was sent, I would favor, the answer to this is yes. I believe that they have shown that the number of events are down, several of the other criteria are

favorable.

DR. DUTCHER: Dr. Johnson.

DR. DAVID JOHNSON: I agree.

DR. DUTCHER: All those who would vote yes on Question No. 1, please raise your hand.

[Show of hands.]

DR. DUTCHER: That was the unanimous vote of yes.

No. 2. Does Droxia have a favorable risk/benefit ratio (especially regarding carcinogenicity) for adult lifetime use?

Dr. Lessin.

DR. LESSIN: I think here we don't have sufficient data to answer that question. We don't really know about carcinogenicity and the other concerns over the long term, nor do we know about improved mortality or decrease in organ dysfunction that occurs as a consequence of the natural history of the disease. So, I would have to say that is not an answerable question at this point in time.

DR. DUTCHER: Other comments?

DR. KROOK: I would answer the question as no, it does not have a favorable risk/benefit for adult lifetime use. That means long-term use.

DR. MARGOLIN: If we can change the question to say proven, then, we can vote yes or no.

DR. DUTCHER: Can we change the question?

FDA: Sure.

DR. DUTCHER: Does Droxia have a proven favorable risk/benefit ratio for adult lifetime use?

All those who would vote yes?

[No response.]

DR. DUTCHER: All those who would vote no?

[Show of hands.]

DR. DUTCHER: It is unanimous no.

Question No. 3. The Droxia capsules used in the MSH Study are a different formulation than the to be marketed Droxia capsules. The FDA will require verification of the relative bioavailability of the Droxia formulation used in the MSH Study and the to be marketed Droxia formulation. Providing this is satisfactorily accomplished, does the committee recommend approval of this Supplemental NDA?

Any comments? Dr. Johnson.

DR. DAVID JOHNSON: I would say yes. I would answer that yes.

DR. KROOK: I would agree, yes.

DR. DUTCHER: All those who would vote yes? We are voting for approval of the Supplemental NDA.

[Show of hands.]

DR. DUTCHER: There are 10 yes's.

All those who would vote no?

[One abstention.]

DR. DUTCHER: Are you abstaining? Abstained. One abstention and there are 10 yes's.

No. 4. If so, (a) should the indication be restricted to adult patients with sickle cell anemia with moderate to severe recurrent painful crises?

Or (b) should the indication be restricted to patients with at least 3 crises during the last 12 months (as per the MSH protocol eligibility requirement)?

Or (c) should the indication be restricted to patients with at least 6 crises during the last 12 months (as per the FDA subgroup analysis)?

Would somebody like to comment on the alternative answers?

DR. DAVID JOHNSON: I think that the MSH Study was as nicely done study, and it had very defined entry criteria, and that is the information on which we are being asked to base our assessment. For that reason, I think one would make a strong argument that one would attempt to use the same criteria for approval.

One of the reasons I asked the question about how these three crises were defined was to get at this issue,

and it is I think fairly clear to me that it was something of a physician's discretion as to what constituted a crisis.

I think most of the patients treated in this trial were cared for by individuals who do have above average knowledge about this disease, and very likely were selective in their patients.

I think if this restriction were made, if that is the right word, indication, there will still be wiggle room in there, but I think that that, in my view, is what we should do is we should stick to that.

I don't like the idea of doing the subset analysis that the FDA did for the very reason that Dr. Swain brought up. We don't know what the compliance data say regarding that, and I think that any subset analysis in that regard is questionable.

DR. DUTCHER: Dr. Krook.

DR. KROOK: Of the three choices, and I have changed my mind as I have read this I think three or four times, I think (a) is the choice. I think trying to ask somebody to define three crises or six crises, I think as clinicians we can probably talk to our patients and we can make things a crisis real quick, and if I would talk to the people who have sickle cell crises, I suspect that they would say, hey, I am having a fair number of moderate ones.

Now, as Dave says, it was much more rigorously defined here, but I would prefer not to put a number on here. I think that is just asking for problems.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I think functionally, there is going to be no difference in how the drug is used, whether we vote to have the indication read (a) or (b).

DR. DUTCHER: Dr. Lessin.

DR. LESSIN: I think even though numbers are hard to determine, moderate to severe is a rather vague terminology, and what is moderate to one person is mild to someone else, and severe to someone else.

I think some sort of way of quantitating this has to be addressed as an important guideline to practicing physicians, many of whom will be primary care physicians, not hematologists.

In addition, I think put into this package -- and I don't know if we can change the question or add caveats -- but it is very clear that a patient who does not agree or cannot have access to regular hematologic monitoring for toxicity should not go on this drug. In addition, to avoid forcing doctors into using a dose which may be too high or too low, the issue of alternate dose forms of the drug somehow has to be put into this equation also.

DR. KROOK: I agree with you, Larry, and I guess I am going to add to what you are going to say, is that the people who are in this room, I don't think there is any problem using this drug. I agree it does have its problems and I don't know how it can be written a little bit different to say that that discussion that we all like to say occurs between a health care provider and a consumer -- as we now say in Minnesota, I am now a provider and we have consumers, we are into that -- goes on, the risk-benefit ratio, and I don't know how you put that in here.

I think that is much more important than the number of crises is that that discussion occurs, and it is the usual issue of how is informed consent in a written document, it is easy, but in a discussion between two people, I mean I can see here is a drug, please try it, out the door. There are problems with it, and somehow that should be written into however this is written into the final whatever in the PDR.

DR. DAVID JOHNSON: Is it possible to meld (a) and (d) into a single statement, that basically says this, that patient should have moderate to severe recurrent painful crises, generally recognized as at least three episodes in the preceding 12 months or something to that effect? That would solve that issue.

DR. DUTCHER: Dr. DeLap.

DR. DeLAP: I think we put a few alternatives down here because we were struggling with exactly what the wording would be for some of the exact reasons that you have been going over, so I think if there is some consensus wording that you can come up with, that represents the best that we can do here, then, we appreciate that.

DR. DAVID JOHNSON: Or maybe instead of generally recognized, "as defined in the MSH as three" or something to that effect.

DR. LESSIN: You could even use the time indicator, as well, lasting more than some period of time. I think four hours was utilized in the study, and that is really what we have to base the recommendation upon.

I think somehow also Dr. Charache's slide that says, "no blood, no pills" has to be in there, because I am quite worried about that.

DR. MARGOLIN: I think maybe the use of the word "chemotherapy" or the strong emphasis on the fact that this is chemotherapy might help the docs and the patients understand although it could have the opposite effect of scaring the patients away, but most doctors understand that chemotherapy implies myelosuppression and that that is usually the thing that needs to be watched the most closely.

DR. DUTCHER: Any comments from the consumer representatives and patient advocates about how you think this drug can be warned about? Ms. Beaman.

MS. BEAMAN: I am very strongly leaning toward the first statement there, that it should be available to adult patients who are experiencing moderate to severe recurrent painful episodes, not necessarily with a time constraint there.

I would like to see maybe added to that with detailed monitoring for the same reasons that were brought up, but any time we have, that three month to six, 12 months, I think at one point it is too severe in one direction, and someone else, as they said, out the door, it is going to be if it's available, it's available. The close monitoring would probably get more attention than a time constraint.

DR. DUTCHER: Dr. Justice.

DR. JUSTICE: I think this is a situation where a patient package insert that writes in lay language what the patient has to be aware of, how important it is to get your blood counts checked, and I think there was also some suggestion of possible limitation in package size, but I am not sure.

DR. DUTCHER: I was just going to say I think what

has been done with the retinoids for the lay public, which is another drug that has potential toxicity in the same population, a younger population, that is potentially child bearing, has been very good in terms of educating the public.

Dr. Temple.

DR. TEMPLE: One of the problems with patient package inserts is that they get discarded and people don't use them. A potential remedy used -- I can't tell you all the times it has been used -- but it was certainly used for halcyon -- was to urge unit of use packaging.

In this case, the unit might be the time period. That is a little tricky because the dose is different, so it is hard to say what the unit of use is, but in any event, have unit of use packaging which includes the material on the package.

There is a cost to doing that, of course, and companies may object, but unit of use packaging is standard throughout Europe, for example. Everything is done in unit of use packaging, so it can't be that much more.

DR. DUTCHER: I don't know if any of you have seen the packages for the cis-retinoic acid that is used for dermatology, but they actually have a cross over pregnancy on each of the pill bubbles.

I guess we should vote on the (a), (b), or (c) or the revised. I actually personally like Dr. Johnson's suggestion that not should it say moderate to severe, but it should define what is considered that category, such as prolonged crises, three or more during the last 12 months. It doesn't require that that be the only group that gets treated, but it would at least give an example to the reader.

Shall we vote on this revision? Let's have a couple of comments. Does anyone wish to restrict it to the 6 or more based on what we have seen?

MS. WISE: I think I would like it to be restricted to 6 or more. When you are dealing with sickle cell patients, and like drawing and everything like that, it is kind of difficult to draw sickle cell blood because of their vein and everything like that, and I would wonder how you would monitor that, if you don't limit it to a longer period of time.

DR. DUTCHER: On the other hand, it may well be that someone who is not having that many crises may decide it is worth taking the drug because they don't feel bad. This is just to say that if you had 6 or more crises in a year, that would be the indication for taking the drug versus 3 or more crises in a year, so it would be a

definition of the different kinds of patients that would need the drug.

DR. SANTANA: Can I have a comment while we decide between (a) and (b) or a marriage of those two?

DR. DUTCHER: Yes.

DR. SANTANA: You know, we really haven't heard any pediatric data, and I know there are studies that are ongoing, I am aware of those, but based on the information that we have in front of us with adults, should we remove the qualifier of adults and allow this drug also to be available for children?

DR. DUTCHER: I honestly don't think we are in a position to do that yet.

Dr. Temple.

DR. TEMPLE: A lot of drugs are not labeled with respect to adult or children unless you particularly want to make that point, and are just said for people, and then over in the pediatric section you point out that there are no data on how to use the drug in children. I mean that is another way to do it. That is not unusual for many drug classes.

DR. SANTANA: Just the qualifier adults seems somewhat restrictive in the discussion. Clearly, I am aware of the comment that you made, for many drugs there is no

pediatric indication or data to support the indication, but the safety data from adults justifies its use in children.

DR. MARGOLIN: I think considering the carcinogenicity issue was one of the biggest topics of safety that remains an unknown, I don't think we could in good conscience recommend that the safety data show adequate safety for its use in children where we are automatically looking at years and years more and developmental things that may predispose these children to cancers and other secondary malignancies.

DR. TEMPLE: So, you really want to have that limitation there. It is not just a passive thing. You really want it to say adults specifically. That is a reason for putting it in the indication.

DR. DUTCHER: How do other people feel?

DR. DAVID JOHNSON: I actually agree.

DR. KROOK: I agree.

DR. DUTCHER: All right. Question No. 4. Should the indication be restricted to adult patients with sickle cell anemia with moderate to severe recurrent painful crises with an explanation that this suggests at least 3 crises during the last 12 months?

All those who would vote in favor of that indication, please raise your hand.

[Show of hands.]

DR. DUTCHER: Eleven. It is unanimous in favor of the indication, the combination of 4(a) and (b).

The last question. Is the dosing regimen used in the MSH Study appropriate for labeling?

Who would like to tackle dosing?

DR. KROOK: I am not sure that we can. I think that if I remember what was on the slides, we had people who went down, we had people who went up per protocol, and I think what they are asking or what the gentlemen are asking there is -- I guess I am not convinced that escalating the dose, if 35 is an MTD, that that has to be. I think we are asking for more problems, so if the intent of this question is to ask for escalation, I would prefer that not be done, if that is the intent of the question is to follow the study, I would vote no on that if that is the intent of the question.

DR. DUTCHER: So, you would vote for a standard single dose?

DR. KROOK: I would vote for a standard dose. I don't have any problem choosing 15, but somehow in there, like we do in medicine a lot of times, you have to titer the dose. I think that is what you have to do.

I think you have to have a starting dose, and it

looks like what they chose, but I don't think we should ask people to go to MTDs.

DR. DUTCHER: But that is what they did sort of, they titrated it based on tolerability based on hematologic toxicity.

DR. KROOK: Based on tolerability, and I don't think that should be there.

DR. DUTCHER: Dr. Johnson.

DR. DAVID JOHNSON: To me, this is the most difficult issue because, again, one of the questions that I asked was what was used for titering, I mean what was the endpoint. I mean was it the MCV, was that an appropriate surrogate? Was it the actual white count level, and was there a correlation of any of these features with the clinical outcome in the patients?

I didn't see data that convinced me that any of those things, in fact, correlated. I think this is the more difficult issue. I agree with Jim that the starting dose seems fairly easy to me. It was picked out of a Phase II and then verified in the Phase III type trial that that was sort of a median dose that worked in patients.

But in terms of what to tell, it is easy to tell what to do when the dose is too high based on the white count going too low. You can fix that. But I don't know if

the patient's white count isn't all that low, should we necessarily push it up? I think that is the issue that I don't have an answer to, and I guess it seems to me that at this point, without further study -- and I got the impression from reading the material provided to us that additional studies were either underway or planned to assess optimal dose, that we are a bit left with what we have, which is this 15 mg/kg dose with appropriate caveats for toxicity monitoring.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I have a real concern about a labeling process that would allow titration up. We have already discussed the fact that we are not quite sure who will be supervising this treatment, and I think that when you release what is essentially a cytotoxic drug into a relatively unrestricted environment with caveats that allow a relatively creative approach to dosing without absolutely defined rules that Dr. Lessin talked about with respect to timing of blood sampling, you compound that with generalists who are moderately inexperienced in the use of these drugs for potentially a condition that may not be life-threatening, I think you have a very bad situation.

While I accept that there may be underdosing if one has a fixed prescription, and that obviously is an

important problem, that is probably going to be less dangerous than the risk of overdosing in an unqualified fashion. Given the fact that the dose response implication suggests that, implications rather than proven statements, I don't really see how we can put in a labeling indication for incremental dosage without a scientific justification and without appropriate controls.

It seems to me that if a generalist is using this agent for a patient who is getting unsatisfactory results, the logical extension of that is referral for further advice. If we put in a varied dose prescription, that is a recipe I think for disaster.

DR. MARGOLIN: I think that Dr. Raghavan is very wise, but I think also we need to make sure that we don't ask for results of a therapy to be the same as the results in the study unless we take an approach that is similar to the results in the study, and if we are too cavalier about looking at safety -- I mean we have to look at safety obviously -- but keeping the doses down, we may not see the same benefits.

The documents that we obtained before this, which were not really mentioned here, stressed the potential that the way this drug works has to do with neutrophils, as well, and the other thing is that since hopefully most of these

patients are being taken care of by hematologists, and hematologists generally know their way around blood counts, and we are stressing the importance of compliance with the regular blood counts, I don't think we want to cut corners too much on pushing the doses.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I agree with that point of view. I think the study was done in a certain way and unless you can somehow reanalyze the data from the study -- which I question whether that is really possible -- to convince yourself in some reliable way that you would have still seen the benefit had you used only either a fixed dose or just titration downward, then, by changing the dosing schedule, you run the risk of eliminating the effectiveness.

DR. DUTCHER: I happen to agree with you, as well.

Dr. Lessin.

DR. LESSIN: The area under the curve, when the pharmacokinetic study is done, it is variable, it depends heavily on renal function, which is again going to be quite variable in this population. So, predictability of response and the bioavailability of the drug at the various levels is really -- there is a complex equation that determines all of that.

I understand Dr. Krook's concern about the guy out

there in practice trying to interpret the blood counts and decide about increasing the dose, but I think some general guidelines based on the experience of the study could be given both on the protective side, you get away from excess toxicity, and on the efficacy side.

The problem we have is the one Dr. Johnson brings up, and that is, you know, what are you looking for in terms of an endpoint, and I suppose, and maybe we can take a hard look at the data and come up with this or get some advice from the investigators, and that is, if one indeed can use an MCV as a surrogate for a response. That is something that everybody has available to them, the same day or the next day, and can be used as a way of modifying dose, just as we do in treating patients with hypertension or using the A1C and treating patients with diabetes, and so on.

DR. DUTCHER: Another drug that has gone from oncology into general uses, I mean it is not cytotoxic, but it has the same effect, is interferon, in using it with hepatitis, where again there is a depression of the white count, and that is used to sort of titrate how the drug is given.

Now, if we could look at the data in a way that we could see an effect, I mean the median dose ended up being 15, so there were many above that, that, you know, we think

got some benefit from the drug.

I think we need some type of algorithm derived, I agree with you, and I think maybe MCV would certainly show you drug effect. It wouldn't necessarily correlate with benefit.

DR. DAVID JOHNSON: Well, we don't know that. I mean that is something that wasn't done in the data analysis. There was an inference in the data presented to us that suggested that there wasn't a correlation per se, but there was never a definitive study done that I heard or read that said as much.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I apologize for belaboring the point, but I think there is a certain naivety around the table, because we are trying to extrapolate from a very carefully prescribed study done in a series of centers of excellence, with a very defined population of clinicians.

We are now ignoring that as a variable in our assessment of outcome. On the one hand, we say we need to have flexible dosing, so we can be like the study, but then at the same time, we are just letting who has prescribing rights use the agent.

I think that I would reiterate that we are talking about a disease that certainly affects to some extent a

population of patients who have less good access to health care, who in some cases are less informed about the risks of health care, who will have fiscal constraints that will prevent them getting access to health care in some cases.

This is kind of a different situation from the way the study was run, and while I understand completely the fact that we want to duplicate what happened in the study, I am not really certain that we can do it by saying yes, let's have flexible and incremental dosing, but then not have all the other constraints built in.

I think you only need to lose two or three patients from hypoplastic crises or to start to see the evolution of leukemias if they occur and if they are dose related to discover that you may have a problem.

It seems to me that having a prescribing pattern that allows the most people the maximum safety and then puts in a caveat that says if this isn't working, referral for dosing implementation or something like that is the safer way to go for when it is out there not under direct supervision.

I think those of us around the table see this, who see novel cytotoxics being prescribed, get very uneasy about some quarters where there is a relatively laissez-faire approach to prescribing without data to back it up.

DR. DUTCHER: Do you get the sense?

[Laughter.]

DR. DUTCHER: I would say we have got securists and the realists, or the realists and the realists.

DR. DeLAP: I guess my only thought would be that that there was a cap, of course, in this study, at the 35 level. Perhaps people are uncomfortable that that cap is too high. Is that partly what I am hearing?

DR. KROOK: No, I don't think we know, Bob. I don't think we know what the cap is. I don't think the sponsor pushed it, I don't think they tried to.

DR. DeLAP: But I mean for prescribing information.

DR. DUTCHER: I personally think that if you give any dose of hydrea, you can make somebody neutropenic, and the real issue is getting the blood tests every two weeks and stopping, and you can see that happen at 15 or you can see it happen at 30, so I mean I think that maybe we are over-concerned about somebody moving the dose around. I mean if they have got the blood counts, they ought to be able to see where they are going, and in two weeks' time you will see that.

I think the real concern is if somebody is just given, you know, three months' worth of pills and never gets

a blood test. That is the less experienced physician approach that I personally think would be more dangerous.

DR. KROOK: My other concern, it depends on how the labeling is written -- I actually have two now -- is that we have some way of escalating the dose for a better effect, and I don't think the sponsor showed that -- I mean that the sponsor showed that even some people could take less and have the response, and my second comment is in the labeling, that somehow if there is not a clinical response, and you have to decide what that is, you may do it laboratory-wise, then, the drug should be stopped.

I mean I think we are saying that with the first question also, and however the labeling is written, I mean sometimes out in the community, these prescriptions go on forever and ever. That is a problem.

So, if you don't perceive as the physician a clinical response, the drug should be stopped, and perhaps prescriptions for 100 tablets should not necessarily be written or a large quantity. Again, that gets into packaging and labeling.

DR. DeLAP: I am not sure that we need an exact prescription from you all as to how this should be worded, but the general sense that I get from the discussion is that there is a lot of concern about how this drug will actually

be used in the community and particularly as it is used by people who are not experienced in using these kinds of drugs.

Certainly we have a lot of traditional cancer drugs out there that say things in labeling, like this drug is only to be used by practitioners who are experienced in using these kinds of drugs, some kind of threatening language like that, you can do that sort of thing, but that only really has meaning if that is really the person that is going to be using it, and I think the concern here is that the person who is prescribing this drug is many times likely not to be someone who has got a lot of experience in prescribing these kinds of drugs.

So, how do we build in the safety and yet ensure that we are still going to be using the drug in an effective fashion?

DR. DUTCHER: The safety issues are really related to the blood counts, so I think you have to put in guidelines for levels of white count and platelet count that say stop the drug, I mean there are just going to have to be some stop rules regardless of efficacy, and then recheck blood count.

I mean it would almost be an algorithm like the page in the protocol where it said stop here, this is toxic,

this isn't, and that should probably be in the patient insert, too.

DR. DeLAP: I think the best we can do without -- I can't be too specific here -- but I think we could go back and look and see what actually drove the dose adjustments. It probably is primarily the blood counts.

Albert, perhaps you have some other thoughts on that, exactly what usually, most often drove the dose adjustments in the patients? We can go back and look at that again and see if we can come up with some kind of relatively simple algorithm.

Would it be desirable to have some kind of a cap on top, as well, that was more conservative than the 35, do you think?

DR. DAVID JOHNSON: I would personally advocate for a cap. Again, I would, at a minimum, do what the MSH Study did, and it seems to me that the one option here would be to have all the caveats that were placed within the MSH Study with regard to dosing, maximum, et cetera, and I would also be interested, because in reviewing the material, it is never really terribly clear to me what drove the decision to change the dosing.

I think in most cases, it was white count, but I don't that for a fact.

DR. LIN: I believe that Dr. Charache's presentation, it also mentioned that the cell counts determined the adjustment for the dosage.

DR. DAVID JOHNSON: Right. So there was a feeling that -- I mean as long as you were at a safe level, you could just keep pushing the dose up to an arbitrary max of 35/kg, and that to me seems like, if that somehow could be incorporated into the guidelines, that would be a reasonable thing to include within the package insert.

DR. DUTCHER: Dr. Johnson.

DR. JOHN JOHNSON: I am puzzled about the question as what drove the changing of the dose, because this was a very well run study, the investigator had not option to change the dose. The only people who could change the dose were the people in the central lab, and they had only the criteria in the protocol. So, there is no question about what changed the dose.

DR. DAVID JOHNSON: That wasn't made clear until this presentation actually. That is not made clear in the paper that that is who made the decision to change.

DR. JOHN JOHNSON: I wouldn't argue with that.

DR. DAVID JOHNSON: I think, you know, you are going to now suggest that someone call centrally to change this -- because I am not waiting by the phone, I can tell

you that.

DR. JOHN JOHNSON: I would like to have the recommendations of the investigators on this issue. We haven't heard what their recommendations are.

DR. DUTCHER: That is true.

Dr. Lessin.

DR. LESSIN: Just an observation. From the data, if you look at slide C24 on the handout, only 10 percent or so of the patients, it is actually about 8 percent of the patients ended up with a dose of 15 mg/kg, 30 percent were less. Thirty percent were in the greater than 15 to 30 range, and then 20 percent were at 35.

So, if you stuck to a 15 dose, you would be overdosing 30 percent, you would be underdosing 40-plus percent. So, somehow dose adjustment needs to be built into this recommendation as a guideline.

DR. DUTCHER: Is there a recommended dose from the investigators of the MSH Study? From the sponsor?

DR. CHARACHE: There is no specific dose that we can recommend. It is just what you all have been saying. I agree that if you stuck with 15 mg/kg per day, some patients will get too much, and some won't get enough, but we can't say that there is some particular way of doing it other than what we did.

DR. SMYTH: I actually have a copy of the proposed labeling if you want specific wording on what the current version of our proposal is.

DR. DUTCHER: Do you want to hear that, Dr. Johnson?

DR. JOHN JOHNSON: I don't care.

DR. SMYTH: It essentially mimics the study, but I mean I can read it and just tell you what it says. Do you want me to do it very quickly?

It says, "The initial dose of Droxia is 15 mg/kg/day as a single dose. The patient's blood count is then monitored every two weeks. If the blood counts are in an acceptable range" -- which is defined -- "the dose may be increased by 5 mg/kg/day every 12 weeks until a maximum tolerated dose" -- which is defined -- "or 35 mg/kg/day is reached. If the blood count is between the acceptable range and the toxic range, the dose is not increased. If the blood counts are considered toxic" -- which is defined -- "Droxia should be discontinued until recovery. Treatment may then be resumed after reducing the dose by 2.5 mg/kg/day from the dose associated with hematologic toxicity. Droxia may then be titrated up or down every 12 weeks in 2.5 mg/kg/day increments until the patient is at a stable dose for 24 weeks that does not result in hematologic toxicity.

Any dosage on which a patient develops hematologic toxicity twice should not be tried again."

That is version 2.7 or whatever.

DR. DeLAP: I think the other factor here, though, that is of some concern, at least to me, is that the definition of the myelotoxicity includes neutrophils, reticulocytes, platelets, hemoglobin, and, you know, then there is a pre-toxic level and there is toxic level, so it is a little bit complicated to do this.

What I was alluding to before is if we could figure out that most of the time what ended up dictating the dose was neutrophils, then perhaps this could be simplified a little bit, but that would require some further exploration of the data.

DR. DUTCHER: I think you will have to look at the data and see if it is that clear. It may not be.

DR. DeLAP: The default position is always to fall back on what was actually done in the study and say that only certain people have any business prescribing the drug.

DR. DUTCHER: I think if the dosing turns out that you can't pick the cell line as your endpoint, you are going to have to say that, that it should really be given by people experienced with the use of these kinds of drugs.

Dr. Krook.

DR. KROOK: Jan, a couple small points since we have got Bob over there. One is neutrophils, can it be white count rather than neutrophils? I mean hematologists and oncologists are used to absolute neutrophils, but I mean you have got to do a little bit of calculating to get neutrophils, and when I talk about neutrophil count, a lot of people don't know what I am talking about. I am just saying I realize that, but there is a difference.

Secondly, to the sponsor, at least I have seen what the size of a hydrea capsule looks like and, at least in my practice, the size of the capsule, I don't know what it is going to be or what you are going to put it in, is a deterrent to people taking this long term by itself anyway, it is a huge capsule, if I am right. I am just saying that to the sponsor as they reproduce this in different doses. I would rather make it smaller.

DR. DeLAP: Well, I don't think we really need a vote on this unless there is something that you wish to vote on. I appreciate the discussion.

DR. DUTCHER: Any other comments?

All right. Thank you very much.

We are going to take a lunch break. We don't have to vote on that either. We will be back at 1:15.

[Whereupon, at 12:20 p.m., the proceedings were

recessed, to be resumed at 1:15 p.m.]

AFTERNOON SESSION

[1:35 p.m.]

DR. DUTCHER: Good afternoon. This is the Oncologic Drugs Advisory Committee.

We are here to discuss DepoCyt. First of all, I would like to go around the table and ask -- we have some new people here this afternoon -- to introduce themselves.

DR. WILLIAMS: Grant Williams. I am medical team leader.

MR. GIDDES: Ken Giddes, Patient Representative.

MS. BEAMAN: Carolyn Beaman, Consumer Representative.

DR. RAGHAVAN: Derek Raghavan, Medical Oncologist, USC.

DR. OZOLS: Bob Ozols, Medical Oncologist, Fox Chase.

DR. DAVID JOHNSON: I am David Johnson, Medical Oncologist at Vanderbilt.

DR. KROOK: Jim Krook. I am a Medical Oncologist, in Duluth, Minnesota.

LT O'NEILL-GONZALEZ: Jannette Gonzalez, Executive Secretary.

DR. DUTCHER: Janice Dutcher, Medical Oncology, Albert Einstein, New York.

DR. MARGOLIN: Kim Margolin, Medical Oncology, City of Hope, Duarte, California.

DR. SANTANA: Victor Santana, Pediatric Hematologist/Oncology, St. Jude's Children Research Hospital, Memphis, Tennessee.

DR. SIMON: Richard Simon, Biometrics, National Cancer Institute.

DR. DeLAP: Bob DeLap, Oncology Drug Division Director, FDA.

DR. JUSTICE: Bob Justice, Deputy Director.

DR. DUTCHER: We will begin with the applicant's presentation on DepoCyt. Thank you.

NDA 20-798 DepoCyt

(cytarabine lipid-particle injection)

DepoTech Corporation

Applicant's Presentation

Introduction

MR. THOMAS: Good afternoon, members of the Oncology Drugs Advisory Committee, representatives of the U.S. Food and Drug Administration, and guests.

[Slide.]

I am David Thomas, Senior Vice President, Quality Assurance and Regulatory Affairs at DepoTech Corporation.

My purpose is to introduce the presentation of safety and efficacy data supporting the New Drug Application for DepoCyt. DepoCyt, also known as DTC101 or lipo-C during its development, is a sustained release formulation of cytarabine.

[Slide.]

The NDA under consideration is for the treatment of patients with neoplastic meningitis arising from solid tumors.

[Slide.]

In the product, cytarabine in saline suspension is encapsulated in microscopic, multivesicular spherical lipid particles. The freeze fracture photomicrograph on this slide shows a particle displaying the structure of the individual chambers.

The drug is released from these particles by erosion or reorganization of the chamber walls. The particles are formed from phospholipids negotiated cholesterol and are cleared by the normal lipid metabolic pathway.

The direct formulation is preservative-free and has been optimized for intrathecal administration.

[Slide.]

The development work for DepoCyt was carried out

as a joint program between DepoTech Corporation and Chiron Corporation.

[Slide.]

In developing this formulation, intrathecal studies in rodent and non-human primate models were undertaken. Following this, a Phase I clinical trial of intrathecal drug administration in patients with neoplastic meningitis was carried out at the University of California, San Diego. Dr. Senil Kim and Marc Chamberlain were investigators.

After reviewing the results of this trial, especially the pharmacokinetic and response rates, a representative of the FDA, ODAC, and the sponsor agreed upon a Phase III trial design taking into account the following considerations:

One, due to the limited availability of appropriate patients, each arm of the trial was limited to a minimum of 40 patients. It was understood the differences between treatments were unlikely to achieve statistical significance. Therefore, it was agreed that comparisons between treatments would be based on examination of trends and patterns of convergence of evidence.

Secondly, considering the limitations of current therapy for neoplastic meningitis, each arm of the study,

leukemia, lymphoma, and solid tumor, would be submitted for marketing approval as it was completed.

The Phase III multicenter controlled trial comparing DepoCyt to available treatments was started in March 1994. The solid tumor arm of this trial is now completed, and the available data are provided in the NDA under consideration. The lymphoma and leukemia arms of the trials are still open, although interim analyses of these arms are provided in the NDA as supporting data.

A multicenter Phase IV trial of DepoCyt in solid tumor patients was started in June 1996 and continues.

[Slide.]

The next speaker will be Dr. Marc Chamberlain, an investigator in the Phase I and III trials, who will review the natural history and treatment of neoplastic meningitis and Phase I results.

Following this, Dr. Wayne Cowens will review the efficacy data supporting the DepoCyt NDA.

After Dr. Cowens, Dr. Michael Glantz, a Phase III investigator, will present the safety data from the Phase III trial.

In conclusion, Dr. Kurt Jaeckle, an investigator in the Phase III and IV trials, will provide a physician's assessment of DepoCyt.

Following these presentations, I will direct your questions to an appropriate person to answer.

Dr. Chamberlain.

Disease Overview and Phase I DepoCyt Trial

DR. CHAMBERLAIN: Good afternoon.

[Slide.]

I would like to address in my talk three aspects. First, I am going to talk about an overview of neoplastic meningitis and why it is a complicated disease to treat.

Secondly, I am going to review the two prior randomized Phase III trials.

Lastly, I am going to talk about the DepoCyt Phase I study performed at the University of California.

[Slide.]

This is a disease that occurs in 7- to 9,000 patients in the United States each year. In an autopsy series of patients with cancer, 5 percent of patients overall have neoplastic meningitis. This is higher in patients with hematologic cancers, particularly in AIDS-related lymphomatous cases.

Overall, patients with solid cancers have a 1 to 5 percent incidence of neoplastic meningitis.

[Slide.]

This is a complicated disease to treat for a

number of reasons. Firstly, approximately three-quarters of patients have progressive systemic cancer.

Secondly, approximately one-quarter of patients, who have neoplastic meningitis, have concurrent metastasis to the central nervous system, either parenchymal brain metastasis or epidural spinal cord depression.

[Slide.]

Secondly, this disease is complicated because of its presentation. It affects all aspects of the nervous system. It affects the entire neural axis, in fact, three domains are affected primarily by this disease: the cerebral hemispheres, spinal cord, and cranial nerves. Essentially, all patients have signs and symptoms compatible with disease involvement, and in addition, patients with progression develop increasing signs and symptoms related to this disease.

Finally, this is the way that these patients are followed and managed clinically, and that disease progression is assessed by clinical assessment.

[Slide.]

Now, it is a different metastatic disease in terms of its evaluation, which makes it complicated. These patients frequently undergo CSF analysis vis-a-vis cytopathology in an attempt to document neoplastic cells

circulating in CSF, however, 40 to 50 percent of patients have negative cytology.

Secondly, all patients need to undergo cranial imaging studies. The reason for this compartmentalization vis-a-vis hydrocephalus or evidence of parenchymal or subarachnoid bulky disease.

Thirdly, patients often need to undergo spine imaging studies in that these patients very frequently have spinal cord dysfunction, and again this addresses bulky disease.

Finally, many institutions utilize radioisotope CSF flow studies to evaluate compartmentalization, an important feature in the treatment of this disease by regional chemotherapy.

[Slide.]

Although this side is entitled "Standard Therapy," I don't mean to imply that there is a standard therapy for this disease. That is in evolution. But there are three primary modalities that are utilized.

Radiotherapy is used to treat bulky disease and symptomatic sites of disease, and in addition, it is used to treat sites of CSF flow obstruction.

Intra-CSF chemotherapy is utilized primarily to treat small-volume disease that is both in aqueous phase and

in the leptomeninges. There are some problems, though, with intra-CSF chemotherapy. We only have three agents: methotrexate, cytarabine, and thiotepa, all of which have short half-lives. Now, this is problem in that tumor cells frequently have very slow cell kinetics and, as a consequence, exposure is a major issue with these agents.

Finally, penetration of these drugs into tumor nodules, which is very common in patients with leptomeningeal cancer, is problematic. Glassberg has shown that penetration is limited to 3 to 4 millimeters.

Lastly, concurrent systemic chemotherapy is utilized both because patients have progressive systemic cancer, up to three-quarters, and in addition, there is breakdown in blood-brain barrier and blood-spine barrier which permits elevated CSF-to-plasma ratios.

[Slide.]

Now, there are two primary large studies that have addressed neoplastic meningitis in prospective randomized Phase III manner.

The first is Hitchens. This is a study that compares methotrexate to dual-agent methotrexate plus cytarabine. Forty-four patients were enrolled and the study was conducted in the mid-eighties.

What has been a problem in the literature is how

to define response. Their definition of response, which was defined at four weeks, was that patients had to have negative CSF cytology at one site, either ventricular or lumbar. The patients had to have normalization of CSF biochemistry. Lastly, the patients had to have an improved clinical exam.

[Slide.]

If we look at response data, 17 percent of patients had a complete response, and if we look at cytologic response, 50 percent of patients had response. This is irrespective or dissociated from clinical response.

Median survival did not differ significantly between the two treatment arms, methotrexate slightly favoring dual chemotherapy. But perhaps most importantly is that this was the first study to show that there is a benefit to treatment in this disease and that patients who respond -- which admittedly are difficult to define -- have approximately a threefold increase in survival as compared on non-responders.

[Slide.]

The second large study is that of Grossman. This was a study that was conducted in the late eighties, 59 patients were enrolled, and this was comparing methotrexate to thiotepa, so single-agent therapy.

Their definition of response was defined at eight weeks following study entry, and was far more restrictive and difficult, and it was defined as follows: complete response required clearing of CSF cytology at two locations, both lumbar and ventricular.

Patients had to have normalization of CSF biochemistry. Patients required a normal neurologic exam, which was particularly problematic in that up to three-quarters of their patients at study entry were not ambulatory.

Lastly, patients at entry underwent both brain and spine imaging and at eight weeks were reevaluated and had to have normalization of neural anatomic imaging studies.

[Slide.]

Not surprisingly, their complete response data was rather meager, at 0 percent. The cytologic response was slightly less, but comparable to that seen in the Hitchens study, 31 percent overall, and 21 percent in the subgroup of patients with solid tumors.

They for the first time introduced the concept of time to progression, basically looking at time to clinical progression based on neurologic disease progress, however, at eight weeks, when they evaluated patients, 75 percent of the patients had progressed clinically.

The median survival was not different in comparing the two arms, showing that methotrexate and thiotepa were equally efficacious in this regard, at approximately 100 days for median survival.

[Slide.]

What can we conclude from these two large randomized Phase III trials? First, that treatment is palliative and treatment intent is to stabilize neurologic function, thereby improving quality of life in patients who have terminal cancer.

Secondly, that neurologic deficits rarely, if ever, improve, so that can't be a basis of treatment.

Thirdly, that the results of treatment, regardless of the agent used, are comparable, and lastly, that chemical meningitis, which was not studied prospectively in either of these studies, was shown to be the primary toxicity seen with regional chemotherapy.

[Slide.]

Next, and finally, I would like to speak to the Phase I trial conducted at the University of California, San Diego. This was a study that enrolled 19 patients with a median age of 41 years. All had high performance status, and all patients, unlike the prior studies, had been heavily pretreated with intra-CSF chemotherapy, 16 of 19 patients

were evaluable for cytologic response in the study.

[Slide.]

It was a dose escalation study and as can be seen in this cartoon, looking at free Ara-C concentration levels in _g/mL as a function of time with dose escalation from 12.5 to 125 mg. Excluding the 12.5 mg dose, it is clear that prolonged concentrations of cytarabine were obtainable following intraventricular injection of drug.

I will point out that minimum cytotoxic concentration level, which is perhaps somewhat new to many of the panel members, was defined based on NCI in vitro studies suggesting prolonged exposure to Ara-C lowers the minimum cytotoxic concentration approximately 10-fold.

[Slide.]

One of the questions that we asked as part of this study, if patients received drug intraventricular, could we achieve cytotoxic concentrations in the lumbar space. As we can be seen again on this slide, plotting free concentration of Ara-C versus time, following intraventricular injection, that there is equilibration between both lumbar and ventricular compartments, suggesting this was, in fact, achievable with intraventricular injection of DepoCyt.

[Slide.]

Next, we asked if this is achievable following

intraventricular injection, could we do the same vis-a-vis intralumbar. In a seminal paper by Dr. Shapiro some years ago, in The New England Journal of Medicine, this was a major issue in dealing with methotrexate. It was shown that following intralumbar injections with methotrexate, quite inconsistent levels were achievable in the ventricular compartment.

Following injection, however, with DepoCyt into an intralumbar space, we can see on the cartoon on the left that free Ara-C concentrations equilibrate with ventricular at approximately four hours.

When we extend this time curve out, it is clear that we can maintain cytotoxic concentrations following intralumbar administration in both compartments, both lumbar and ventricular, for long periods of time, similar to what was demonstrated following intraventricular injection, although the total achievable doses were approximately 10-fold less.

[Slide.]

The last aspect discussed in the Phase I trial was that of toxicity. If I can draw your attention to the 125 mg dose, which was the highest dose level achieved, four patients were treated with four cycles, and we had a 25 percent incidence of this constellation of symptoms, which

henceforth will be referred to as chemical meningitis. This was one of the first studies to attempt to identify and lay out criteria for chemical meningitis, and it was chemical meningitis that limited the dose of DepoCyt in looking at Grade 3 and 4 toxicities only.

[Slide.]

Another aspect as part of the Phase I study was the literature has indicated that the use of concomitant steroids may mitigate chemical arachnoiditis, but this had never been formally addressed.

In this study, patients treated without dexamethasone had a 60 percent incidence of chemical arachnoiditis of all grade. With dexamethasone, this could be reduced 4-fold to approximately 16 percent, and the chemical arachnoiditis is a syndrome that occurs over five days evolves, and clearly with dexamethasone was manageable.

[Slide.]

So we can conclude from the Phase I trial the following. Firstly, that we increase the effective half-life of Ara-C from 3.4 hours to 141 hours. That is a 42-fold increase in the effective half-life of cytarabine.

Secondly, that we can maintain cytotoxic concentrations for 14 days, and thirdly, this led to the rationale for a Phase III trial of using 50 mg as our dose

as a schedule of every 14 days.

Fourthly, that irrespective of the site of administration, whether the drug was given intraventricular or intralumbar, that we could maintain cytotoxic concentrations.

Lastly, although chemical meningitis is the limiting toxicity seen with regional chemotherapy, not unique to DepoCyt by any means, is manageable with the use of concurrent oral dexamethasone at a dose of 4 mg twice per day for five days.

Thank you.

I would next like to introduce Dr. Wayne Cowens.

Efficacy of DepoCyt

DR. COWENS: Good morning.

[Slide.]

I am going to focus my talk on three themes that run throughout the efficacy data in the NDA.

The first theme is that treatment with DepoCyt is more convenient than methotrexate. The second theme is that trends in all measures of efficacy favor DepoCyt.

The third is that the effect of DepoCyt is consistent across all the studies in the NDA.

[Slide.]

There are four studies in the NDA. The basis of

the NDA is the solid tumor arm of the Phase III study in which 61 patients were enrolled, and those patients are the ones that I will focus on.

There are three supporting studies: the PK study, the leukemia and lymphoma arms of the Phase III study, and the Phase I study.

[Slide.]

The Phase III study was an open-label, randomized, trial that was stratified into three arms by tissue type: solid tumor, lymphoma, and leukemia, because these tissue types have different treatments and different natural histories.

The control treatment for the solid tumor arm was methotrexate, and the control treatment for the leukemia and lymphoma arms are Ara-C.

It was required that all the patients have a positive CSF cytology at entry, either from the lumbar or the intraventricular site or both, and all CSF cytologies were reviewed by an independent cytopathologist who was blinded both to study treatment and to the timing of the samples.

[Slide.]

There were three phases to the study: induction, consolidation, and follow-up.

The induction phase consisted of 2 doses of DepoCyt or 8 doses of methotrexate. Both treatment groups received concurrent dexamethasone to suppress the symptoms that Dr. Chamberlain has just described.

If the patient was in complete remission after the end of induction, they went on to consolidation, which consisted of 4 doses of DepoCyt or 8 doses of methotrexate, again with concurrent steroids.

It is important to note that a complete course of DepoCyt is 6 intrathecal doses, which is less than half the number of doses for a course of methotrexate.

If the patient was in complete response after the end of consolidation, they went on to follow-up for three months for adverse events, and then on to long-term follow-up for time to clinical progression and survival.

[Slide.]

Now, the randomization was successful in that the treatment groups were balanced for prognostic characteristics including age, the Karnofsky Performance Score, tumor histology, and neurologic deficits.

[Slide.]

The primary measure of efficacy for this study was the attainment of a complete response. The secondary measures were clinical progression, survival, and quality of

life.

[Slide.]

I will discuss the complete response data first.

The definition of complete response was the same in the Phase III and the Phase I study. At anytime following induction, the patient had to have a negative CSF cytology from all sites positive at baseline, and no evidence of clinical disease progression.

This definition builds on the data that Dr. Chamberlain just showed you from the Hitchens and the Grossman studies, and includes both cytologic and clinical observations in its execution.

[Slide.]

In the analysis of response, there were two populations analyzed. One was all patients randomized or the intent to treat, and the other was an evaluable population, the patients that had all the clinical characteristics required to observe a response.

To be evaluable, you had to have received study drug and have adequate baseline and follow-up studies to determine a complete response.

[Slide.]

In the methotrexate group, there were 30 patients in the intent-to-treat population and 29 patients in the

evaluable population.

In the DepoCyt group, there were 31 patients in the intent-to-treat population, however, 2 patients did not receive study drug, and 7 patients did not get follow-up, so there are 31 patients in the intent-to-treat population for DepoCyt and 22 patients in the evaluable population.

I will discuss the intent-to-treat population first.

[Slide.]

In the protocol-specified primary analysis, we should require two consecutive negative cytologies from all sites positive at baseline. There was a 10 percent complete response rate in the DepoCyt group, and a 3 percent complete reponse rate in the methotrexate group.

[Slide.]

Now, from the data that Dr. Chamberlain just showed you, the response rate in the methotrexate group is unexpectedly low, however, if you expand the definition of complete response to include patients who had a single negative cytology from all sites positive at baseline, there is a 26 percent response rate in the intent-to-treat population in DepoCyt and a 20 percent response rate in the methotrexate group.

[Slide.]

If you focus now on the evaluable population, there is a 36 percent response rate in the DepoCyt group and a 21 percent response rate in the methotrexate group.

It is important to note that whatever population you use or whatever definition of complete response you use, DepoCyt treatment leads to a greater proportion of complete responders than methotrexate although the differences are not statistically significant.

[Slide.]

I will now go on to a discussion of the secondary measures of efficacy, which are clinical progression, survival, and quality of life.

Now, clinical progression is assessed by the investigator by the appearance of new neurologic findings or the worsening of existing findings that are attributable to neoplastic meningitis, or is determined by other events, such as death.

This measure of efficacy is an attempt to capture the focus of treatment for this disease, which is palliation and the maintenance of the patient's function.

[Slide.]

This is a Kaplan-Meier plot of the time to clinical progression. On the y axis, there is fraction clinically stable, and on the x axis is time in days.

[Slide.]

If you draw a life at the 50th percentile, you can see that the median for the two treatment groups is similar, which is what you would actually expect with a small proportion of complete responders in each treatment group.

However, if you allow time to elapse, you notice that the curves continue to separate and by 100 days, almost all of the methotrexate patients have progressed clinically, whereas, 25 percent of the DepoCyt patients are still stable clinically.

[Slide.]

This tail on the DepoCyt curve suggests a trend to delayed onset of clinical progression, which in this case is statistically significant, and at the 75th percentile, the time to clinical progression for the DepoCyt-treated patients is three times that of the methotrexate-treated patients.

[Slide.]

The 75th percentile for the methotrexate group occurs at 47 days, which is consistent with that reported by Grossman in the study Dr. Chamberlain just described to you.

[Slide.]

Now, this is a Kaplan-Meier plot of survival. On the y axis is fraction surviving, and on the x axis is time

in days.

[Slide.]

Again, the medians for the two treatment groups are similar, however, there is a tail on the DepoCyt curve, which suggests a trend toward prolonged survival in these patients although this is not statistically significant.

[Slide.]

At the 75th percentile, the survival of the DepoCyt patients is approximately 2 1/2 times that of the methotrexate patients. It is possible that this trend in survival can be explained by the fact that 46 percent of the patients in the DepoCyt group died from the progression to neoplastic meningitis in comparison with 62 percent of patients in the methotrexate group.

[Slide.]

The median survival for the methotrexate group is 78 days, which is similar to that reported by Hitchens.

[Slide.]

The FACT-CNS is a quality of life instrument that has two components. The first component is general quality of life questionnaire that is tailored for cancer patients, and then there is a module that is specific for neoplastic meningitis.

As you can see, there is no difference in change

from baseline for the two treatment groups, again not an unexpected finding given the small proportion of complete responders in these treatment groups. However, complete response is associated with stability in this quality of life measure.

[Slide.]

Now, a very important clinical question is does complete response predict for good outcome for the patient. The usual techniques used to make this kind of a comparison are biased since complete response or response is a time-dependent covariate.

However, by using the landmark technique with a landmark set at 28 days, we analyzed this data and removed the bias, and you can see that complete response is associated with delayed time to clinical progression and prolonged survival.

[Slide.]

So far I have been discussing only the randomized patients in the solid tumor arm of the Phase III study. Now I am briefly going to discuss supporting data from two other groups of patients, one, the solid tumor patients that were entered into the Phase I or the PK study, and the second was the lymphoma patients.

[Slide.]

Now, this is a tabulation of complete response across all the solid tumor patients in the NDA. Note that in the Phase I study, there was a 36 percent complete responder rate, and remember these patients all had failed previous intrathecal chemotherapy.

If you look across all the studies, the complete response rates are remarkably similar and all of them exceed that of methotrexate.

If you look at patients with durable complete remissions, that is, complete responders that last greater than 60 days, you see the same pattern. The data is consistent across the studies, and this measure favors DepoCyt also.

[Slide.]

Another group of supporting data comes from the lymphoma patients. Here again you see a slide with the complete responders for all the patient in the NDA shown. The pattern is the same that you saw for the solid tumor patients. The complete responses are all consistent across the studies and the percentage of complete responders with durable remissions is consistent across the studies, and both measures for the DepoCyt group exceed that of methotrexate -- excuse me -- the control group is Ara-C for this treatment arm.

[Slide.]

I think that with the data I have shown you we can draw several conclusions.

The first is that DepoCyt is much more convenient to the patient and the physician to administer than is methotrexate.

Secondly, with this convenient dosing schedule, trends in all efficacy measures favor DepoCyt over methotrexate, and, in fact, for time to clinical progression, this difference is statistically significant, and the efficacy results are consistent across all the DepoCyt studies.

The final conclusion is that the body of evidence, taken as a whole, suggests that DepoCyt treatment confers clinical benefit on patients with neoplastic meningitis from solid tumors.

Dr. Michael Glantz will now discuss the safety.

Safety of DepoCyt

DR. GLANTZ: Thank you all very much for letting me come speak to you.

[Slide.]

I would like to present some data regarding the safety of DepoCyt in the treatment of patients with solid tumor, neoplastic meningitis. It has been derived almost

entirely from the Phase III randomized study that Dr. Cowens has talked about.

[Slide.]

As a preview, I am going to discuss the toxicity, the adverse events in the DepoCyt-treated patients, and then I am going to put them in the context of the side effects that methotrexate-treated patients received, the same or a comparable group of patients treated on the same study protocol, and primarily we will see that the side effects were all ones that involved the central nervous system.

In both groups, the primary toxicity was this chemical meningitis or what the briefing book describes as chemical arachnoiditis. I won't spend a lot of time on that.

Then, we will also talk about how, in both groups again, concurrent use of oral dexamethasone could either prevent or ameliorate this particular side effect.

[Slide.]

First, though, in order to make sense of the numbers, I would like to just briefly talk about two definitions. Not surprisingly, in a disease where drug-related side effects and disease-related symptoms are both predominantly neurologic, it is sometimes real hard to tease the two apart.

In this study, we used the four categories of drug relatedness ranging from definite to we couldn't tell, and just to avoid ignoring an adverse event that might have been drug related, all of those are included in the toxicity data that I am going to show.

The result of that, though, is that a fair percentage of what we term "drug-related" side effects really weren't felt by the particular investigators to be very likely drug related, but are included just as a conservative measure.

[Slide.]

The second brief definition that I have tried to illustrate on this kind of unwieldy treatment schema is this study-specific concept of a treatment cycle, that kind of operationally we define that as the time interval between DepoCyt treatments, but conceptually, really, we defined a treatment cycle in terms of therapeutic equivalence, so one cycle of methotrexate equals one cycle of DepoCyt even though the dosing schedule was different for the two drugs, and as a result, in patients who were able to complete the entire time on the study, they were all going to receive the same number of treatment cycles regardless of the specific drug that they were assigned to.

[Slide.]

As it turned out, though, in this study, patients who received DepoCyt ended up remaining on study considerably longer than patients receiving methotrexate, and as a result, received more treatment cycles, so when I show you the toxicity data, we are going to show by patient and then also in an attempt to sort of control for this discrepancy in number of cycles received, I am also going to show the toxicity data by cycle.

[Slide.]

Now I have muddled through the definitions, I am going to really show you the numbers. In patients with neoplastic meningitis treated with intrathecal chemotherapy, we expect side effects to fall into these five general categories really: acute neurotoxicity, which is really the chemical arachnoiditis; subacute neurotoxicity, chronic neurotoxicity, leukoencephalopathy, for example, which we didn't see any of in either treatment arm in this study; CNS infections, and myelosuppression.

[Slide.]

As I have alluded to at the beginning, chemical arachnoiditis is far and away in both treatment groups the most common side effect, and, in fact, in most of the studies published on the topic where the issue is addressed, so surprisingly, you can't find in the literature a good

formal definition.

So, as a result, we have had to create a definition which I think is rational, straightforward, reproducible even though the slide I have chosen to illustrate it looks like a brunch menu order for Sunday morning.

What we have said, though, was we have two categories of chemical arachnoiditis. People who had three of those signs and symptoms we felt to have definite chemical arachnoiditis, and patients who had one of the major and two of the minor, we felt had possible arachnoiditis, and in addition, we categorized the arachnoiditis as serious if, in addition to the signs and symptoms, it was associated with an alteration in level of consciousness.

[Slide.]

So, with that definition, you can see that if we look by patient, that there was in fact substantially more chemical arachnoiditis in the DepoCyt-treated group, but when we attempt to correct that for the number of cycles, the difference between the groups, and look at it by cycle, that difference really narrow considerably.

[Slide.]

Now, I mentioned at the beginning of the talk that

we also distinguished between serious arachnoiditis and the total incidence. Most of those patients had mild symptoms, usually mild headache, mild nausea.

If we just look at the serious cases of arachnoiditis, whether by patient or by cycle, the numbers drop dramatically, and there is essentially no difference between groups.

[Slide.]

I also alluded to the fact that concurrent oral dexamethasone can prevent in most patients, or ameliorate the side effect of chemical arachnoiditis, and that actually is the case both in the methotrexate-treated groups and the DepoCyt-treated groups. Most of the episodes occurred in patients who did not receive dexamethasone, and, in fact, it occurred really primarily in the first or second cycle, as we all, as the investigators, convinced ourselves that this was true, that dexamethasone really did have an effect on this particular side effect.

[Slide.]

That is the case whether we look at all cases or just serious cases of chemical arachnoiditis.

[Slide.]

Similarly, if we look at the subacute neurotoxicity, very few cases overall, and I have listed

them by specific type, but the differences between groups is really indistinguishable.

[Slide.]

The same trend if we look at culture-proven bacterial meningitis, there is really only one case, and that occurred in a patient who was treated with methotrexate.

[Slide.]

And then if we look at myelosuppression, again, not a whole lot of episodes and really no difference between treatment groups in any of the categories of myelosuppression.

[Slide.]

But then finally, I guess the real bottom line in any chemotherapy trial that you could ask is how many patients discontinued therapy because of a drug-related adverse event or how many patients died because of drug-related toxicity.

There was really only one patient died from a clear drug-related side effect, and that patient received methotrexate, withdrew from study, and subsequently, because of drug-related neutropenia, died because of sepsis.

One patient in the DepoCyt group also withdrew voluntarily from therapy. She had had an episode of

chemical arachnoiditis on her first treatment cycle, and didn't want to take the risk of a second cycle, so withdrew from the study.

[Slide.]

So, in summary, the spectrum of toxicities of drug-related side effects in both groups, DepoCyt- and methotrexate-treated, are really comparable, and are really quite tolerable to people who received treatment. In a way, the most common one in both treatment groups is chemical arachnoiditis, and again in both treatment groups easily abrogated or ameliorated by concurrent oral dexamethasone treatment.

To conclude, Dr. Kurt Jaeckle is going to make the final presentation.

Potential Advantages of DepoCyt

DR. JAECKLE: Good afternoon ladies and gentlemen.

[Slide.]

I am a principal investigator in the Phase III trials of DepoCyt and the Phase IV trial, as well. What I would like to do is to present you my personal impressions, as well as provide a clinician's perspective on what I see as the potential advantages of DepoCyt in the treatment of patients with neoplastic meningitis.

[Slide.]

I think that they are summarized here basically. First, DepoCyt addresses some of the major pharmacologic limitations that have existed to standard intrathecal therapy to date. I will talk about that a bit more on the next slide.

In addition, it provides a much more convenient dosing schedule. At the same time there is comparable toxicity and equivalent efficacy with trends favoring DepoCyt.

[Slide.]

The standard agents that have been available for treatment of neoplastic meningitis have largely failed to have a significant impact on the survival of our patients, and this has resulted in a therapeutic nihilism among clinicians that are treating patients with this disease.

We have thought about that over the years and we think that that potentially relates to several road blocks which exist to therapy of these patients, some of which are pharmacologic, and the pharmacologic ones are summarized here.

First, the standard agents we have been using have very short half-lifes in CSF, measured in minutes to hours. The drug isn't around long enough to do any good in this situation. It drops below cytotoxic concentration usually

within hours or a day.

Secondly, this is compounded by the problem that there are few cycling tumor cells in CSF at any given moment. Even after 10 days, only half of the cells have cycled, just not long enough if the drug only lasts a day or so to do any good.

Then, we have always been troubled by the fact that after intralumbar dosing, there are uneven or inadequate levels produced within the ventricular system of the brain at a site where tumor cells may be located.

[Slide.]

Now, DepoCyt addresses many of these pharmacologic limitations primarily through the sustained cytotoxic CSF concentration to greater than 14 days. Basically, the drug stays around long enough for the cycling of the tumor cells, and this is particular important for an agent, such as Ara-C, which is S-phase specific.

In addition, as we have seen from the PK data from the Phase I study, there is even distribution, relatively even distribution with the intralumbar or intraventricular administration. This allows the physician for the first time to make a choice of either the intralumbar or intraventricular route based on some solid data, and he can choose this for his patient based on the individual needs of

that patient.

[Slide.]

Now, the second major advantage that I see for DepoCyt is the dosing advantage. Clearly, it is more convenient to administer this medication every two weeks rather than twice a week or more.

A case in point is a patient that I had who was able to fly all the way from Iowa to Houston to receive her treatments, and this just would have not been possible or very easy if she had to come twice a week for her treatment.

If you are using the intralumbar approach, which is the most commonly utilized, there would be less patient discomfort because there are fewer spinal taps. It is hard to rationalize putting an 18-gauge needle in the back of a cancer patient twice a week when you know that you have something potentially that could be done every two weeks.

This allows patients to spend more time at home with their loved ones, and not at the clinic or hospital with me. In addition more patients can receive treatment because of the practicality of this treatment. This allows patients to drive further to get the treatment because of the time spread, and it allows physicians to incorporate more of these patients into their busy schedule.

The bottom line of that is on a logistic, for

logistic reasons, more patients will have access to or receive this medication.

[Slide.]

Now, at the same time, and despite the sustained levels of DepoCyt in the spinal fluid, the toxicities remain comparable to standard methotrexate. Now, in my own personal experience, I feel that the arachnoiditis is slightly higher with this medication with methotrexate, but the arachnoiditis was mild and was preventable with the steroid administration, and even the more significant episodes could be managed with dexamethasone and supportive care, and in no instance, in my own personal experience, did I have a patient who had any kind of permanent residua from the arachnoiditis. This was reversible.

[Slide.]

In addition, the efficacy of DepoCyt remains equivalent to standard therapy, and, in fact, as we have seen, there are trends favoring DepoCyt for all of the usual outcome parameters including a complete response rate, the duration and overall survival, and death due to neoplastic meningitis.

I think more importantly this is the first intrathecal agent which in any prospective randomized trial of this disease has ever shown any statistically significant

improvement for any outcome parameter.

Even if you consider this time to clinical progression as a relatively soft outcome point, the point is that it is at least equivalent to a standard therapy we have out there, and there certainly are some exciting hints that it may be more efficacious.

[Slide.]

In conclusion, I think DepoCyt is the first drug which really addresses the problematic pharmacologic limitations of intrathecal therapy.

My personal experience has been consistent with the clinical trial data. What got my attention really is the fact that the clinical response remained good despite the more stringent criteria utilized in this trial, and my own personal observation of patients who had durable responses of up to 16 months.

Now, we have to put in perspective and keep in perspective that this is a disease which is an advanced stage of cancer and is terminal. We have very few agents out there which are of any help in this disease, and there certainly has been nothing new in years.

I think the risk-to-benefit of this agent is favorable. The toxicity and efficacy are at least comparable to the standard agents. It is clearly more

convenient for patients and physicians.

My patients have tolerated DepoCyt well and have given me positive feedback on the relaxed dosing schedule. Personally, if this was available on the shelf, I would choose this first over methotrexate and Ara-C, largely because it is just easier for the patients.

MR. THOMAS: That concludes our presentation.

DR. DUTCHER: Thank you.

Committee Questions to Applicant

DR. DUTCHER: Are there questions for the sponsor from members of the committee?

Dr. Santana.

DR. SANTANA: I am going to start from the beginning and ask some questions relating to some of the Phase I data and then later on, if any of the committee members ask, I will ask some other questions.

Is there any animal preclinical data that gives us some idea about toxicology of using the liposomal product in the absence of the chemotherapeutic agents and what happens to those animals?

MR. THOMAS: I think Dr. Dale Johnson, who is head of Toxicology with Chiron, and responsible for the primary toxicology study can answer that.

DR. DALE JOHNSON: Yes, I can answer that. In a

non-human primate model where you could look at both DepoFoam as the vehicle itself versus DepoCyt, you could study that particular question, and actually replicate the design of the Phase III trial.

So, in that particular study, we saw no evidence of any acute toxicity, such as neurotoxicity, with the vehicle itself, or no long-term effects, and those long-term effects extended out to three and six months past the last cycle.

DR. SANTANA: Another question. I had difficulty coming to the conclusion of what dose you called the MTD in the Phase I trial. If you look at the slide that you showed, page 25, with the exception of the first dose group, or dose level, all the other levels in terms of an incidence of side effects were relatively similar.

So, I had difficulty choosing the 50 mg as the dose that you are recommending for your Phase III trial. Would you comment on that, please?

MR. THOMAS: Dr. Chamberlain.

DR. CHAMBERLAIN: I showed only data for Grade 3 and 4 toxicity. As the dose was escalated, it was clear that there was an increasing incidence of chemical arachnoiditis at the maximum tolerated dose, which we felt was 125 mg. One of these individuals expired due to the

toxicity that relates to a meningoencephalitis as part of this chemical arachnoiditis syndrome.

So, we had a death at 125, and felt that it was prudent to back down from that dose.

DR. MARGOLIN: I was wondering why you didn't present the quality of life data.

MR. THOMAS: Dr. Cowens, would you like to review -- I guess I am not sure what the question is. Why we didn't present the quality of life data?

DR. MARGOLIN: Okay. Dr. Dutcher rephrased the question. Do you wish to present the quality of life data, which are addressed in your presentation materials that we were sent?

MR. THOMAS: Let me first say that the quality of life data are somewhat incomplete, that is, the FACT-CNS and the work that was done on that. We found that in this trial, a number of patients who were failing did not complete the instrument, usually because the investigator felt that it was inappropriate to ask him to complete such a scale given their physical condition.

In that sense, the data is somewhat incomplete. Dr. Cowens showed you the change score differences between the two drugs, which were very similar, although highly biased toward patients who had a good response, again

because of the patients not completing the results.

So, we considered the use of the QOL instrument, which this is the first time this has been done with this disease, largely an exploratory activity, we are using it again in the Phase IV trial and hope to get more complete results.

DR. RAGHAVAN: I have a couple of questions. I don't really fully understand why Dr. Cowens presented the intent-to-treat versus the evaluable data in the sense that there is one real problem with the evaluable data, and that is that you have roughly 30 patients in each group, and for some strange reason, in the methotrexate group, only 1 dropped out versus 9 in your trial drug group.

Now, if I were a suspicious character, I would say that that seems a pretty good opportunity to alter outcomes. So, since I am Australian, and we are a little slow-witted, maybe you can explain to me why -- [Laughter.]

DR. COWENS: Yes. Both the intent-to-treat population and the evaluable population were prospectively defined in the protocol at the time it was written. We made a commitment to analyze both populations, and all the definitions we used were prospectively defined.

It is actually a matter of chance that those patients happened to be all in the DepoCyt arm in that

trial. If you would look at the same phenomenon in the lymphoma and leukemia data, you would find it flipped, that is, all of the patients in the DepoCyt group are evaluable, so there is no dropout, and there is a lot of dropouts in the methotrexate group. So, it is an analysis, fundamentally, we committed to performing and showing prospectively in the protocol.

MR. THOMAS: If I may add to that, there is 2 of those patients who dropped out -- recalling that this was not a blinded study because of the very large differences in dosing, in 2 cases patients withdrew after assignment of treatment because the referring physician knew they had been assigned cytarabine and felt this was unlikely to be useful, so that it was not random loss, it was a bias against the drug.

DR. RAGHAVAN: If I could ask one more question, perhaps either Dr. Chamberlain or Dr. Jaeckle. In reviewing this area, you didn't really talk about the hard evidence that even methotrexate has a role.

My friends in Radiation Medicine would say that a good dose of steroids and 20 Gray will do maybe a little better without the need to violate the cerebrospinal space, and if one is talking quality of life, you could make the case by saying that that is a reasonable way to go, in other

words, using rads and parenteral steroids will give you pretty much a similar survival figure. It is pretty hard to get incredibly excited when you are looking at the first hundred days where most of your patients have died.

So, my basic question is can you just review for me why you think intrathecal chemotherapy has a role for solid tumors? No argument about lymphoma, no argument about leukemia, but in the solid tumors, what do you think is the hard evidence that you really make a difference?

DR. CHAMBERLAIN: Well, I believe there is a role for intra-CSF chemotherapy in treating both carcinomatous meningitis, leukemic and lymphomatous meningitis.

I would agree with you that the data is softest with respect to carcinomatous meningitis. In taking a composite from the literature, most patients with this disease, without treatment, die in a month. Non-responders, with treatment, on average survive two to three months, and responders typically have a 2- or 3-fold advantage over non-responders.

I don't know of any data aside from fairly modest data from Israel that speaks to the role of standard-dose systemic chemotherapy and radiation therapy without the inclusion of intra-CSF chemotherapy.

So, it is not a very easy question to answer. I

am not sure if that illuminates this any further.

DR. MARGOLIN: I have two questions. One of them, I am not sure whether you have somebody representing your central pathology reviewer, but the decision to change the definition of CR, of cytologic CR from twice with at least a three-day interval between the taps to one unconfirmed negative CSF cytology was somewhat bothersome to me, because I think we are taught, at least in medical school and in our oncology fellowships, that one negative tap doesn't necessarily mean someone has a negative CSF.

I have another question, but they are two separate things.

DR. CHAMBERLAIN: I would agree with that. It depends on which study you look at. If you go back to the old literature and look from Sloan Kettering and Wasserman's data, it suggests that a 55 percent positivity rate in patients who are positive will be demonstrated following a single CSF examination.

More recent data from Kaplan suggests that that figure may be as high as 70 to 90 percent in patients who are positive. So, I am not sure where the figure is. That certainly increased in all series up to 75 to 80 percent positivity following two CSF examinations.

DR. MARGOLIN: I think most of us in oncology,

even though we are beating our heads against the wall much of the time in terms of treating solid tumors with drugs, try to be somewhat strict about response definitions and for tumors outside the CNS when we can measure them, we always require a certain interval during which the measurements have to have met the criteria for a response.

DR. CHAMBERLAIN: In this study, all patients at entry had positive CSF cytology, so clearly, these are slightly different patients than your general patient, necessarily with carcinomatous meningitis, and upwards of 40 to 50 percent of patients are cytologically negative regardless of how often you access the CSF.

Secondly, at the conclusion of induction when response was evaluated, all patients at prior positive sites had CSF examined again at those sites, and then reconfirmed one week later. There is no other Phase III trial in this disease that has ever asked that definition or required that definition, and we believe that this is the most rigorous of definitions so far to date in this disease.

DR. SANTANA: As a corollary or an addendum to that question, I presume many of these patients had diagnostic imaging at study entry, and how did that diagnostic imaging relate to the cytology that you called positive or negative, and if those studies were also

repeated at the time you quoted patients as being responders?

DR. CHAMBERLAIN: Imaging was done at time of entry. Cranial imaging was required on all patients. That was primarily to define bulk disease. Bulk disease, whether it is intraparenchymal or subarachnoid, is disease that does not respond to intercavitary chemotherapy, as you well know. It was solid tumors.

Patients were not required at conclusion of induction to have that reanalyzed unless that was clinically relevant to the patient's management.

DR. SWAIN: I had a question about the time to progression data, actually, several issues regarding that.

Were the patients on the methotrexate arm seen more often than the patients and followed up more often than the other arm since they received more drug more often?

MR. THOMAS: Yes.

DR. SWAIN: So, there is a potential for bias there, that they were seen more and had more time to be called progressive disease?

MR. THOMAS: Dr. Cowens?

DR. COWENS: The examination schedule was fixed for the two arms, so the evaluations, even though they received more cycle, more drug doses, they exams that were

counted were those on the same schedule for both arms.

DR. SWAIN: How exactly did you define progression? I would think it would be very difficult in this population who has a lot of significant neurologic problems, to begin with, and also since there is so much evidence of arachnoiditis, too, how was it defined, was it looked at by outside observers or did each individual investigator define it?

DR. COWENS: There was guidance in the protocol that the investigator was to use neurologic signs and symptoms and neuroradiological evaluations. The judgment was made by the investigators using this form that you see here, but further than that, the database was monitored and audited, and the sponsor made an effort to reconcile the date checked on this form with all the other data in the CRF, so that independently, you could compute the same data progression, and this was done both at DepoTech and at Chiron.

Those cases where we could not construct or reconstruct the investigator's logic, we did queries and either asked for information to resolve it or asked the investigator to clarify why they made the judgment they did. So even though it is subjective in the sense that one person is doing it, there was a great deal of effort made to make

it based on fact, and make the data for each patient consistent.

MR. GIDDES: I was just wondering, not being a medical man, how many samples are needed to be taken from the patient that would give confidence that the CSF is free from any malignant cells, how many samples do you take? A follow-up to that is how confident that we can be that negative CSF means that the patient has benefitted?

DR. JAECKLE: This is a very good question, and to follow up to the prior question, none of us believe that a single CSF in itself stands alone, because, you know, you will be getting a negative CSF sample about 50 to 60 percent will be positive, about 40 percent will be negative. So, this can be increased to 80 or so percent with two samples, but this study, I want to stress, was not just looking at spinal fluid. It was looking at spinal fluid at all sites, number one, which was an extension of anything that had been done, but in addition, had to be in the presence of clinical stability or improvement.

We tied both together because we were trying to develop the best surrogate marker for time to progression in this disease, and no one has been able to do that in any type of uniform fashion. So, we believe if we check at all sites, and especially if we can do that twice, and put that

together with the clinical disease, that is the best we can do right now, and I think that is what is done in clinical practice, as well.

DR. RAGHAVAN: One of the issues that always makes medical oncologists very nervous, I think, is when people talk about the comparison between responders and non-responders, and I think this dates back to papers written by Ken Anderson and Jim Anderson, and others, many from the Harvard Medical School back in the 1980s.

The issue that keeps coming up for discussion is that when you compare responders and non-responders, sometimes what you are actually doing is comparing different natural histories of disease, and that is even within tumor type that you might theoretically argue that the patients with a long natural history artifactually are seen to be responders, particularly when you have soft endpoints.

Now, this is a very tough group to work with, and I understand that, and they are hard to get cases and I understand that, as well.

Could you give us a sense within the breakdown of responders and non-responders, within the two treatment arms, and I understand we are talking small numbers of cases, is there any obvious histological breakdown or time to presentation with CNS involvement breakdown, that would

make you feel that you have either accidently sorted a subset into the responding category or that you actually don't have that pattern, that there is an even distribution of growth rates and tumor types?

MR. THOMAS: I think we have looked at that question and have a slide that shows the array of responders, which I think you will find is quite heterogeneous.

DR. CHAMBERLAIN: I will try to speak to some of this. Clearly, there is a sense amongst oncologists -- and I think we all share this -- that there are chemo-sensitive and chemo-insensitive subgroups in patients with carcinomatous or solid tumor, neoplastic meningitis.

This study I think documents that they were balanced upon entry, and furthermore, that patients who are a responder could be in any of those groups. So, our perception that there were chemo-sensitive and chemo-insensitive groups was not corroborated by our responder types, as you can see from this slide.

DR. SWAIN: In this slide, these patients didn't have confirmation of a response rate, because it was much lower in the patients who had confirmation. They just had one negative.

MR. THOMAS: Did not have confirmation from all

sites necessarily, that is correct.

DR. DAVID JOHNSON: I would like to follow up on the point being made by Dr. Swain because I am troubled by the study design, as well, and need to have a clearer understanding of your time to progression definition.

It is still unclear to me what represents regression. I think, in an unblinded study like this, especially when the patients are coming back more frequently for visits, regardless of whether they are scheduled for examination or not, I don't know of a single patient I have ever put intrathecal medicine into that I didn't examine or talk to.

So, I can't imagine that if a patient complained of a symptom at that point in time, even though it wasn't a defined assessment time, that that patient wasn't called a progresser if she or he had a symptom that clearly was indicative of progression.

So, I am trying to understand this much more clearly.

DR. CHAMBERLAIN: It is difficult because these are complicated patients that have both a systemic tumor burden and a central nervous system tumor burden, but we attempted to find time to clinical progression as based on neurologic disease progression. So, these are parameters

that neurologists -- and there were many neurologists involved in the study, these are the neuro-oncologists -- that defined based on one of the disease parameters that we associate with leptomeningeal disease progression.

It was a clinical determination as we use in our daily practices to determine if, in fact the patient is failing treatment based on that particular organ site involvement with this particular form of metastatic cancer.

DR. SANTANA: You usually try to corroborate that with other neurodiagnostic imaging or some other modality, and that is kind of what I was getting at when I asked the question did you have other confirmatory evidence independent of the CSF cytology in these group of patients.

DR. CHAMBERLAIN: I don't know of any data that supports neuroradiography as showing that patients who are failing with leptomeningeal cancer corroborates that as an independent measure of disease progression.

DR. SANTANA: I guess the question was these patients were having a lot of toxicity and how you could separate neurologic toxicity from the therapy versus disease progression.

DR. CHAMBERLAIN: I understand.

DR. SANTANA: I am trying to look for an objective criteria independent of the observer.

DR. CHAMBERLAIN: Chemical arachnoiditis -- and perhaps I didn't make this clear -- is a well-defined syndrome. It peaks at one to two days following intra-CSF chemotherapy administration, and then subsides by day five and is resolved.

I think none of us would look at disease progression based on an acute blip that lasts approximately five days in duration, and is mitigated by steroids. This is not a disease leptomeningeal cancer that is mitigated in any form by the co-administration of oral dexamethasone, but rather the chemical arachnoiditis, that symptom complex would resolve with the use of steroids, and five to seven days later, that patient will be back to baseline prior to receiving treatment.

DR. SANTANA: But dexamethasone also ameliorates or relieves some of the symptoms related to tumor.

DR. CHAMBERLAIN: It only does that in patients with parenchymal disease or large bulky disease that in itself is causing vasogenic edema. I think this is a concept in neuro-oncology which is well ingrained, but perhaps somewhat more evanescent outside of neuro-oncology. This is not a disease that is responsive to steroids. You don't treat this disease with steroids. You treat parenchymal brain metastasis with steroids and ameliorate

symptoms, but you don't do that with leptomeningeal cancer. You create toxicity, but you don't ameliorate the disease.

DR. SIMON: Two questions. One, I am also skeptical of the time to progression just because the neurologic symptoms seem soft and confounded with toxicity, and you basically are comparing two groups, one of whom are probably fairly anxious to get off of twice-a-week LPs.

So, I really question that. But I had two other questions. One, as I understand it, partway through the study, there was a question as to whether the study should continue, and the resolution was you permitted cross-over after I think 8 weeks or something like that, but yet there were only 4 patients in the methotrexate group who crossed over to DepoCyt. Why was that?

MR. THOMAS: Well, the simple reason for the cross-over was it was introduced very late in the trial, and the trial was closed shortly after that was introduced as a protocol amendment. So, it had really only effect on several patients.

DR. SIMON: The other point I guess I should know, but could you clarify, was it only the DepoCyt patients who received the dexamethasone?

MR. THOMAS: No, both groups, and your point on getting off of LPs, there was only one or two patients on

the trial who did not receive drug through the intraventricular route.

DR. SIMON: They got it intraventricularly, but still it was a much less convenient schedule.

MR. THOMAS: Yes, but again, for 95-plus percent of patients, cross-over was not available.

DR. MARGOLIN: I have two questions. One is whether you wish to comment on the role of the concomitant use of radiation and/or chemotherapy, which was in the package, but not in the presentation, and the other -- well, the other question I will ask separately because it is unrelated.

DR. GLANTZ: The use of concurrent systemic chemotherapy was equivalent in both groups, and although it may be a good prognostic factor in general, it was evenly distributed, as was the concurrent radiotherapy. I didn't hear the second part of the question.

DR. MARGOLIN: I didn't ask the second question. The second question is a more general one, and it is a little bit off the subject, but if you will, it seems by the demographic data that we were presented earlier and by what we all know who practice oncology and hematology, that the availability of patients with lymphoma and leukemia who have CNS involvement is higher than solid tumor patients who have

a pretty good performance status and who are going to live long enough to go on a study such as this, and furthermore, I think we have a general concept that their responsiveness to this chemotherapy, which in this case was the unencapsulated Ara-C, is higher, so you can get better statistics. You ought to be able to accrue more patients faster and perhaps answer the question.

So, my question is really where is the accrual to the lymphoma and leukemia studies, why isn't it going faster, and why aren't we having this presentation about that which might have made our jobs a lot easier?

MR. THOMAS: Well, the current status of the lymphoma trial, it is somewhere on the order of 90 percent accrued, but the patients are still on follow-up, and the protocols are not equivalent. There is approximately four months longer duration of treatment with lymphoma patients, so that trial will be going on before it is completed well into next year.

As far as the leukemia trial is going on, the enrollment has been much slower, probably because of exclusionary criteria, although a pediatric study, a dose-finding study, has started and is underway, and will continue on through next year, and is expected to be completed in 1999.

DR. DAVID JOHNSON: I want to again come back to some points that were made earlier, but just for my personal clarification, as was pointed out by Dr. Raghavan, you had 61 patients in this trial, 30 and 31. The DepoCyt arm had 9 patients that you considered non-evaluable, 3 of whom you have listed as without adequate time on study. I don't know what that means. Can you define that for me, what does not adequate time on study mean?

DR. COWENS: That was prospectively defined at the time protocol was written, that the patient had to be on study at least 12 days to be evaluable, so that a response could be seen if it were going to occur.

DR. DAVID JOHNSON: And how did you arrive at that figure?

MR. THOMAS: All three of these patients died for reasons unrelated to their CNS disease.

DR. DAVID JOHNSON: Okay. The point was how did you arrive at that 12-day benchmark point, and might you not have replaced those 3 patients? I understand you consulted with the FDA about this trial, I understand that there were a lot of real compromises made in the design of this trial.

By the same token, it seems to me that the trial then should have been adhered to very, very closely, and 3, that a tenth of your patients on the trial. If we had a

1,000-patient trial with 100 patients that were excluded for whatever reason, I don't think that would fly.

I am just interested in how you arrived at your 12-day figure.

MR. THOMAS: I think the answer is that the 12 days was considered approximately one drug cycle, and it was felt that it was unfair to try to evaluate patients with less than one drug cycle.

DR. DAVID JOHNSON: Any drug cycle is a drug cycle, so if they got drug, that is an evaluable patient in theory, I think. So, those patients would be considered not unevaluable, but evaluable, and non-responders. Right?

MR. THOMAS: And are so treated in the ITT analysis, as well as patients who received no drug.

DR. DAVID JOHNSON: And then also the fact that 4 of the patients didn't have adequate cytologic follow-up, I think is also very disturbing. I mean I don't understand. Why did they not get adequate cytologic follow-up?

DR. COWENS: Three of those patients were diagnosed by the LP route. They went on study, and they eventually had a reservoir, a ventricular reservoir put in. They were evaluated at the end of the induction by the ventricular site only. What we understood was once the reservoir was in, the patient would not agree to an LP, so

it was simply not the desire -- it wasn't a desire not to try, it's that the sample just couldn't be obtained.

DR. DAVID JOHNSON: But a sample was obtained.

DR. COWENS: Ventricularly.

DR. DAVID JOHNSON: And do we know the results of that?

MR. THOMAS: These were negative in all cases.

DR. DAVID JOHNSON: Just one last question, because you made a point about the fact that the dropout was the opposite in the leukemia/lymphoma trials, in other words, you said these 9 dropout in this trial, on the DepoCyt arm, was "by chance," because in the other trials that were being conducted, it was a higher dropout in the leukemia/lymphoma Ara-C arm. Is that correct? Didn't you say that?

DR. COWENS: That is correct.

DR. DAVID JOHNSON: Now, you had 23 patients that you listed here for supportive data, and I just heard a minute ago that this trial was 90 percent completed. Is that what you said?

MR. THOMAS: No, I said the enrollment is 90 percent completed.

DR. DAVID JOHNSON: And the dropout rates are?

MR. THOMAS: I don't have those figures.

DR. DAVID JOHNSON: Thank you.

DR. COWENS: I just want to make one point that the focus of our discussion about the effectiveness of the product is really based on the ITT, the ITT patient population. We presented the evaluable because we had prospectively defined it and committed to analyze it and present it. All those patients that "dropped out," are all in the analyses that I showed you in the ITT. No patient, even the ones that did not receive drug, are excluded from that analysis.

DR. DAVID JOHNSON: In response to that, though, you and several of your colleagues made inferences about trends which don't exist when you got to the ITT. They certainly exist when you did the evaluable patients, I will agree to that, but there is no trend if you do the ITT.

DR. COWENS: The trends we are referring to are not -- they are internal consistency trends. We are talking about numerical differences. We realize they are not statistically significant, and we realize that any one measure can be criticized justifiably, but what we have is all the measures go in the same direction, and that is what I was referring to when I was talking about trends. It is convergence of all the evidence in all the different measurements that we made, and we are not relying on one

measurement to try to make a statement.

DR. CHAMBERLAIN: And all of the data shown is with respect to the ITT patient population, so these are not based on evaluable patients and favorable trends, but these same favorable trends are seen in the ITT analysis, and perhaps that was somewhat confusing. We apologize.

DR. OZOLS: On the imaging studies, what percent of the patients had bulky CNS disease?

DR. CHAMBERLAIN: I don't know that figure. I can't answer that. They were balanced in both groups.

DR. OZOLS: Would it be just that those that responded to therapy did not have bulky disease?

DR. CHAMBERLAIN: That actually in analysis not presented here has shown to be an independent prognostic variable predicting for survival. Patients with bulky disease by and large tend not to be responders and fail early. That data has been presented -- not presented -- but is published. Bulky disease is seen in both groups, and they were balanced with respect to that, but it was clearly an independent --

DR. OZOLS: So, how many actually received radiation therapy, as well as intrathecal treatment?

DR. CHAMBERLAIN: If we go to the demographic slides, either slide 2 or 3. I can show you that on a

slide, sir.

DR. DUTCHER: Actually, I can read it to you from the handout that you provided. There were 4 patients in the DepoCyt concurrent and 8 in the methotrexate.

DR. SANTANA: But if I understood the data that is in the application correctly, of the patients that responded, now just looking at patients that responded, 3 of the patients that responded received the study drug, and also concomitantly the therapy at one point or another. Is that correct? That is my looking at the original data.

DR. CHAMBERLAIN: Yes, sir, and concurrent radiation therapy doesn't imply necessarily that these patients had bulky disease, but had symptomatic sites of disease. For example, a patient presenting a cauda equinus syndrome, who would have paraparesis, without evidence, neuroradiographic by spine MR, of bulky disease, would be radiated to that site. That is not entirely apparent from this slide presentation.

DR. SIMON: When you compare time to progression of patients who are still without progression at 28 days, and compare the CR patients to the non-CR patients, implicitly, you are trying to validate your definition of CR.

Are those two groups balanced with regard to the

number of patients that have bulky CNS neurologic disease? Do you have the same number of patients without progression at 28 days who have bulky disease in the CR group compared to those who have bulky disease in the non-CR group?

MR. THOMAS: We have not looked at that.

DR. SIMON: The landmark method doesn't really validate, you know, a definition of CR, unless you can demonstrate that those who were without progression at the time of the landmark were prognosticly similar with regard to other things, and I would think bulky neurologic disease would probably be a more important thing to look at rather than the site of the primary tumor.

DR. CHAMBERLAIN: I want to make the distinction, I am not sure it has come across and been entirely apparent, and that we return to this theme of bulky disease. Bulky disease is not disease-responsive to regional chemotherapy whether it's methotrexate, cytarabine, or otherwise. That is disease that is responsive to systemic chemotherapy and radiotherapy, so those are adjunctive modalities to the primary investigative instrument we used in this study, which is looking at regional chemotherapy, DepoCyt versus methotrexate.

DR. JAECKLE: I also want to mention that in the trials to date, although there is some small numbers in

these trials that look at bulky disease as an independent prognostic variable, these are very small trials. This was not subjected to any kind of multivariate analysis looking for covariation or any type of independent -- and so we are saying this based on our clinical judgment, but it is not really known whether bulky disease really make a difference.

DR. RAGHAVAN: We have done our jobs on this side of the table in the sense that we have identified that there are real problems with the study in the sense that you just don't have a lot of numbers, and there are all sorts of flaws that have crept in inadvertently.

On the other hand, I would hate to lose a potentially useful drug, and I would like to take you back to -- I forget who actually presented the data, it might been Dr. Cowens -- but there was just sort of a one liner in there about in the Phase I, patients who had had previous lots of different types of treatment, that you had seen objective evidence of activity.

Could somebody tell us a little about that, in other words, people who have had prior intrathecal therapy, what have they had, what is the patient benefit? Sell the product.

DR. CHAMBERLAIN: I think I can do that. It is convenient. It is every two weeks. I think that component

is the strongest aspect. And it is at least equi-efficacious with existing agents.

The patients who we had treated in the Phase I trial with a variety of intra-CSF agents were all treated according to I think a fairly well-published UCSD approach to this disease, which is a C times T method of drug administration. That is 2 mg of methotrexate, five consecutive days, every other week, for eight weeks. That is called induction.

If the patients fail at that time, then they are crossed over to C times T Ara-C. That is 30 mg, three times per week, on consecutive days, for four consecutive weeks. That is considered induction.

If the patients fail that therapy, they are then, and if still eligible to continue on therapy, are then moved to thiotepa. Thiotepa is given 10 mg on consecutive days, three times per week times 4, and that is considered thiotepa induction. That is the kind of therapy that all patients in the Phase I trial have seen prior to entering the DepoCyt investigations.

DR. RAGHAVAN: Can you just remind us of the responses you then saw in that Phase I? I understand Phase I was not looking for responses, but someone said that there was clear evidence of patient benefit. Can you quantify

that a little bit?

DR. CHAMBERLAIN: The degree of complete response was comparable to that seen in the Phase III trial, and was approximately 40 percent in patients with solid tumors. It was somewhat higher in patients with hematologic malignancies. So, these are rescuing patients as you are asking who had seen prior standard therapies.

DR. SWAIN: I just had one more question about the toxicity. I think in one -- I don't know if it was in your table or the FDA's -- there were at least 6 patients with severe headache on the DepoCyt arm, and yet you say that severe chemical arachnoiditis is basically about the same in the two arms.

Can you kind of try to explain that to me, so I can understand what those numbers mean?

MR. THOMAS: I assume that you are talking about the data in the NDA?

DR. SWAIN: Right, that there were I think 6 severe headaches for DepoCyt and 1 for methotrexate. I think that is what I counted.

DR. GLANTZ: Two things that I hope maybe will answer your question. One is that the data that I have presented on toxicity was restricted to the prospective randomized study in solid tumor patients, and also I think

in the NDA and in my presentation, we may have used different definitions of severe.

When I said severe, we were talking about association with altered level of consciousness.

DR. SWAIN: I am sorry. With what? Somebody is talking here, and I can't hear you.

DR. GLANTZ: Severe chemical arachnoiditis in the slides that I showed implied that there was an alteration in level of consciousness. Also, this was restricted to the 61 patients in the trial.

[Slide.]

DR. PARADISO: I am Dr. Linda Paradiso, Vice President of Clinical Development at DepoTech. I am not sure that this will completely answer your question, but let me try.

We looked at arachnoiditis according to the algorithm that we explained to you earlier, but we also examined it this way, in a more traditional manner, looking at the worst severity of any one of those signs and symptoms that went into the algorithm.

So, if a patient had a severe headache as part of that algorithm, you would see it defined in that severe line. So, this slide shows arachnoiditis across all the DepoCyt studies including the Phase I, and then it also

shows the two, Phase III control arms across all patients enrolled in all the trials, and it is only by cycle, and it is with and without dexamethasone treatment, but you can see that the incidence of severe arachnoiditis -- and that is where your severe headaches would fall -- are quite low relative to the mild and moderate signs and symptoms that were part of that algorithm.

Does that help? Okay.

DR. DUTCHER: Let's take a break, a 15-minute break, and then we will come back to the FDA presentation.

[Recess.]

FDA Presentation

DR. DUTCHER: We are going to go ahead with the FDA presentation.

Dr. Hirschfeld.

DR. HIRSCHFELD: Good afternoon, Dr. Dutcher, members of the panel, colleagues, guests.

I am going to discuss some aspects of our review of the data that was submitted to us regarding DepoCyt. I want to clarify that I will not be discussing, nor making any comments, nor should any be inferred about the vehicle DepoFoam.

I also want to acknowledge the cooperation and the excellent presentation of the NDA material to us and the

thorough analysis that was done by the sponsor in providing us with the results of a randomized controlled trial.

In addition, we were provided with electronic data in a format that allowed us to ask a number of questions, and that also is gratefully acknowledged.

[Slide.]

I am representing an entire team in these remarks, and I want to acknowledge the contribution of all the team members beginning with our directors, Drs. Temple, DeLap, and Justice, who are not only distinguished by their last names, but by their accomplishments and, in particular, the individual advice and interest that they provided on this particular application, and Mr. Gensinger for his gracious support and interest in my work and the entire project was coordinated by Dianne Spillman, and the various review teams had a number of contributors, all of whom had input into the final process, which I will add is still ongoing, and we take the advice of our panel members into account in arriving at our conclusions.

[Slide.]

The scope of the presentation will be to state some of the major issues for discussion. It is impossible to cover all aspects in the allotted time, a brief review of current literature, a review of selected aspects of the

submission, and summary.

[Slide.]

The two proposed major issues for discussion that we would want to submit before the panel is what types of conclusions can be derived from small datasets, and what is the value of using cytological response of the cerebrospinal fluid as a surrogate endpoint for patients with solid tumors and carcinomatous meningitis.

[Slide.]

A review of the literature illustrates that carcinomatous meningitis has many forms and many synonyms. It is also known as leptomeningeal meningitis or neoplastic meningitis, and it considered a late stage and ominous complication of solid tumors.

Median survival in many series on both sides of the Atlantic is about three months following diagnosis, and about half the patients die from causes than the presenting lesion of carcinomatous meningitis, which is the term I will tend to use in the discussion, including systemic disease.

More importantly, prognosis is dependent upon the initial staging and is perhaps independent of intervention, and this raises an issue which we will explore further in the discussion, and the literature in a number of series questions the value, at least in some diagnoses, of using

intrathecal therapy, which has been brought up in earlier discussions this afternoon.

[Slide.]

By our estimates, based on SEER data, there is probably around 2,500 patients in the United States annually, and that is using conservative figures of an incidence of 1 percent in breast cancer patients, small cell lung cancer patients, or patients with intracranial parenchymal tumors.

[Slide.]

Current therapy is multimodal and selective. Some patients receive radiation, some receive systemic chemotherapy, some receive intrathecal chemotherapy with the primary agents being methotrexate, cytarabine, or thiotepa. There are cases of patients who receive surgical resection for solitary lesions with apparent patient benefit, and combinations of any of these modalities.

[Slide.]

There is no consensus on management due to a variety of issues, which are discussed in an excellent review article by Jason, and I uses the conclusions from that article to form some of the points on this particular slide.

Most published series include patients with

varying tumor types and patients with and without brain parenchymal disease. In addition, there are difficulties in interpreting studies due to alterations in cerebrospinal fluid flow caused by the lesions of the disease.

[Slide.]

The absence of consensus again depends on an absence of uniform criteria on how to address clinical or laboratory endpoints, and a reliance on surrogate markers rather than neurologic improvement or even stabilization or survival as study endpoints, and in this setting and with the difficulties in interpreting data, I am afraid that the rest of my comments will reflect the fact that the only aspect that will be black and white will be the format of the slides.

[Slide.]

There was a meeting in October 1992 between the sponsor and the FDA, where a proposed controlled study design was discussed, and again maintaining consistency with the nomenclature initiated by the sponsor, there were three separate trials, according to conventional nomenclature, but these were termed "arms," one for solid tumors, one for lymphoma patients, and one for leukemia patients.

Reading between the lines in the discussion, I think it was anticipated that the lymphoma or the leukemia

patients would be the first to meet the accrual targets and that the solid tumors were added because this is a vexing clinical problem.

History showed otherwise. In a series of accommodations, primary brain tumor patients were allowed into the solid tumor arm, and in each trial or arm, patients were to be randomized to one of two treatment groups - DepoCyt or an active control.

For the solid tumor control group the active controls was intrathecal methotrexate.

[Slide.]

Response was to be determined by CSF cytology, but that was considered inadequate as an index, so a quality of life assessment component was deemed necessary. There was to be stratification according to tumor type, and a minimum of 20 patients per group and 10 in each strata per group were to be enrolled.

[Slide.]

We now come to a critical assumption, and that is that intrathecal therapy, and in particular intrathecal therapy with methotrexate at a dose of 10 mg given twice a week, is of benefit to patients with carcinomatous meningitis secondary to solid tumors.

This assumption is somewhat different than the

training I received at several medical centers where patients with parenchymal brain disease, for instance, were not treated with intrathecal methotrexate 10 mg twice a week as a response to the complications from their disease, but it is important to bear this in mind in analyzing the study data.

[Slide.]

The primary endpoint was a cytological endpoint, was defined as follow: After week 4 or approximately day 29, the CSF pathology had to be negative at a single site of choice -- and this is anatomic site -- previously documented to be positive and -- and this should be underscored -- no clinical evidence of progressive disease.

A confirmatory sample taken from all previously positive sites between weeks 4 and 5, or approximately day 32, should be negative, and the definition of positive cells is cells that are positive for malignancy or suspicious for malignancy.

[Slide.]

The definition of negative is cells that are atypical or absent.

If a patient meets the above criteria, the patient will be ruled a complete responder and receive study drug for 12 more weeks.

If there was a CSF sample that was positive or there was clinical progression, the patient will be considered a non-responder and will discontinue study treatment, but would be followed clinically.

[Slide.]

This leads to the second critical assumption for understanding the results of the trial. That is, that cytological response is a surrogate marker for patient benefit, and in order to validate this assumption, other measures of patient benefit were incorporated into the study design.

[Slide.]

The study regimen, just to refresh your memory, was that all patients were to receive dexamethasone prophylaxis. The methotrexate patients received a regimen of 10 mg intrathecally twice a week, and the DepoCyt patients 50 mg intrathecally every two weeks during the induction phase. There was a later phase where the dosing schedule was adjusted, but for most of the patients, that wasn't a relevant factor.

There was an assessment at 30 days to determine response, and the patient could continue to receive study medication if a response was detected or if the patient wished to cross over to another study group. Both of these

points required some adjustment during and following the course of the trial.

There was a category of patients, as mentioned earlier, who had a negative cytology, but didn't have a confirmatory cytology within the time frames that were defined, and so these patients were deemed responders, but not confirmed responders in the analysis, and we agreed to accept that interpretation, and the cross-over group, as mentioned earlier this afternoon by Mr. Thomas, was a late addition to the study, so the number of patients who had that option again doesn't constitute a statistically significant subgroup.

[Slide.]

The proposed submission to review was to receive controlled randomized trial, 20 patients in each treatment group, and 10 patients in each strata in each group.

What we received was a controlled randomized trial meticulously documented, 30 patients in each treatment group, and more than 10 patients in each strata in each group.

[Slide.]

The characteristics of the 61 patients were that there was a median age of 49 with a range of 20 of 74. There were 44 females and 17 males. There were 52

Caucasians, 5 African-Americans, 3 Asians, and 1 Hispanic.

The tumor types were 22 breast cancer patients, 14 patients with CNS primaries, 6 with non-small cell lung carcinoma, 5 with melanoma, 4 with small cell lung carcinoma, and 10 other diagnoses.

The Karnofsky status had a median of 70 and a range of 50 to 100, and perhaps an explanation as to why the solid tumor phase of the development of this therapy came in ahead of the others was that one of the study sites contributed 31 percent of the patients.

[Slide.]

There were 7 patients that received concomitant chemotherapy, 18 patients that received concomitant radiotherapy, and if one asks the question how did the randomization fall out, there were 10 patients on the DepoCyt group who had concomitant therapy and 15 patients in the methotrexate group who had concomitant therapy.

The patients that crossed over were 2 assigned to DepoCyt and 4 assigned to methotrexate.

[Slide.]

So, we will touch on efficacy.

[Slide.]

The primary endpoint was defined as cytological response underscore in the absence of clinical progression

showed that 23 percent of the patients with the somewhat relaxed criteria met this definition or 14 out of the 61 patients.

There were 8 females and 6 males among the responders, and the response rate overall for males and females was different, but not statistically significant.

There were 4 patients who fell into the breast or small cell lung cancer strata, and 10 patients who were of the other tumor types. Again, there was a difference in the response rate, but this was not statistically significant.

Four of the 7 patients who received concomitant chemotherapy had a response, and 3 of these 4 were assigned to methotrexate. Five of the 18 who received concomitant radiation achieved a response, and 3 of the 5 were assigned to DepoCyt.

Six of the 19 patients from the single study site that contributed the most patients to the study achieved a response.

If one now looks according to the medication group, 8 of the 31 patients, or 26 percent, randomized to DepoCyt, had a response, and it is of note that 6 of the 8 were female patients. I don't know the significance of that.

Six of the 30 patients randomized to methotrexate

had a response, and 4 out of the 6 were male patients.

[Slide.]

So, a statistical analysis shows that there was no detectable difference in response rates according to study medication, no difference in response rates according to gender, but there was a hint that there may have been a difference in response according to study medication and that there was a significant difference in the ability of males versus females to respond to methotrexate.

Now, I put this number in somewhat intentionally because although the numbers have a statistical significance, personally, I believe that this is probably a quirk of the study randomization, and doesn't have any biological interpretation.

In terms of geography, there was a single site that had 32 percent response, and all other sites had a 19 percent composite response, no statistical difference, and in terms of tumor strata, there was no statistical difference between the breast cancer patients or the other patients.

[Slide.]

Looking at the secondary endpoints, it is even less clear what one may conclude because of the small population size, and I want to acknowledge that this has

been the largest single randomized study that was done in this patient population that has been either published or reported to us, and nevertheless, the power of the study to draw conclusions make conclusion difficult to extend to a larger population.

So, there were no differences in overall survival or clinical duration of response between medication groups or any groups that one might define based on other variables.

There was a statistically significant difference in cytologic response based on geography, which probably means nothing biologically, and there was statistically significant difference in time to clinical progression defined according to protocol criteria based on medication, but we also found that if we looked at the same parameter, using the same definitions on the basis of gender or race or concomitant treatment effects, meaning the radiation or the chemotherapy, it is possible to also change the numbers or come to conclusions that may show differences, so the power of the statistical significance of this is difficult to extend to a larger population.

[Slide.]

Survival data for all patients with DepoCyt had a median of 107 days, and for methotrexate 82.5 days, and

there was statistically significant difference by log-rank test.

[Slide.]

There were no significant differences in Karnofsky Performance Status, mental status, or quality of life between treatment groups among those patients who were able to complete those studies.

[Slide.]

So, the efficacy conclusion is that DepoCyt showed activity in patients with carcinomatous meningitis associated with solid tumors and had a response rate that did not statistically differ from a methotrexate based regimen.

There was a difference in clinical time to progression, but due to the small sample size and multiple analyses, this cannot necessarily be ascribed to study medication. It would require a larger, more robust study before one could come to any conclusions.

[Slide.]

In terms of safety, there were significant differences in the Phase III study in several types of adverse events, and this is not graded, this is just looking at overall adverse events. This is on a per-patient basis.

There was a significant difference in the number

of patients that had headache, back pain, fever, or nuchal rigidity, and there was a significantly higher rate of serious adverse events defined according to the FDA regulations in patients that received DepoCyt compared to methotrexate where the difference in this case was a rate of 83 percent versus 50 percent.

[Slide.]

There was a trend for more drug related, but this was not statistically significant for patients who received DepoCyt.

[Slide.]

The incidence of chemical arachnoiditis, which was addressed, and addressed in I think a fairly careful way by the sponsor, showed that 20 of 29 patients that received DepoCyt, or 69 percent, had some form of chemical arachnoiditis, and there was a significant difference between those patients who had the misfortune to not receive dexamethasone prophylaxis and those who did.

The same can be stated for methotrexate, that there was a significant difference between those patients who did not receive dexamethasone and those who did in the percentage of patients that had chemical arachnoiditis.

Now, on a per-patient basis, the difference between treatment groups was statistically significant and

it favored methotrexate, and this is despite the fact that the patients were, as again illustrated in previous remarks in this session, coming in twice a week for their therapy.

On a per-cycle basis, this was not the case. I should point out that there were several patient in the DepoCyt arm who received more cycles than any of the patients in the methotrexate arms, so when one adds the population of total cycles that were administered, it is a much larger number in those patients who were randomized to DepoCyt than those who received methotrexate. So, the denominator is larger.

[Slide.]

In my capacity as a clinician, I always ask the question, okay, what can I anticipate is going to happen to this patient given an intervention, and one of the concerns that one may have, and certainly I have in my experience treating intrathecal diseases, that patients have the capacity to have terrible pain, and I wanted to ask the question where is there any difference in analgesic use if one examined the patients on the basis of medication groups, and 100 percent of the DepoCyt patients required analgesia while on study, and 83 percent of the methotrexate patients, and this difference is not statistically significant.

If one restricts the analysis to the first 60

days, which incorporates most of the patients, a variant on the so-called landmark approach, and the rationale for this was perfectly arbitrary. It was to pick the so-called induction period and then look at the number of patients that received cycles after that induction period.

There was still no difference in the total analgesic use that was statistically significant either on the basis of medication that was given to ameliorate symptoms or specifically on opiate use, but again, if one uses the same approach of looking for trends, which I can't necessarily subscribe to, but there was a trend that would have favored the control arm in this case.

[Slide.]

So, the safety summary on the Phase III pivotal study is that there were significantly more serious adverse events per patient with DepoCyt than with methotrexate, and 35 percent of the serious adverse events were thought by the investigators to be medication related for DepoCyt with 17 percent thought to be medication related to methotrexate, not statistically significant.

[Slide.]

The profiles of adverse events were similar for the two treatment groups, however, there were some numerical differences in that DepoCyt had a significantly higher

incidence of headache, back pain, fever, neck rigidity, and these might be all folded under the umbrella of chemical arachnoiditis on a per patient basis.

Treatment with dexamethasone, which was used in both study arms, significantly ameliorated the incidence and severity of chemical arachnoiditis, but it didn't necessarily prevent it.

[Slide.]

A pharmacokinetic supporting study, which I will just touch on briefly, enrolled a small number of patients to examine or reexamine the pharmacokinetic parameters of the 50 mg dose in contrast to the 75 mg dose, and the patient population characteristics were very similar to those that were enrolled in the solid tumor study. The efficacy data showed that 2 out of 4 patients in this study group had a response rate. The safety data showed a similar safety profile. The conclusions were again similar.

[Slide.]

I will just touch on the solid tumor patients in the Phase I study, which was discussed in some detail earlier this afternoon. The study design was a dose escalation study. The patient population characteristics were a little different than the other study populations in that we had patients who had been pretreated, sometimes

significantly pretreated. In that sense, significant is not the statistical use of the word, but the vernacular use of the word.

The efficacy data showed that there were responses in this patient group, which I will summarize at the end. The safety data showed a similar profile, but it was possible to get a better handle on an issue which emerged earlier, and that is the dose-response relationship between study medication and adverse events, and the conclusions are similar in that one can see a measure of activity, but that there are also some safety concerns.

[Slide.]

There was in the Phase I study the opportunity to examine the effect of cumulative dose on different dosing schedules, so one could then tease out whether it was an initial dose or cumulative dose that had the effect, and as one reached a threshold above 200 mg, the incidence of the Grade 4, the highest severity serious adverse events increased proportionately, although serious adverse events, as defined by Grade 3, could occur at any dose.

[Slide.]

To summarize the efficacy for the submission, in the Phase III study, there were 29 solid tumor patients, 4 in the pharmacokinetic study, 11 in the Phase I study, for a

total of 44 solid tumor patients.

Using study criteria, 14 responded for an aggregate response rate of 32 percent.

[Slide.]

An integrated summary of safety looking only over the solid tumor patients showed that headache, emesis, and asthenia were the most common adverse events, followed by some of the other symptoms and signs associated with chemical arachnoiditis.

I will summarize off the handout, and because I wasn't going to show any more new data, the frequency of serious adverse events showed that headache again was the most serious adverse event followed by convulsions, fever, and neutropenia, and the frequency of chemical arachnoiditis showed that there was an overall frequency of 64 percent of chemical arachnoiditis of which 4 percent were considered on a per-patient basis definite and serious, another 15 percent possible and serious, for an aggregate serious adverse event rate of close to 30 percent.

So, the summary of risks and benefits is that, number one -- and I will state these slowly -- DepoCyt has activity that is not statistically different from methotrexate in patients with solid tumors who have carcinomatous meningitis.

The second conclusion is that DepoCyt has a statistically significant higher incidence per patient of adverse events and serious adverse events than methotrexate.

The third is that the dosing schedule of DepoCyt is more convenient than that of methotrexate.

The fourth is that the types of adverse events that occurred were similar to those seen with other intrathecal medications.

The fifth of seven is that the adverse events are generally, but not always, but generally amenable to treatment.

The sixth is that dexamethasone will significantly decrease, but not prevent, the incidence of chemical arachnoiditis.

Lastly, and I regret this can't be shown, but that dexamethasone prophylaxis and careful observation must be employed when using DepoCyt.

I will conclude my comments with just two brief observations on the study endpoints and pose the reflection on these questions to the panel.

First is a brief comment on the cytological response. As was pointed out in the literature and in previous discussions, there is a lack of uniformity in how to define endpoint in this disease setting, and the sponsor

and the Agency undertook an experiment to see if it were possible to use a cytological endpoint which would reflect patient benefit in a randomized prospective controlled study.

Using the data from the Phase III study, it was not possible in our analyses to demonstrate any correlation between cytological time to progression or cytological duration or response, overall survival, or any other measurement included in the data of patient benefit.

In addition, it was not possible to demonstrate a correlation between cytological time to progression and clinical time to progression.

So, we are left with the dilemma is cytological response just another way of staging the patients, and is not really of clinical benefit to the patient, should there be some other parameter that we should be examining.

I think the conclusion one can come to is that there was insufficient data in the study to provide definitive comment on the utility of cytological response as a marker of patient benefit for patients with solid tumors who have carcinomatous meningitis.

In short, we can't say it wasn't supported, but there was insufficient data. However -- and thank you for your improvisation in recapturing the slides -- the issue of

clinical time to progression is intriguing because intuitively one would think there would be some patient benefit reflected in that endpoint, and using the criteria in the study and the study data, which we I think mutually acknowledge have some shortcomings, but just to get some insight into this parameter, there was a difference between overall survival and clinical progression in all patients, but there also seemed to be a correlation between the two.

[Slide.]

So, on the last slide, we will undertake, and hope that we can receive some guidance from the panel, in how to use time to clinical progression as a potential endpoint for future studies.

I thank you for your attention.

Committee Questions to FDA

DR. DUTCHER: Questions for Dr. Hirschfeld from the panel? Dr. Simon.

DR. SIMON: You have made the distinction in the toxicity analysis between when you do it on a per-patient or per-course basis. Doing it on a per-course basis, the way you have done it, I don't think is necessarily the way to do it, in other words, if the adverse events are occurring early rather than late, then, just sort of cumulating all the courses and considering them equal does not really

adjust properly. It over-adjusts for the fact that patients may be remaining on study longer for the DepoCyt than for the other.

I think the way you would really need to do it is to do it course by course or time, week by week, or two-week course by two-week course, and compare the incidence of serious adverse events in one randomization arm to the other, and then cumulate -- essentially, it is a stratified analysis in which you combine then those strata rather than the other way.

DR. HIRSCHFELD: I actually did that analysis, and I mentioned it the other way because in the analysis package presented to us, it was expanded to that broader, and I think non-rigorous, definition of per course, and those numbers were presented previously in the discussion, and I wanted to make a comment that we, in fact, have reservations about that approach, too.

If one does the analysis looking at the -- trying to equilibrate over the first three treatment cycles on a per-course basis, there is no statistical difference, but again there is a numerical difference that favors methotrexate.

If one looks at it on a per-patient basis, that difference becomes significant.

Does that answer your question, Dr. Simon?

DR. SANTANA: A corollary question to that is does the sponsor have any information about the pharmacokinetics of repeated courses, or the pharmacokinetic data was only done in cycle one on the 8 or so patients that were studied? Can the sponsor comment on that?

DR. BROCKMAN: I am Dr. Rene Brockman from Chiron. There is virtually no accumulation looking at rough levels in the first and the second cycle in our Phase III PK study. You could not really conclude that there is an accumulation of the CSF levels of cytarabine.

DR. MARGOLIN: A similar question either to the sponsors or to Dr. Hirschfeld, whoever knows the answer.

Is it possible to tell -- and I think it was suggested by this little graph that you made -- whether the incidence of chemical arachnoiditis with either drug is based in part on cumulative and repetitive dosing, which would suggest that even if the frequency per course or on early courses was not higher with the DepoCyt, that this conclusion that patients are doing better and therefore are treated for longer periods of time, they might also run into more likely trouble with the arachnoiditis over time?

DR. HIRSCHFELD: I have looked at that, if I may respond first. The advantage of looking at the Phase I data

were that it was possible to look at if there was a threshold for a particular adverse event, and looking at those data, it seemed that at least posing the question, that that impression could be confirmed.

The difficulty in extrapolating to repeated doses lies in an understanding of the pharmacokinetics, and that is, if one is building a cumulative dose, and the patient then receives over time, within the CSF, a level that would be increasing, that would be of concern.

The data submitted to us didn't seem to underscore or subscribe to that interpretation. It seemed that each dose was in effect a new event for the patient, and so when one would look at patients who received many doses, they were not having a higher frequency of adverse events in their later courses compared to their early courses.

There were some patients who had adverse events throughout their study cycles, and some patients who had adverse events early in their study cycles, but either because they adjusted to it or because they had their prophylaxis adjusted, it was not evident that repeated exposure increased the incidence of the adverse events.

Was there something you wanted to add?

DR. GLANTZ: Probably not something new, but we did display the data in a way that might answer the

question. Most of the incidence of chemical arachnoiditis occurred early on, and was correlated with the use of concurrent dexamethasone. Speaking for myself and lot of the other investigators, we just didn't like the idea of giving patients dexamethasone unless we were sure they needed it, and we became sure fairly quickly, but it took a cycle or two to see that.

DR. MARGOLIN: I think it would be dangerous to interpret these data, to take it too far, because I think two things. One is obviously the denominator is dropping and obviously, you can't tell that that isn't because of patients coming off study because, in part, of the development of arachnoiditis.

The other thing is I think pharmacologically, it may well be that the drug is gone, but the inflammation ma not be, so you could still be introducing new inflammation on top of suboptimally resolved prior inflammation even in the absence of any active drug.

DR. HIRSCHFELD: We actually concur with that and also with the interpretation. One may be, in a setting like this, just be selecting out the patients who are able to tolerate the therapy, whereas, those who don't tolerate it for any number of reasons are no longer being exposed.

DR. SIMON: This is the methotrexate arm?

DR. HIRSCHFELD: No, this is the DepoCyt arm.

DR. SIMON: This then would suggest -- going back to my question -- you know, saying that there is not an increased incidence of chemical arachnoiditis per course, but that is really misleading, because you are adding in all of these later courses where really they are sort of redundant with each other. It is in the early courses where things are happening, you are actually having a higher incidence per course of chemical arachnoiditis in the DepoCyt arm, I would think.

DR. HIRSCHFELD: That is correct, and we did one of our analyses exactly in that way, looking at first course comparisons, second course comparisons, third course comparisons, the first three-course comparisons, and that is as far as one could take that analysis because there weren't patients who extended beyond that.

DR. DeLAP: I am having a little trouble reconciling that with one of the slides you showed that you suggested that -- if I can read from the bottom of the slide -- is said although SAEs could occur at anytime, the highest rate SAEs occurred at cumulative dose above 200 mg, which would imply that the serious adverse experiences might have come about more frequently later.

DR. HIRSCHFELD: They well may, but the

discrepancy arises I think in the study design, comparing the Phase III study to the Phase I study where patients were on different dosing levels, and while the schedule may have been the same, patients would reach cumulative doses at different time periods after starting, and this was then equilibrated, so that all patients received the same starting dose for a period of time.

The affect tended to not be as apparent, but I hesitate to draw any profound conclusions because the number of patients is so small, particularly patients who received cumulative doses above a threshold of 200.

DR. DUTCHER: But when was the decision made to introduce the prophylactic steroids?

DR. HIRSCHFELD: That was prospectively.

DR. DUTCHER: In the Phase III study.

DR. HIRSCHFELD: That was in the study design, yes.

DR. DUTCHER: So they had to have an episode of arachnoiditis before they were given it?

DR. HIRSCHFELD: No.

DR. DUTCHER: Or once you knew that was going to be a problem, they were given it, everybody got it?

DR. HIRSCHFELD: Everyone got it. Everyone was supposed to get it in the Phase I design in each treatment

group.

DR. DUTCHER: In the Phase III design.

DR. HIRSCHFELD: In the Phase III.

DR. DUTCHER: But some of them didn't.

DR. HIRSCHFELD: Some of them didn't.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: We have gotten fairly caught up in trial design issues and things like that. You have had the unique chance to look at all the raw data provided electronically in multicolor.

DR. HIRSCHFELD: In black and white actually.

DR. RAGHAVAN: Or black and white through rose-colored glasses. When you treat patients with carcinomatous meningitis, mostly you treat a very tangible entity. It will be someone with cranial nerve palsies, headache that doesn't relate to chemotherapy, confusion, disordered mentation.

From your looking at those data, do you have a sense of patient benefit? The group I am particularly interested in are the ones who had previously had treatment, so out of the Phase I, do you have data or does the company have data on what actually happened to the patients? Maybe just a few clinical anecdotal or stylized in some fashion.

DR. HIRSCHFELD: The Phase I data are different

than the Phase III data, as you pointed out, there are patients who received regimens and sometimes multiple regimens including intrathecal treatment, whereas, the entry criteria for the Phase III study specifically eliminated patients in that category.

They may have received systemic therapy, but not high dose systemic therapy, and they may have received radiation, which many did, but they could not have received what we would colloquially call local treatment, where one anticipates a significant level of cytotoxic drug in the cerebrospinal fluid.

The Phase I study allowed such patients in, and there were cases where patients, who had not responded to previous therapy, responded to DepoCyt.

The difficulty in interpreting is the small numbers and again we are faced with the issue of the confounding variables of gender, race, tumor bulk, and whatnot. I think and I feel comfortable making the statement that in each of the studies that were looked at, which were really only three, and which is not a large number of patients to extrapolate from to the estimated 2,500 patients per year, but nevertheless, there was evidence of activity, which activity on various counts could be considered patient benefit. That is, from the data we

were given, we could see that patients may have changed their level of analgesic use or may have achieved some intangible benefit, and it is this impression which we are struggling with, because the defined study endpoints, which not to over-discuss the issue, but the defined study endpoints didn't give us the insights into patient benefit, which I think prospectively everyone hoped they might.

DR. DUTCHER: Does anyone from the sponsor want to respond?

DR. CHAMBERLAIN: Yes. I can give you a case scenario from the Phase I trial. A 67-year-old patient with non-small cell lung cancer with metastatic disease at time of presentation received radiotherapy both to lung and femur and eight months later he developed carcinomatous meningitis manifested by impairment in memory, difficulties with gait.

He was treated with C times T methotrexate that I outlined earlier, two months of induction, failed that therapy, was then crossed over to C times T Ara-C, that I also outlined. He failed that therapy, and the patient was then place on DTC101 or DepoCyt in the Phase I trial.

He received four doses and they were dose escalated, and he remained stable for six months following that salvage therapy, until he ultimately manifested disease progression.

DR. DUTCHER: Did his symptoms improve?

DR. CHAMBERLAIN: His gait disorder did not worsen. An important point that is perhaps not evident here, or we haven't made it clear, is that fixed neurologic deficits don't improve in this disease. That has been shown in all three randomized Phase III trials of this disease.

DR. DUTCHER: Confusion?

DR. CHAMBERLAIN: He had modest memory impairment, I didn't say confusion -- I am sorry if I misspoke.

DR. JAECKLE: We are always careful about anecdotal remarks, but the patient from the Phase III study that might be pertinent was a patient who was crossed over. She is a 46-year-old woman with an unknown primary who had gone into remission from her unknown primary source. Systemic disease was controlled. She was found to have carcinomatous meningitis based on severe headaches.

She was randomized to the methotrexate arm, received 9 treatments on the induction, and did not respond. She was crossed over to the DepoCyt arm, received 2 of the cycles, and went into remission. She went through her entire series of treatments as specified in the protocol, went off drug, and remained off drug 16 months without progression, at this time is still doing quite well and is back to work.

Her headaches did go away and she did develop severe headaches early which required shunt placement, and during the time of her 16th month of remission she was no longer shunt-dependent and was able to keep her shunt valve open or closed, and it didn't make any difference.

So, I think in that situation, that is probably the best example from the Phase III study.

DR. GLANTZ: I also hate to talk about just a handful of patients, but we were responsible for a third of the patients in this study, and have had a number of people who have survived for more than a year, and that is just not incorporated in the natural history of this disease.

A young woman who developed leptomeningeal spread of a medulloblastoma on the day she delivered her first baby, and then was treated extensively with systemic chemotherapy and craniospinal radiotherapy, still had the disease at the end of that therapy, and we treated her on protocol. She received DepoCyt. Her headache and her cranial nerve palsy both resolved. They were both mild, and they both resolved. She is now alive and at home three years later. So, benefits of that type do occur.

DR. HIRSCHFELD: I would comment that in reviewing the data, I didn't find the criteria of response as defined to the protocol to be helpful in predicting survival.

Indeed, in all of the studies, there were patients who were called "non-responders," who managed to live quite a bit longer and there are several who are still alive today, who were so-called non-responders. So, it is difficult to tease out all the various factors.

DR. JAECKLE: If I might make one more comment, that the survival data that you have was tabulated as of October 1 of last year, not this year, so there is additional survival in some of these patients that are not incorporated in the data you have.

DR. HIRSCHFELD: We have received those data about 10 days ago, and have incorporated into our comments, and it doesn't change the conclusions.

DR. DUTCHER: Any other questions?

Thank you. Discussion.

Committee Discussion

DR. DUTCHER: Does anybody have any comments they want to make or issues to discuss before we look at the questions?

DR. SANTANA: I just have one comment. I still have a lot of problem equating a cytologic response to a complete response in the way this therapy was given, and therefore how it resulted in benefit to the patient, so I would like to hear comments from one of the committee

members regarding that point, if anybody wants to comment.

DR. HIRSCHFELD: Could you repeat the question?

DR. SANTANA: I said I have trouble equating cytologic response to a complete response in the absence of other supporting evidence. I am using oncology as my background that when a patient is called a complete responder, you look at various parameters to substantiate that response. You don't only use one parameter.

As part of the discussion that we have heard this afternoon, cytology is an issue here in this disease, in which it potentially could lead you one way or another in the absence of other objective data.

So, that was my comment, that I still have trouble equating cytologic response to complete response and how it was defined in this study, and how it benefitted the patients.

DR. HIRSCHFELD: We struggled with that issue, too, and I think everyone has struggled with the issue. The cytologic response should not, and I think never was intended, to be considered in a vacuum, but it had to be in the context of the absence of clinical progression.

Given that, there was a rather narrow definition established in the protocol for what we normally would call CR, when we all know that this wasn't a patient who had a

complete response. This was a patient who had a definition that was met, and to equate the use of complete responder, a complete response in this context to the broader context, so we understand is not correct, and one of the issues again being addressed is what is the value of having this cytological response for future designs.

Another aspect that was struggled with, at least we struggled with, was how to interpret imaging, and the difficulties with imaging is aside from knowing who has a bulky lesion and who doesn't, we all know that because of the heterogeneity and the exquisite detail and architecture of the central nervous system, a patient can be asymptomatic with a fairly large lesion, and a patient with a very microscopic lesion in a particular anatomic site could suffer greatly or could have a fatal event.

So, to use imaging as a confirmatory modality, we couldn't find a way to work that into an algorithm other than progression.

DR. KROOK: At least in the clinic, in answer to your question, the way I would look at it is when you do these, look at the spinal fluid, the patient becomes very much aware very quickly what does the spinal fluid show, and I, as a clinician, am always grateful to say negative.

However, I am the first to also realize, but I

don't tell, it doesn't mean as much as they think it is. Now, one can see clinical improvement when one tells a patient that suddenly what is positive becomes negative, and that confounds the issue even more, and I agree, I don't think that you can call a complete responder -- I mean a cytologically clean one -- a complete responder, so it is a different thing.

But, boy, people can change once you say it is negative, although you realize the next time they come in, you could reverse it all. That is just dealing with people.

DR. DUTCHER: Why don't we look at the questions.

Carcinomatous meningitis is a late stage complication of solid tumors for which there is no consensus treatment. There are two currently approved medications for intrathecal use, methotrexate and cytarabine. This NDA presents data from 3 small trials of patients with carcinomatous meningitis, 61 patients in a Phase III randomized comparative study, 4 patients in a pharmacokinetic study, and 9 patients in a Phase I study. The efficacy results are summarized in the following tables.

We will take a few minutes to look at the tables.

The first shows summary of response in solid tumor patients.

DR. HIRSCHFELD: I just wish to clarify that the

tables represent only a subset of the total patients, and not all of the patients, and that is an important point to clarify, although having said that, I don't think the conclusions differ. The tables include only the ones that were called responders, and not all of the patients, but I think whatever conclusions one may draw, the strength of the conclusions didn't vary between looking at the subset that was called responders or the total population.

DR. DUTCHER: So, Question No. 1. Can the trials that produced these data be considered adequate and well-controlled studies?

DR. MARGOLIN: I guess I can throw myself to the lions. I don't think that the trials that constitute the support for this NDA can be considered adequate and well controlled for the purpose of approving this drug, for this indication.

My primary reason for saying no to this is that we have really the results of one very small Phase III, I would say in quotes, trial, because of all sorts of statistical problems in terms of what you called the trial and what kind of comparisons you can really justify making.

The most compelling piece of evidence favoring the DepoCyt is the single graph with a significant p value favoring the difference in clinical time to progression,

which I still feel progression, which I still feel could conceivably be strongly biased by many other things, most of which we talked about, and I think it would be very important to have some kind of a confirmatory trial before being willing to take the data from this study to approve this drug.

DR. SANTANA: I was just going to say I voice the same concerns and have the same opinion.

DR. DAVID JOHNSON: I would like to offer a slightly counter view in the sense that the question -- we went through this once before at one of these sessions about the adequacy of the trial and whether or not we could go forward with it or not, and I think there is a couple of issues here.

I think in a traditional sense of trial design, most of us would prefer to see a larger trial with larger numbers of patients in which we could do the kinds of statistical gymnastics that we have been talking about this afternoon.

I think, pragmatically speaking, the point was made by Dr. Hirschfeld that this is the largest such study that has been conducted to date, published or otherwise I suppose, and it is a group of individuals in whom -- I mean that we are not likely to achieve the kinds of numbers of

patients in our lifetime in a prospective way.

So, with that caveat, it is clear to me that the sponsors and the FDA came together to come up with a compromise, that at some point five years ago was felt to be a reasonable compromise, to begin to look at the data to ask the question, and I wonder if maybe the way we should answer this question is in that context.

Was the trial adequate and do the data we have give us sufficient confidence to make a conclusion about the efficacy or lack thereof? I think that is a slightly different question that I can answer maybe in a different manner than I would answer this. I think the trial is designed, given all the caveats that we have said, to the extent that one can design such a trial that try to answer the question that was posed to us.

So, I would say in deference to my colleagues I agree with them, know where they are coming from, I would say yes, given the situation, given the disease type, I would say yes, this is adequately designed and controlled.

Now, we can talk about the data in a moment.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I actually disagree with Dr. Johnson's view, and I would like to take the question as it is placed. This is not a criticism of the investigators, it

is not a criticism of the FDA. I always thought I would like to play professional basketball, but I am 5 foot 9, and untalented in sport. That is just an observation. The two things are completely separate.

So, the question here is, is it an adequate and well-controlled trial, and because they don't have the patients to answer the question, the answer I think is a no-brainer. No, it isn't. There are a lot of extenuating circumstances and what we do with this information comes up in the subsequent questions.

The reason that I tend to agree with the first two speakers is that I don't think we should be setting precedents of what constitutes adequacy. It is tremendously unfortunate that the investigators had an impossible target that was set. That is not their fault, they didn't do badly, but the reality is that because it is an uncommon heterogeneous entity, they were set an impossible target, so the answer to the first question I think is easy. It is not an adequate trial. It may well be that we can say that and then still say what can we do with the data coming out of a trial that doesn't answer the question.

DR. DeLAP: This reminds us of a discussion we had a recent prior meeting where there was a discussion of adequate and well-controlled trials, and then there seemed

to be some misperceptions of what could be done after it was determined that the trials were not considered adequate and well controlled.

It really is regulatory point. Do these trials provide the kind of data that can be used to make a regulatory decision, and that is really the meaning of it. Certainly it is not are the trials perfect. I don't think any of us would go to that length. But are the trials suitable for reaching a regulatory judgment, I think that is the way you have to look at the adequate and well controlled phraseology.

If you indeed believe that there is no way based on the way the trials were designed and conducted to reach any regulatory conclusion from the trials, then, they may not be considered adequate and well-controlled trials for the purpose, but if you do believe that there is any possibility of reaching a regulatory conclusion based on these data, then, I do think you are saying that you do think that they are adequate and well controlled to be able to make a decision.

DR. WILLIAMS: Part of it depends on which endpoint you are talking about, and I think with the last advisory committee, we started going back and forth with the data and to this question, and I would suggest maybe we

answer this question a little later after we talk about what endpoint we consider sufficient.

If you consider response rate in an uncontrolled trial to be sufficient, then, you might give one answer. If you consider a comparative analysis of time to progression to be the pivotal factor, then you might not consider it.

So, I think maybe it might be wise to put this off a bit and find out what you think the main endpoints are.

DR. SIMON: I guess I would disagree with that. I would interpret it as meaning for determining the safety and efficacy of the treatment.

DR. WILLIAMS: But it depends on what you define as efficacy.

DR. SIMON: Well, we will get into that in later questions.

DR. WILLIAMS: Right, but now we are answering the question before that.

DR. SIMON: It means do we find that these trials are well controlled and adequate for judging that there is clinical efficacy and safety for this treatment.

DR. SWAIN: I think that the primary endpoint at least that the sponsor said was the cytologic response, that was the primary endpoint for efficacy, so I think we have to make a judgment as to whether we think that that is

appropriate.

DR. MARGOLIN: I think probably, if I can interpret Grant correctly, is that the last time we had this discussion, if you answered no to the first question, you couldn't even answer any of the other questions because they became moot. If you sort of quickly skim over the other questions, I think we can probably answer Question No. 1 and still give a stab at answering the other questions on a certain assumption that we can use the data.

DR. HIRSCHFELD: I just want to clarify that the cytologic endpoint by itself is not the entire endpoint. It has to be the cytologic endpoint in the absence of clinical progression, that is, clinical progression will negate any so-called response.

DR. DUTCHER: I would like to add that our interpretation of all of the endpoints is what goes into the decisionmaking here.

DR. OZOLS: I think that what the Agency and the sponsor looked at five years ago, and what they came to the agreement, I think takes into account all of the problems that we talked about, the disease, and the problems in it, and so they put as many patients on as was expected of them to do. So, I think in this particular instance, I think this trial was -- I would agree with Dr. Johnson -- is yes.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I would strongly disagree with that because I don't see anything in this trial that provides any evidence of clinical benefit, and I think the time to progression is totally biased and unreliable, and I don't see -- if we confirm cytologic response as originally defined in the protocol, the response rate is very, very low, which would make you question if there is any efficacy, and the other, the redefined cytologic response rate seems to be an unconfirmed thing. My understanding is that that really is just not acceptable.

So, I don't see any evidence of clinical benefit here.

DR. DUTCHER: That is not the question.

DR. SIMON: No, so, well -- I mean I think the --

DR. DUTCHER: The question is can you determine that from the study.

DR. SIMON: The trials, part of the endpoint I would think would be -- I mean part of the way the trial was done, and the endpoints that it evaluated, would be part of the structure of the trial that we would be judging.

DR. DUTCHER: That question is does the study as designed provide sufficient data to come to a decision about the drug. That is what an adequate and well-controlled

trial is. It can be a negative trial, but the question is did the study provide sufficient data to answer the question about the drug.

DR. DAVID JOHNSON: This is a tremendous dilemma I think for the company.

DR. DUTCHER: Let's go to the other questions.

DR. DAVID JOHNSON: I think we need to decide whether we -- I mean if we decide -- there is no reason to go to the other questions if we don't think that we can derive any useful information, and I think this is -- this is the second straight session this issue has arisen, and I think we are trapped in some of the activities that we are accustomed to doing, and with larger numbers of patients in trials that are more easily -- with more easily definable endpoints, and I don't think any of us are disagreeing that if this disease were rampant in the community, we could to the kind of trial we want to do.

But I do think that we do have to take into account the decisions that were made five years ago, the company was asked to do those things, and it seems to me that whether we agree now that that was the correct thing to do or not, they did in fact do that.

Now, that doesn't say that I am going to tell you that I think that they did it correctly, but the question

was did the trial -- is it adequate and well controlled, and I think it was controlled, and it was adequate as defined by their consultation with the FDA.

Five years later, we can hindsight and say, well, we wish we had done this, or we wish we had done that. We are going to talk about that if we decide the trial was well controlled and adequately designed.

DR. DeLAP: Again, I would just add that it is a separate question than outcome. We are asking this to -- because before you can judge the outcome of a trial, you have to say that, well, the trial was done in such a way that the outcome has meaning, and that is really what I think the adequate and well controlled phraseology means, was the trial done in such a way that the outcome has meaning, and now, if so, then, we can discuss what the meaning is of the outcome.

DR. MARGOLIN: I do agree with Dr. Johnson in terms of the frustration about having to deal with a trial that is not quite as pristine as what we would like to see, but I also think it would be a lot easier for all of us if during the these discussions and these trial designs, some very specific statistical outcomes and requirements were outlined, and then it would be a lot easier once the study is closed and analyzed, to simply ask whether the original

statistical plan was followed, whether the original requirements for showing X, Y, or Z were met, and whether the data are clean as evidenced by appropriate audits, et cetera.

It seems like there is quite a lot missing from the way this trial was designed and the various things it went through in discussions with the FDA, which left us to try to analyze it without really knowing what it set out to do and what the requirements were, and now we are trying to decide post hoc whether it met requirements that weren't set out at the beginning.

DR. DUTCHER: Shall we vote on the first question?

Can the trials that produced these data be considered adequate and well-controlled studies?

All those who would say yes?

[Show of hands.]

DR. DUTCHER: Three.

All those who would say no?

[Show of hands.]

DR. DUTCHER: Seven.

Abstentions?

[One abstention.]

DR. DUTCHER: One.

So, we have a split vote about the adequacy of the

trial. Do you want us to proceed? 7 to 3 and 1 abstention.

DR. DeLAP: Well, I think the second question still has meaning. I am just looking here to see.

DR. WILLIAMS: I would suggest we go ahead and vote on the others as if the other one were answered, because it could always be reconsidered by the Agency.

DR. DUTCHER: In patients with carcinomatous meningitis from solid tumors, is the cytological response of the CSF sample in the absence of clinical progression a surrogate endpoint that predicts clinical benefit?

Discussion. Dr. Santana.

DR. SANTANA: The problem with this question is obviously the sensitivity and specificity of the cytologic response, and I think we have heard some discussion this afternoon about how inaccurate sometimes cytology can be in assessing these patients.

So, my comment would be that in order to answer that question, one has to consider the adequacy of using cytology as the primary variable to assess response, and therefore how that can be tied in to the absence of clinical progression.

So, it is a tough one, too.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I would simply say that despite al

the technical things which I think is just a matter of people agreeing on who looks at the cytology, is that until we have a therapy that we know actually works in a fraction of patients, we are not going to be able to really correlate the cytologic response or the clinical response or absence of progression.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I think the problem -- and I understand the trap we are in -- but the problem is that you sort of worry about logic here. By definition, in this clinical context, the absence of clinical progression predicts benefit because these patients die, so it is hard to say no, because if you have cytologically negative patients who happen also to have absence of clinical progression, those people who treat this disease know that no clinical progression is good, because otherwise they die, and they mostly do.

So, I am just very perturbed that we are kind of going to come up with the wrong answer in way for good reason, so I think, for me, even though -- I mean I like the way the question is phrased. It doesn't say is it a wonderful surrogate, it just says is it a surrogate, and for ten cents, cytological negative and no clinical progression is a perfectly fine surrogate in the real world in this

disease.

DR. DUTCHER: Dr. Johnson.

DR. DAVID JOHNSON: I just want to make one observation, and it is an obvious one, but it probably ought to be restated for the record, and that is, in the presence of a positive cytology you are sure what you have. So, cytology can't be ignored. I mean it's an obvious, a positive is positive. A negative is, in this case, we are not terribly sure about.

I mean I agree with the comments that Derek has made about if it looks like a duck and walks like a duck.

DR. HIRSCHFELD: After Dr. Simon -- I know he wanted to make a comment -- I would like to follow up with a comment on the value of the cytology.

Dr. Simon.

DR. SIMON: The concept of surrogate means that essentially, that if you have a therapy that increases the cytologic response rate, that you believe that that would cause clinical benefit, in other words, so you could have a situation where patients, you have a certain distribution of time to neurologic progression, and you may have a new treatment that provides cytologic response before you get neurologic progression, and that new treatment may have no effect on time to neurologic progression, and it may have no

clinical benefit whatsoever, but what it may do is cause cytologic response.

With this definition -- this endpoint given here of cytologic response in the absence of neurologic progression is not a valid surrogate because a drug which causes -- because you can have a drug which causes cytologic response without prolonging time to neurologic -- so that is the distinction. There is a distinction between saying is this prognostic, is this definition, does it define a prognostic factor, and does it define a valid surrogate endpoint.

I would agree with you that it defines a prognostic factor, but it does not define a valid surrogate endpoint.

DR. HIRSCHFELD: The phrasing of the question may reflect, for those who would understand, some aspects of mid-rush, in the sense that what we are asking is cytological response, and not necessarily negative cytology, and we have seen patients where the cell count goes from several hundred to some low number, but it never gets to zero, and those patients percolate along for quite some period of time, but never reach negative or zero, and so I wanted to put that point in the discussion, that we are looking for some guidance on how to use the cytology, and

not necessarily to consider that the cytology has to be negative.

DR. KROOK: I guess I am going to speak from experience because the presence of a positive cytology in the presence of a stable patient has not stopped me from giving more drug.

Now, obviously, if you have positive cytology and clinical benefit, you are going to go on, but as I look at this question, if I have a positive cytology, and the patient is stable, I am going to go on and treat him again. So, I think it becomes, in my mind, a bit -- I mean it is nice to tell the patient it is negative, but I also realize the problems with the cytopathologist looking at it.

So, as a clinician, I am trying to say is the patient better or worse, and I would base that on my clinical judgment, not on the cytology.

DR. MARGOLIN: I think the other problem with using the data from the study is that these two things were linked in the study. These were the two criteria for the response, and so we almost really have to look at the literature or people who do this a lot, and look at what the splay is between the development of a negative cytology after it has been positive, and the correlation or lack of correlation between that and clinical progression.

DR. DAVID JOHNSON: Can I clarify, because this is a new phenomenon to me, to know that you can quantify cytology in the CSF. To me, it is positive or negative. I mean is this suddenly a new phenomenon, or is this something that everybody knows and I don't?

DR. HIRSCHFELD: I found it different in submitting patient samples, that there is some pathologists that will --

DR. DAVID JOHNSON: You can take the same sample and send it 50 times and get a different number.

DR. HIRSCHFELD: Right, so that is part of the difficulty.

DR. DAVID JOHNSON: No, it wasn't part of the difficulty for me because I understood a cytologic response to be exactly that, a negative cytology.

DR. WILLIAMS: I think our main thrust is the way that they are used in this trial as in the next question.

DR. DAVID JOHNSON: Are the sponsors using a different definition of cytologic response, are you quantifying it?

MR. THOMAS: No. The protocol was written at a time when there was no quantitative method developed. The study was started. The central cytopathologist, Dr. Barry Schuman, who did the secondary and blinded reviews,

developed a quantitative algorithm for measuring cell counts and change in cell counts. Those data were submitted as part of the NDA, but since that was not part of the prospective endpoint, it was not used for making any of the decision criteria you have seen, but the data are available.

DR. DAVID JOHNSON: I would like to see it, but it sounds like being a little bit pregnant to me. Are there data, I mean did he show a correlation?

DR. CHAMBERLAIN: Actually, I have written on this subject. It is probably not familiar with all of you or at least it would seem to by this discussion. This was an article that was a subset study of the Phase I trial. I didn't present that data. It was done by our cytopathologist at UCSD, and we actually quantified CSF cytology and looked at this concept presented that there are, in fact, PRs and MRs much as we have become accustomed to in radiographic responses.

So, this has been done, but since this is somewhat idiosyncratic with institution, we didn't feel that this was appropriate to expand to all centers involved in this trial, but this is certainly -- probably speaks to this concept that you have a diminution in total tumor cell burden as assessed by cytology and a stable disease state that allows these patients to continue on therapy as you see in your

clinical practice.

DR. DAVID JOHNSON: You were able to do this on a Phase I trial?

DR. CHAMBERLAIN: We had innumerable CSF cytologies, and we could follow the cytologies serially over time.

DR. DAVID JOHNSON: In a Phase I trial?

DR. CHAMBERLAIN: Yes.

DR. DUTCHER: Can I just ask that for the purposes of the cytology as purported here and in this NDA, it was positive-negative, correct?

MR. THOMAS: Yes, but then data was submitted along with this quantitatively, and Dr. Schuman, who carried out this analysis, can explain the data that was submitted.

DR. SCHUMAN: I would like to introduce myself. My name is Dr. Schuman. I am a consultant to this project. I was asked to review the slides that were sent from multiple institutions to determine if they were positive. That means whether they were numerous or a few malignant cells or suspicious, also, if they were negative or if they were unsatisfactory or they could not be evaluated.

Since 1985, there have been institutions involved because there is a problem, and I do think clinicians need to know if the therapy has had a reduction of the cells or a

decrease in perhaps the amount of disease.

I think one of the problems that I saw in the field of hematology is quite often we feel we have a positive response, but we cannot always get rid of the rare numbers of cells.

I think in this study, as defined by both parties, a rare event would still be considered positive. Clearly, we have quantitative data. I am very, very pleased to be a part of the study because we had agreement of positivity at a very high rate with multiple institutions.

Clearly, I am not able to comment on the response as it relates to duration of cure because we are still evaluating that, but I have seen situations where upon therapies, a reduction in the number of cells, from 100 percent, greater than 10,000, to less than 5,000, at which there are no malignant cells is a fairly common occurrence.

So, I do think clinicians -- and I am not here to endorse cytology -- but I am here to endorse the need for clinicians to have something to go along with them as an objective measure as they look at clinical status of disease.

DR. MARGOLIN: Just one more question for Dr. Chamberlain. In your study, you didn't mention, was there a correlation between these quantitative groups and a clinical

outcome? I am sorry, I didn't read it.

DR. CHAMBERLAIN: That's okay. It was in an obscure neurologic journal. I would expect none of you to probably have seen it. But, no, that correlation was not made. This was strictly an evaluation, was it possible to quantify CSF cytology, and to perhaps derive some new meaning to the concept of cytology response.

DR. OZOLS: I think there is a logical problem here. I am absence of clinical progression is a clinical benefit. So, you are asking cytologic response in the absence of clinical progression, is that a clinical benefit, well, there is two factors, is there a cytologic response in the absence of clinical progression. Are you really asking is a cytological response per se a predictor of clinical benefit?

DR. SIMON: Suppose you had two patients, both of whom have an absence of clinical progression, one of whom has a cytological response, and the other one doesn't. Do you believe that the one who has a cytologic response is demonstrating clinical benefits more than the other?

DR. OZOLS: Well, that is the question.

DR. SIMON: But that is what this is asking.

DR. WILLIAMS: I would agree that is what we are asking.

DR. DeLAP: I would phrase it slightly differently. I would say that in this definition, we are saying given that the best that you can do in terms of clinical status is no further progression, if we are talking about deficits from meningeal disease that may be fixed, the best you can do is no further progression. For cytology, the best you can do is reversion from positive to negative.

So, if we take those two domains, as it were, when you say we get the best result we can get in each of those, does that make a surrogate? No. If I had this condition and my choice was to have cytology negative and no progression, or cytology positive and no progression, I know what I would choose.

DR. SIMON: You don't know that the drug caused the lack of progression, and so given that the patient -- I mean since you don't know whether the drug will cause a lack of progression, given two patients, both of whom who have a lack of clinical progression, this proposed endpoint says that the one who has cytologic response is considered to have clinical benefit, and the one who doesn't have the cytologic response is not considered to have clinical benefit.

DR. DUTCHER: And the answer once again is we don't know because you can have a negative cytology and

still have disease.

DR. OZOLS: As Dr. Krook pointed out, in practice, if you decide to treat this group of patients who became symptomatic, and they become -- they are not progressing, you probably aren't completely influenced by the cytology, you would continue to treat until something happened.

DR. DUTCHER: Can we answer this?

DR. DeLAP: I think what we are asking is, is there an acceptable -- unless the question has changed given the answer to the first question -- at least what I am interested in hearing is, is there an acceptable surrogate marker here, and if so, is this it, or there something else you would say.

I mean clearly, if the cytology doesn't get better, and the patient doesn't progress, then, it is hard to say if the drug is doing anything. It may be the patient just hasn't happened to progress yet.

DR. SIMON: I think the appropriate endpoint on a study like this would be a neurological evaluation by someone who is blinded to the treatment that the patient is receiving, and that is what the endpoint should have been.

DR. RAGHAVAN: That speaks a lot more faith in the neurological evaluation than I have, and the problem is it depends who does it, and it depends on whether they fought

with their wife on the way into the room, and it is another one of these non-quantifiable things.

Given the fact that the role of this committee is to advise, I am really worried that we are going to go and get so incredibly tangled up in jargon that the Roberts won't have any idea what we are trying to say.

So, I would like to just go on the record as saying what I think, and then I feel I have done my part, which is to advise the Roberts.

So, what I think is the following. I think that this was a flawed trial, not flawed in design, but flawed in execution because of the numbers, and I don't think that it is possible to do a very good trial because people just don't put patients into trials.

I don't think there are data that make me think that this product is better than methotrexate, and that's fine because that is not what they, I don't think, are claiming. I think the data, as I read it, say it is approximately equivalent as best we can tell, but more toxic, and so as a clinician who treats carcinomatous meningitis once in a while, I would normally go for the less toxic drug.

What I learned today, which I think is actually important, and I hope doesn't get thrown out with the baby

when the bath water is going down the drain, is that this is an agent that sounds to me like it could potentially be a useful drug second line.

It seems to be associated with -- whether it actually causes them or whatever the association -- it seems to be associated with sustained responses in some patients who failed other treatments including a different formulation of cytosine.

So, I don't know how we are going to answer all the questions, but I just think it is important that someone says that it sounds from the data we have heard that there are patients that benefit from this, and there may be a small and defined role for it.

I don't disagree with any of the statistical comments made because they are valid statistical comments, but we just have to keep the broad clinical context in mind, as well, I think.

DR. DUTCHER: Do we define for the Bobs, the Roberts, a surrogate? That is really what Question 2 is asking. I mean is it a combination of neurologic evaluation and clinical progression and cytology? Would you put all of that together when you are making a clinical gestalt of how somebody is responding or not responding?

DR. MARGOLIN: I think if we are looking for a

good trial -- and I think this one was actually better executed than it was designed -- but I think 2 and 3 go together and that it would be quite reasonable to use the combination of a cytological response, and then you can decide whether you believe in quantitative responses or not.

In the absence of clinical progression, that is a very reasonable endpoint since we don't have any better one for meaningful responses and clinical benefit in these patients.

DR. WILLIAMS: Why don't you vote on No. 2.

DR. SIMON: I am sorry. Wasn't that what was used?

DR. WILLIAMS: That is, right. That is No. 2.

DR. MARGOLIN: Which means I am saying the answer is yes.

DR. SIMON: So, you believe that is a valid surrogate?

DR. MARGOLIN: I think what we have seen is that, in practice, different members at the table believe different things about the meaningfulness of the cytology, whether it is quantifiable, whether it means anything, so obviously, the strictest you can be is to have a negative cytology in the absence of clinical progression.

If you do a trial like that, you have more

patients, you have more differences, et cetera. I don't think anybody would find fault with --

DR. WILLIAMS: So, you are saying if there is a way to truly define negative cytology, combine that with the absence of clinical progression, and that is the question.

DR. MARGOLIN: And that would be, as Bob DeLap said, the best of both worlds and the best you can do.

DR. SIMON: Well, I mean to me the problem would be -- I mean it sounds like the clinical -- again, I guess I haven't heard here why you believe the negative cytology is evidence of clinical benefit. So, I guess I haven't heard anything that really provides evidence that negative cytology -- because in these two patients that I was hypothesizing, that the one with the negative cytology does anything that indicates that that patient is receiving benefit, and the other one is not.

The problem with absence of clinical progression is the subjectivity of it, at least the way it was implemented.

DR. MARGOLIN: Then, you have to say the same thing. You have to trust your tests. So, these I think imply that you trust your tests, you trust your neurologic tests, and you trust your negative cytology, because if we can't trust any of the tests, we can't vote on any of the

questions.

DR. DeLAP: I would come back to how I would interpret the word surrogate, and surrogate means that you are not absolutely certain. Unless you are absolutely certain that cytologic response meant that the person is going to live longer, then, it is no longer a surrogate, it becomes a legitimate endpoint in its own right.

DR. DUTCHER: Well, the fact of the matter is this is what we use. I mean what do we use? We use the physical exam, the neurologic exam, and the cytology, and we use two points on the curve sometimes. We may not accept one. I mean we have all argued about what does a negative cytology mean. Well, if it is negative this week, next week, and the week after, and the person is still walking straight with no new findings, then, you might believe that the first one was really negative, but sometimes you need two or three points on the curve.

So, I mean there is nothing else we can use. Right? I mean what else are you going to use? CT scan is not going to help you.

DR. DeLAP: And the fact that we don't know for sure how good it is doesn't mean that it can't be used. It simply means that once you see it, you have to have other evidence to validate whatever finding you obtained.

DR. SIMON: We are talking about 2 or 2 and 3?

DR. DUTCHER: Let's vote on 2. You have read it.

All those who think that absence of progression of clinical findings and cytologic response are surrogate markers for clinical benefit, please raise your hand.

[Show of hands.]

DR. DUTCHER: Five.

All those who believe it is not?

[Show of hands.]

DR. DUTCHER: Five.

Abstention?

[One abstention.]

DR. RAGHAVAN: Do you sense confusion?

DR. DUTCHER: Five yes, five no, and abstention.

No. 3 is going to also probably have the same outcome.

The results show a longer Clinical Time to Progression for DepoCyt, together with evidence of cytologic responses in the controlled and two other very small trials. Is the clinical endpoint, together with evidence of cytologic response, substantial evidence of the efficacy of DepoCyt?

I suppose that in this, the clinical endpoint is time to progression.

DR. JUSTICE: If you vote yes on 3 and 4, we have to go back and change your vote on 1, which would be unprecedented.

DR. DUTCHER: Does anybody want to talk about time to progression?

DR. DAVID JOHNSON: I think those issues were pretty well fleshed out in the discussion for this trial, and I think that really is -- that is the flaw, and that is the bottom line on the trial. That is why even if we all agree that it is an appropriately designed and conducted trial, the bottom line is the endpoint was flawed. I personally would vote no on No. 3.

DR. DUTCHER: So, is time to progression substantial evidence in a comparative trial of the efficacy of DepoCyt?

Those who would vote yes?

[No response.]

DR. DUTCHER: None.

Those who would vote no?

[Show of hands.]

DR. DUTCHER: Ten no's.

Abstain?

[One abstention.]

DR. DUTCHER: One.

Question No. 4 is regarding the incidence of adverse reactions in patients in all trials for treatment of carcinomatous meningitis, chemical arachnoiditis by patients and cycles at various levels.

Given the incidence and severity of chemical arachnoiditis seen with the use of DepoCyt, and considering the efficacy demonstrated, discussed in Questions 2 and 3, do you recommend that this be approved for the treatment of carcinomatous meningitis?

Now, Derek has already stated that he would recommend it?

DR. RAGHAVAN: For methotrexate failures. I could be comfortable to approve it in that, but that is not the question.

DR. DUTCHER: That is not the question.

DR. DeLAP: Well, I think we are interested in knowing if you would like to make it available for some subgroup of patients, if that is something you want to say.

DR. DUTCHER: I think some of the side conversations have been the dilemmas of survivors getting the new drug because there are subgroups of patients that are different, and when we are talking about people that have already had three drugs, and then can get a fourth, that always brings up a discussion of is that an individual

type of patient that is different.

DR. WILLIAMS: Do we have the data on the total number, the response of methotrexate failures? I mean have we seen that?

DR. MARGOLIN: I think we have to be very careful about these anecdotes, that they really sound nice, but I think we all have patients with very indolent diseases, and the other problem is that judging the failure or progression in patients who aren't on a clinical trial is different than judging when patients are on a clinical trial, so you just have to be careful about how they were judged as failures before they came to the clinical trial.

DR. DUTCHER: Any other discussion?

DR. KROOK: Looking and listening, this drug in my opinion is probably similar or equal to methotrexate. I mean that is where I get into problems is that it is at least equal, and if I heard the discussion right, part of the original one was to demonstrate equivalence at least. I mean if somebody can correct me, at least that was some of the initial discussion, and it is a bad disease, we have all said that. It seems like it does have a place in here somewhere, and it comes down to clinical choice for an investigator. Would I use this drug? Yes. I mean I am not happy with methotrexate.

DR. WILLIAMS: One of the reasons for asking the first question later, I think was it depends on which endpoint you think is important.

DR. KROOK: To me, as a clinician, I would use this drug. I am certainly not happy with the results on methotrexate. It is a terrible disease, and I am saying what everybody knows.

DR. SWAIN: But why would you use this drug? I mean I think that we don't really have any evidence of efficacy except a cytological response plus the toxicity is higher.

DR. KROOK: Real simple. I would avoid tapping somebody if I am going to treat them. Now, first, you have got to decide you are going to treat somebody with this disease, and I think, Sandy, a lot of us would not treat people with this disease. Many people, I say, hey, you know, let's find a hospice for you and let's go.

But if I were to, then, every two weeks is a lot easier on me, as a physician, than twice a week although we also use the reservoir, which makes it easier on me, and it is at least equal. So, I guess that is what I look at.

DR. SWAIN: Well, I guess I am still struggling with the clinical benefit that Dr. Simon was discussing before, and I feel like I have not been convinced at all

that there is any clinical benefit to the patient, and that the toxicity is very high, and I wouldn't want to spend the last three months of my life with a severe headache.

DR. DAVID JOHNSON: I think that is the other element. I mean if you look at survival and response, there is no apparent difference for the data the showed us. They chose not to present the quality of life data to us in a detailed fashion, and that is the other reason we have approved a drug is because we have seen an improvement in quality of life.

What we have seen is an increase in SAEs, and I agree with you, Sandy, I don't tolerate a headache very well, and certainly not a three-month headache. Ninety-some percent were getting that. That has not been my experience clinically with methotrexate, which I have used a fair amount intrathecally.

So, my vote, had we gotten to this, would have been no for those reasons. I don't see a clinical benefit, and the convenience factor is nice, but not if it is at the expense of increased toxicity to the patient. I don't think any patient wants to be more conveniently toxic that I know of.

DR. DeLAP: In looking at this indication and to a lesser extent this particular product, one of the issues for

us is that it is just the difficulty in developing products in this indication and again, I think it has been said before this afternoon that this represents one of the biggest efforts to mount a randomized controlled trial that we have seen in this area, if not the biggest. It is probably unrealistic to expect that we would see larger trials that could be sliced and diced in additional interesting ways.

As a practical matter, then, would -- perhaps I am anticipating the vote on this last question -- but would the suggestion then be to look for more patients who are treated in a refractory setting after a failure of methotrexate, and look for more anecdotes, or what is the pathway?

DR. DUTCHER: I guess I am a little surprised that the route here is solid tumor, since this is a drug that has been associated with the treatment of hematologic malignancies, and that certainly leukemic meningitis, lymphomatous meningitis, CNS lymphoma is not terribly rare.

So, I guess I am surprised we haven't seen that, and if we haven't seen that, I mean if that data were spectacular or as good as the drugs that we are using or better, then, that would make it a little easier to say it is available and sometimes it works in solid tumors.

DR. DeLAP: So, you are more willing to accept the

intrinsic activity, say, of cytarabine in hematologic malignancies, and then you wouldn't need to see as much evidence, say, of superiority of a new treatment necessarily to think it was also active?

DR. DUTCHER: That is my opinion.

DR. SANTANA: I think that is an important point that has not come up this afternoon is why use cytarabine in solid tumors. I mean if you believe the NCI panel screen, that is a different story, but I think if you ask around this table, most of us in general would say that Ara-C is not an active drug in solid tumors, that is why we don't use it.

So, I think it poses the question that Janice was presenting, which is I think we need to look at different patient population, and there you probably could demonstrate some benefit.

DR. MARGOLIN: I think when we see the lymphoma data, which sounds like that is going to be the next dataset that we will see, became leukemia is fraught with some accrual problems, and perhaps a single arm, an additional group of patients just treated with the DepoCyt.

It would be very reasonable to revisit this data as data in support or along with the approval for lymphoma, and we might be more convinced. There may be something more

that convinces us of the correlation between clinical benefit and negative cytology, et cetera, and safety.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I think that it would be a shame to ignore data from three neuro-oncologists that while I understand and believe in the flawed use of clinical anecdotes, I think, you know, it is the same sort of story when you go back to the early testes cancer days, we didn't need a randomized trial to support the use of platinum-based chemotherapy.

I don't mean to imply that we don't need data here, but I think there may be a kernel of information that is worth pursuing. On what we have heard today, I think it is perfectly appropriate not to approve this for second-line use, but I think that if the company and its investigators can confirm data that relate to salvage use, I personally don't think that you see patients with carcinomatous meningitis who survive any lengthy period without unusual luck.

There is the occasional anecdote. Dave and I were talking before about our own practices, of patients who have survived with carcinomatous meningitis, and, sure, we have the occasional anecdote. Now, maybe that is all we have heard today.

But if the investigators are convinced that they are having an impact on the natural history of carcinomatous meningitis, I don't think it particular matters that cytosine arabinoside is a very poor drug for solid tumors. If one took that hypothesis and left it there, then, one wouldn't have gencitovine, which is just a modification of the molecule.

I think my point is that this may be a unique clinical indication, and it would certainly be reasonable to pursue this a little more in a very carefully structured Phase II setting you have seen today. You would have to have very good data, but it may be that there is an indication there, but you don't have enough data to prove it today.

DR. HIRSCHFELD: I think also we shouldn't equate free Ara-C with liposomal Ara-C in terms of our perceptions of the utility.

DR. JUSTICE: Hopefully, this is the last comment, but I am just a little concerned about the refractory meningeal carcinoma towards this setting, as to how you are going to demonstrate clinical benefit, because I think you are not likely to see reversible fixed neurologic deficits. You may see some clearing of confusion associated with negative cytology, but I mean if you have any suggestions

how to do that trial --

DR. DUTCHER: I just want to clarify my point about the hematologic malignancies. I understand that there is a pharmacologic difference and there may be even a sensitivity difference. I just think you will see better results in that setting that will be more convincing that you are seeing something real.

I think the problem here for all of us is, you know, the benefit is very, very brief, and if you confound that with a different assessment of time to progression because you have got different time points when people are assessed, you can't tell whether those numbers are different, the same or overlapping, and I think, you know, it is a bad disease, there is no question it is a bad disease, and so we are torn between taking individual cases where people have lived a few extra months as a result, and assume it is a result of this drug therapy -- is it, I don't know -- versus what? Go ahead.

DR. OZOLS: I agree with you and I don't agree with Derek in this regard. I think to try to do a second-line refractory in solid tumor, carcinomatous meningitis, I think that, you know, we are all debating whether we should treat any of these patients with carcinomatous meningitis from solid tumors, and then to say,

well, we will put them through methotrexate, and if that doesn't work, then we are going to go and give them another drug, I think your likelihood of achieving of any benefit in that group is strictly an anecdotal issue, and I don't think you would ever do a trial that could demonstrate that.

You could demonstrate efficacy of this, I think, leukemias and lymphomas is the way to go.

DR. WILLIAMS: If we were to see more data, the primary endpoint was clinical progression, and maybe you see it duplicated or something like that, then, that would be sufficient perhaps I mean in terms of an endpoint.

In this case, time to clinical progression was a secondary endpoint, it wasn't well defined in terms of what neurologic progression was, one of many different analyses, but if it were, let's say there were another trial and it was a primary endpoint, and you verified this, would that be sufficient?

DR. DAVID JOHNSON: If what you are asking is that if the study that was done in this tumor type that most of us intuitively feel is likely to do better, the ones that Jan has been talking about, and the results were favorable, then these data would be supportive of that.

On the other hand, suppose you did this in the leukemia/lymphoma group and you found the opposite, then

these data would be virtually unbelievable it seems to me. I mean that is sort of the issue, but I think it is worth doing getting the data that we have asked about.

MR. GIDDES: In the sponsor's manual on page 29, didn't they say that lymphoma, and so forth, was 67 percent versus the drug that they were using?

DR. DAVID JOHNSON: We have that.

DR. DeLAP: They are not finished yet.

I think we have gotten a lot of good information from the discussion. If there are further comments, we would like to hear them. I was just going to say I don't think we really need a vote on the last question unless you all wish to vote on it, but the most valuable thing for us I think has just been the discussion here.

DR. DUTCHER: That is fine I think. Does anyone feel the urge to vote?

[No response.]

DR. DUTCHER: Thank you. We will adjourn. We will be starting tomorrow morning at 8:00 a.m.

[Whereupon, at 5:15 p.m., the meeting was recessed, to resume at 8:00 a.m., Friday, December 19, 1997.]