DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGY DRUGS ADVISORY COMMITTEE

Thursday, March 13, 2008

8:00 a.m.

Holiday Inn Gaithersburg
Gaithersburg, MD

PAPER MILL REPORTING
(301) 495-5831

C O N T E N T S

CONTENTS (Continued):

PARTICIPANTS

Joanne Mortimer, M.D., Acting Chair
Nicole Vesely, Pharm.D., Designated Federal Official

ONCOLOGY DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

S. Gail Eckhardt, M.D.
David Harrington, Ph.D.
Michael Link, M.D.
Virginia Mason, R.N. (Consumer Representative)
Michael Perry, M.D.
Ronald Richardson, M.D.

INDUSTRY REPRESENTATIVE (Non-Voting)

Gregory Curt, M.D.

TEMPORARY VOTING MEMBERS

Ruth S. Day, Ph.D.
Judith M. Kramer, M.D., M.S.
Timothy S. Lesar, Pharm.D.
Anthony J. Murgo, M.D., M.S., F.A.C.P.
Bruce Redman. D.O.
Helen Schiff (Patient Representative)
David Stroncek, M.D.
Wyndham H. Wilson, M.D., Ph.D.

FDA (Non-Voting)

John Jenkins, M.D.
Vinni Juneja, M.D.
Patricia Keegan, M.D.
Richard Pazdur, M.D.
Mark Rothmann, Ph.D.

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. MORTIMER: Could you please take your seats so we can get started. Thank you.

For topics such as those being discussed at today's meeting, there are often a wide variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum at the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is

reminded to please refrain from discussing the meeting topics during breaks or lunch.

Thank you.

I would like to begin by going around the table and have the committee introduce themselves. I will begin with Dr. Curt.

DR. CURT: Thank you. I am Gregory Curt, medical oncologist and U.S. Medical Science Lead, Emerging Products, AstraZeneca Oncology. I serve as the Industry Representative, Non-Voting member.

DR. DAY: Good morning. I am Ruth Day, Director, Medical Cognition Laboratory, Duke University and former member of the Drug Safety and Risk Management Advisory Committee.

DR. STRONCEK: I am Dave Stroncek from the NIH Clinical Center, Bethesda, Maryland.

DR. KRAMER: I am Judith Kramer, Associate Professor of Medicine, Duke University, and member of the Drug Safety and Risk Management Advisory Committee.

MS. SCHIFF: Helen Schiff. I am Patient Representative and a member of SHARE, a breast and ovarian cancer organization in New York City.

DR. MURGO: I am Tony Murgo. I am a medical oncologist by training. I am with the NIH and I am on the FDA Drug Safety Oversight Board as an NIH representative.

DR. LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center, Drug Safety and Risk Management Committee.

DR. WILSON: Wyndham Wilson. I am a medical oncologist and head of the Lymphoma Therapeutics Section at the National Cancer Institute.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan Comprehensive Cancer Center.

MS. MASON: Virginia Mason. I am with the Inflammatory Breast Cancer Research Foundation, and I am the Consumer Representative.

DR. VESELY: Nicole Vesely, Designated Federal Official for ODAC.

DR. MORTIMER: Joanne Mortimer, medical oncology, City of Hope.

DR. LINK: Michael Link. I am a pediatric hematologist/oncologist at Stanford.

DR. RICHARDSON: Ron Richardson, medical oncologist, Mayo Clinic, Rochester, Minnesota.

DR. ECKHARDT: Gail Eckhardt, medical oncologist, University of Colorado.

DR. PERRY: Michael Perry, medical oncology, hematology, University of Missouri, Ellis Fischel Cancer Center, Columbia, Missouri.

DR. HARRINGTON: David Harrington, statistician, Dana Farber Cancer Institute.

DR. ROTHMANN: Mark Rothmann, Lead Mathematical Statistician, FDA.

DR. JUNEJA: Vinni Juneja, Medical Officer, FDA.

DR. KEEGAN: Patricia Keegan, Division Director, FDA.

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. JENKINS: John Jenkins. I am the Director, Office of New Drugs, FDA.

DR. VESELY: I just wanted to make an announcement. There are two members from the FDA, Office of Public Affairs, here, Ms. Karen Riley and Ms. Rita Chapelle. Please direct any media inquiries to these individuals.

Conflict of Interest Statement

DR. VESELY: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory

Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this committee are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has

authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee the essential expertise.

Related to the discussion of today's meeting, members and consultants of this committee who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves discussions of the cumulative data, including recent study results on the risks of erythropoeisis-stimulating agents when administered to patients with cancer.

Agents to be discussed include Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), sponsored by Amgen, Inc., and Mircera (methoxypolyethylene glycol-epoetin beta), sponsored by

Hoffman-LaRoche, part of the Roche Holding Limited Group. This is a follow-up to the May 10, 2007, Oncologic Drugs Advisory Committee Meeting.

Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note, however, Dr. Gregory Curt is serving as the industry representative acting on behalf of all regulated industry. Dr. Curt is an employee of AstraZeneca.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. MORTIMER: We are going to begin with the

Sponsor Presentation. Dr. Eisenberg.

Sponsor Presentation

Amgen, Inc.

Introduction

DR. EISENBERG: Good morning, Dr. Mortimer, Committee members. My name is Paul Eisenberg.

[Slide.]

I am here today on behalf of both Amgen and Johnson & Johnson. We want to thank the Committee for your time. The use of ESAs, as noted, has been the subject of several ODACs, one in 2004 and one last year in 2007.

FDA has framed a number of very important questions for you today including the possibility of withdrawing the indication for ESAs in chemotherapy-induced anemia or significant restrictions based on tumor type.

We believe these are important issues. We take each of the data that you are going to be asked to consider seriously, however, when we look at all of the data that have become available including new data other than those of the two studies that you will be considering that have shown harm, data recently submitted.

We believe that, in aggregate, these data, while

raising concerns and guiding the need for appropriate use of ESAs, do not justify the significant actions of further restrictions at the level that have been suggested.

Obviously, the judgments of this committee will be critical in guiding the sponsors and the FDA in the appropriate use of ESAs in CIA.

I also want to comment on the actions that have been taken by Amgen and J&J with FDA to address the recommendations of ODAC last year. The label for the ESAs has been modified substantially following the ODAC meeting and the subsequent Cardio-Renal Advisory Committee meeting to include stronger warnings regarding the off-label settings in which increased mortality was observed, including the discontinuation at the end of a chemotherapy course.

In addition, there were further guidances following the Cardio-Renal Advisory Committee on appropriate dosing and nephrology, and it was reflected in the label. And we will be discussing today the importance of recognizing that dosing should be based on a patient's response to ESAs.

We also are proposing a conservative initiation

level of 10 g/dl. I would like to note that that conservative initiation is framed with the view that ESAs should only be used for transfusion avoidance.

We reviewed very similar data in Europe and, in fact, in the European label, which has just been released, this is our recommendation.

An important message from ODAC last year was that there needed to be more data acquired in appropriately randomized studies within the current labeled indication across several tumor types.

This recommendation appropriately reflected concerns reflected by the studies that were reviewed, that had increased mortality, many of which you will review again today. Even though these signals occurred outside the current labeled indication in the 15 years in which ESAs were used primarily for treatment of anemia, these specific questions were not considered and needed to be addressed.

The design of appropriate studies has been extensively discussed with FDA and we will present the designs that we have agreed to today.

[Slide.]

The agenda for our presentation today will include

a few more opening comments summarizing what we will present by myself. Then, Dr. Bill Hait will give an overview of the use of ESAs in oncology. Tom Lillie, from Amgen, will be reviewing the data that are available. Adrian Thomas from Johnson & Johnson will be reviewing our risk minimization program. I will make a few more comments in that regard and then I will summarize.

[Slide.]

ESAs have had substantial benefit in management of patients with anemia due to chemotherapy and they continue to have a clear benefit as a therapeutic alternative to transfusion.

They provide a different type of management of that anemia. It is a sustained management of anemia, a transfusion avoidance rather than transient symptomatic benefit.

There is evidence clearly of unexplained increased treatment-related mortality when ESAs were studied in settings other than CIA and, in fact, outside of the oncology setting when they were studied at high targets in other anemia disease states such as that associated with chronic renal failure.

The risks cannot be excluded in the labeled indication and this has been conservatively communicated in the label since March of 2007. However, and this is a key point, we do not agree that the data in aggregate, where signals have been observed, point to tumor progression as the mechanism for increased mortality.

The data, when looked at across indications, suggest that the increase in mortality is unexplained and that tumor progression as the only mechanism is unproved and not, at this point, a mechanism that should guide immediate changes to the label. It should, however, clearly, as is the case currently, be prominently warned and advised to patients as a possibility.

We are here today to discuss two studies that have emerged since ODAC of 2007 that showed an increased risk. In both these studies, ESA dosing, as was the case in many of the experimental studies that have been done and have shown signals, ESAs were dosed to achieve high hemoglobins to explore the potential of improving outcome in patients treated with chemotherapy.

This strategy was abandoned several years ago as soon as safety signals emerged and there has been no

evidence of such benefit. The studies you will need to evaluate today are the long-term follow-up to the GOG Study GOG-191 and the PREPARE trial.

The PREPARE trial was provided as an interim analysis of a prespecified endpoint which was pathologic complete response to FDA in November of 2007. This, in fact, represented a postmarketing commitment by Amgen to provide these data arising out of discussions from ODAC of 2004 as to which data would be informative in terms of safety of ESAs.

We want to note that at that time we observed numerical increases in incomplete data sets that suggested there might be harm in the ESA-treated arm. We were concerned with that trend, we reported it promptly both publicly and to FDA, however, those data continued to evolve and, in fact, we will provide different data than what you have seen in the briefing book that are based on additional follow-up that has occurred of patients who have been analyzed as part of that interim. And we also have invited one of the representatives of that investigative group here today.

We believe careful examination of these studies in

the context of all the available data do not suggest that the benefit-risk within the labeled CI indication has changed substantially since they were approved.

We note that some of the data that we are going to discuss, and some of the data have only recently become available, were provided to FDA very recently, in early February. FDA has not had a chance to analyze all these data but, overall, represents a substantial exposure of patients to ESAs in controlled clinical trials that are available to your analysis.

In aggregate, the data suggest that the potential mechanisms for increased risk are not completely understood, they are appropriately labeled, and we can provide appropriate guidance to patients and physicians in how to manage the use of ESAs in chemotherapy-induced anemia.

Part of that is a credible risk assessment and risk minimization program that will limit ESA exposure to appropriate and informed patients.

[Slide.]

I would like to briefly highlight the key points of this because I think it is critical that we understand going forward that the sponsors are absolutely committed to

ensure appropriate use of ESAs in chemotherapy-induced anemia. The key elements of our program are continued clinical investigation to characterize the benefit-risks of CIA. The studies that were discussed in 2004 and many of them are nearing completion or have reported interim data, proceed with the exception of one on time and will provide additional data.

We have also agreed along with Roche to provide patient level data to the Cochrane group for an independent third-party analysis of all of the available data to further inform appropriate use.

Additional controlled trials, as we will discuss, have been discussed with FDA and we look forward to your input as to the appropriateness of those designs. Each of the programs, the pharmacovigilance program, the independent meta-analysis and the studies have been discussed with FDA.

Clearly, risk minimization currently should focus in appropriate use again to guide physicians and patients as to what is not known and what is known regarding ESAs in the CIA indication.

The key to an informed decision is assuring that patients and physicians discuss the risks of ESAs prior to

initiation of treatment in CIA. This discussion will be documented and monitored as part of our proposed risk minimization program.

We also propose the distribution of ESAs will be limited to oncology providers who agree to participate in this program. There will be explicit documentation of the patients being informed of the information, as well as explicit enrollment of providers in the program going forward.

The sponsor also do not intend to use any broadcast ETC advertising. We look to work with payers to ensure that there is appropriate use of ESAs and our risk minimization activities, we believe, will be effective in assuring that these ESAs are available to appropriate patients and are use appropriately.

Finally, I want to note that when we look at risk mitigation, we need to consider the impact of the decision and actions that occurred following this committee's recommendations last year. They are, in fact, profound.

ESA used in cancer patients has decreased by 60 percent in 2007 both as a consequence of labeling and as a consequence of reimbursement practice changes which will be

discussed in the FDA presentation.

In aggregate, the additional measures we are proposing are monitorable, verifiable and meet the objective of ensuring appropriate use of ESAs in CIA.

We thank the committee for your attention, look forward to your judgment as you look at the data.

[Slide.]

I will now introduce Dr. Hait to speak to the overall view of ESAs in CIA.

Thank you.

Background Information

DR. HAIT: Thank you, Paul, and good morning.

My name is Bill Hait and I am the head of Hematology/Oncology R&D in the Johnson & Johnson family of companies. It is my privilege to introduce today's discussion on behalf J&J and our colleagues at Amgen.

The use of ESAs in patients with chemotherapy-induced anemia, abbreviated CIA, raises many important questions regarding both risks and benefits. The available data are extensive and complex, yet even when fully understood, do not answer all of the questions.

If we together are to make the best choices about

how to use these drugs and how to study them, it will be only through thoroughly understanding all of the available data and the results of ongoing and proposed studies, and finally, the concerns, questions and needs of people with cancer and physicians who care for them.

Let me thank you, the panel and our colleagues at FDA for the time you have taken to review this information and for the carefully considered comments that you will provide today toward that end.

[Slide.]

We will cover the appropriate use of ESAs in chemotherapy-induced anemia. These include benefits and risks, clinical safety, potential mechanisms for mortality signals and risk minimization. I will begin with the overall use.

[Slide.]

The overall goal of our presentation is to review the benefits and risks of ESAs in the treatment of chemotherapy-induced anemia and to reach agreement on appropriate risk assessment and risk minimization plans.

There is an abundance of evidence that led to general points of agreement regarding ESAs, and this

information is summarized on the next slide.

[Slide.]

The pathophysiology of CIA is multifactorial and can be treated with ESAs, suggesting that a relative erythropoietin deficiency due to end organ resistance underlies part of the problem.

ESAs decrease the number of patients who require blood transfusions and the number of transfusions required by patients undergoing chemotherapy. As a result, these medications decrease exposure of immunocompromised patients to infectious agents, as well as noninfectious complications including acute lung injury and reactions due to blood group incompatibility and medical errors.

Although we believe that the known risks from blood transfusions are less today than yesterday, we do not know if this will be true tomorrow. ESAs increase the risk of thromboembolic vascular events, abbreviated TVEs, and these events increase at high hemoglobin targets across several labeled indications.

The risk factors for TVEs have been extensively studied and therefore these risks are amenable to minimization. Furthermore, the risk of thromboembolic

events has been predominantly displayed in our label.

Unexplained serious safety signals have been seen when ESAs are used in investigational settings, that is, above the FDA-approved label target hemoglobin of 10 to 12 g/dl, or in patients not receiving myelosuppressive chemotherapy.

Data are now available from over 12,000 patients in controlled chemotherapy studies to inform benefit and risk. Qnd the most rigorous study conducted to date, Amgen-145, ESAs did not demonstrate increased mortality or tumor progression in patients receiving chemotherapy for small cell lung cancer. A malignancy included among those found to express putative erythropoietin receptors.

Despite extensive study to date, the FDA and we have concluded, and I quote from the FDA briefing book, "At the current time, a direct relationship between the presence of erythropoietin receptors on tumor cells and tumor cell proliferation in response to exogenous erythropoietin has not been established."

Amgen and J&J are working through NIH to plan research to bring further clarity to this issue.

[Slide.]

The next several slides describe some of the benefits of ESAs in the CIA patient. In studies of 5,830 patients in placebo-controlled clinical trials, ESAs allowed up to one-third of anemic patients receiving chemotherapy to avoid transfusions. This represents a 50 percent reduction in relative risk and supports the licensed indication of transfusion avoidance.

ESA also have certain advantages over blood transfusions and these are depicted in the model shown in the next slide.

[Slide.]

Here, we plot the concentration of hemoglobin on the Y axis as a function of weeks of chemotherapy. As you can see, transfusions are administered to acutely treat symptoms of anemia and the benefits are short lived. In contrast, ESAs are used to maintain hemoglobin in a less symptomatic range.

[Slide.]

Transfusions also introduce challenges to the care of anemic cancer patients. Approximately 50 percent of CIA patients require transfusions when they do not have access to EASs. As shown in the previous slide, the benefit of

transfusions are transient. In addition, despite tremendous strides toward increasing the safety of the nation's blood supply, transfusions carry known and unknown risks of infection. We won't know if today's blood supply is safe from a new pathogen until months or years after the fact.

Transfusion of blood contaminated with a contagious agent has the potential for widespread effects. Furthermore, most patients receive their care in offices of community oncologists where access to blood transfusions are often not available on site, causing disruption in chemotherapy protocols and the overall care of patients.

Finally, the number of patients diagnosed and treated for cancer tragically continues to grow. An increased number of blood transfusions will threaten to deplete this precious national resource.

If we agree that blood transfusions are used to treat symptoms of anemia and that ESAs prevent or decrease blood transfusions, we conclude that ESAs do affect symptoms in anemic cancer patients for the reasons shown on the next slide.

[Slide.]

Since symptoms of anemia, such as fatigue, are

debilitating and are treated with blood transfusion, is it logical to conclude that by avoiding transfusion, that ESAs do not affect the patient's well being? Systematic reviews of data from the Agency for Healthcare Research and Quality and the Cochrane Group support effective medications on fatigue, one of the most debilitating symptoms of anemia.

The recent Cochrane analysis found that erythropoietin and darbepoetin produce statistically significant and clinically recognizable improvements in fatigue.

Previous published randomized, controlled clinical trials reported the ability of ESAs to decrease the symptoms of anemia and several of these reports have met the standards of regulatory agents in Europe and Canada and are included in those labels.

We do, however, recognize that these data do not meet FDA standards for inclusion in the label. But we do not believe that because studies conducted in the past did not meet the standards of the present that we should conclude that no positive data exists.

Having reviewed some of the benefits of treating CIA patients with ESAs, I will now review the risks of ESAs

to CIA patients and ask the following question: Do the totality of the data addressing benefit compare to the studies reporting risk bring the weight of the evidence to a point that would justify withdrawal of the CIA indication?

[Slide.]

The May 2007 ODAC focused on 6 of 55 available investigational studies that used ESAs outside of the labeled indication. Those are the 6. We are here today to discuss 2 additional investigational studies, GOG-191 and PREPARE, that constitute the 8 studies depicted in Table 2 of the FDA briefing book and the new ESA label.

These studies documented an unexplained increase in mortality when ESAs are used for investigational purposes. It is essential to understand that these studies do not represent the totality of the data of the weight of the evidence. Rather, they are selected from a much larger database of 59 studies.

For example, there are over 7,400 patients in the J&J database of patients for whom we have mortality data. Since the 2007 ODAC, we added new or updated mortality data from studies that include approximately 2,500 patients or greater than a third of the total.

Furthermore, these data were reported on or before the date of submission agreed upon with FDA. The studies selected to be highlighted in Table 2 of the briefing book were all investigational. They were designed to determine whether or not increasing the hemoglobin beyond correction of anemia would improve tumor oxygenation and therefore improve the outcome for patients receiving chemotherapy or radiation.

The exception is Amgen-103, a study that targeted a hemoglobin of 12 to 13 g/dl in patients in the palliative setting who, by protocol entry criteria, had progressed to the point that they could no longer receive treatment for their underlying malignancy.

[Slide.]

This slide depicts a forest plot of mortality risk from 59 controlled studies representing over 15,000 patients. Bars moving to the left of the center favor the ESA arm and those to the right of the center favor the control arm. The horizontal line for each study represents the 95 percent confidence interval for the mortality odds ratio.

Lines that cross the vertical represent studies

for which the confidence interval includes no effect. As might be anticipated, when studying a supportive care medication that should not, in and of itself, have an effect on mortality. This large database reveals that some studies trend in favor to the ESA arm, some the control arm, and some are neutral.

The top two groups of studies are in anemic patients not receiving chemotherapy and in studies in patients receiving radiation therapy, respectively. Both of these are investigational uses.

The third and largest group of studies is in patients within the approved indication of chemotherapy-induced anemia although some of these studies included those that used hemoglobin targets considerably higher than approved in those labels.

Highlighted in yellow are the 8 investigational studies selected for inclusion in Table 2. Many fall on the right side of the line thereby raising concerns. Please note, however, that this is far from true for all of the studies. Among the CIA studies and amongst the larger studies with shorter lines shown in this area or in this area more precisely, there are studies that fall

predominantly on the left side of the line favoring ESAs.

There are studies evenly straddling the line, i.e., there are no signals and studies with estimates in confidence intervals predominantly to the right of the vertical line. Therefore, there exists comparably sized studies with long-term follow-up, but not represented in Table 2 of the FDA briefing book, that found either no trends favoring the control arm or a trend that favored the ESA arm. Some of those studies were also imperfect in design and execution.

Furthermore, none of the studies in Table 2 addressed chemotherapy-induced anemia as defined in the FDA approved label at all. We do not interpret the results of the studies called out in Table 2 as, "demonstrating decreased survival, decreased time to tumor progression, or poor local control since many were not robust in design or execution, several did not produce statistically significant results, and at least one listing resulted from an unplanned analysis of an incomplete data set with immature follow-up.

Two of four beyond correction of anemia chemotherapy studies reported statistically significant differences in survival or progression between ESA and

control arms and two did not.

Finally, several studies reported since the May 2000 ODAC overlap with the types of tumors represented by the new studies in Table 2 including the Mobus adjuvant breast study and the Blohmer study of cervical cancer.

These key studies were not described in detail in our briefing book to comply with instructions received from the FDA. We are sensitive to the reason articulated for this instruction, which was that FDA did not have time to review these data before this ODAC meeting and may not be in a position to comment.

However, it is important to remember that members of the May 2007 ODAC viewed these studies as being critically important and that several are as large or larger than those called out in Table 2.

We believe that the available data allow us to recognize and manage risks in CIA patients as follows.

[Slide.]

ESAs should only be administered to patients with chemotherapy-induced anemia. ESAs should be discontinued in non-responsive patients. The risk of TVEs should be appreciated and appropriately managed. Treatment to

hemoglobin targets greater than 12 is outside the label and should not occur.

It is worth commenting here on the difference between the outcomes for patients in whom ESAs were used to target high hemoglobins as compared to the hemoglobins achieved by the patients.

Table 2 include two studies where the majority of patients did not achieve a hemoglobin greater than 12 despite a high hemoglobin target. We do not feel that this result can be extrapolated to indicate a safety problem when the medications are administered appropriately.

This is because attempting to treat a hyporesponsive or a nonresponsive patient to a high hemoglobin target will require pushing the exposure to ESAs in patients with underlying risks. This concept will be elaborated upon by my colleague from Amgen Dr. Lillie.

[Slide.]

In conclusion, the totality of the data and the weight of the evidence show that our medications have a favorable benefit-risk profile when used as they were intended to be used.

Furthermore, when used according to the FDA label,

the data do not demonstrate nor completely rule out tumor progression or adverse patient outcomes. This will require further study.

We propose that TVEs and non-responsiveness underlie the survival signals seen in the experimental setting of high hemoglobin targets and that these risks can be minimized.

Finally, we will implement and execute comprehensive rigorous risk management programs and pharmacovigilance trials to understand and improve the benefit-risk profile of ESAs by minimizing exposure of specific populations at risk and by eliminating the use of ESAs in patients for whom the medications are not indicated.

[Slide.]

I thank you for your attention and now turn the podium over to Dr. Tom Lillie.

Benefits-Risk of ESAs

DR. LILLIE: Thank you very much, Dr. Hait.

[Slide.]

As Dr. Hait has described during this presentation on ESAs, benefits and risks in the labeled indication of CIA, we are going to cover three key topics. These will

help inform both our discussions today and future risk management plans particularly in the context of the observed safety signals.

Dr. Hait has already reviewed both transfusions and ESAs as management strategies for anemia in chemotherapy patients and how these differ. We will now consider the rationale and the history for the expiration of improved survival with ESAs at higher target hemoglobins in anemia patients and how, in the light of observed safety signals the use of ESAs can be optimized to minimize exposure and maximize benefit in avoiding transfusion.

Then, we will briefly examine a number of mechanistic hypotheses that are being proposed to underline the observed safety signals. Specifically, this ODAC is being triggered by two new data sets, that from GOG-191 and the PREPARE study. We will review this data in some detail and are privileged to have the investigators from both of these studies available to answer questions.

[Slide.]

So, as we step back in time and look at the history of how ESAs have been studied to look at survival, this really started back with the publication of the

Littlewood study, which was with epoetin alfa.

This study showed a potential for improved survival with ESAs and treating patients with anemia receiving chemotherapy. The hypothesis was based on a number of clinical and preclinical observations and, based on these, a number of studies were set off at the same time to look at high hemoglobin targets, mostly greater than 13.

They were studies looking at survival endpoints based on superiority and requiring long-term follow-up. Some of these studies, but by no means all, have caused safety concerns which have been included in the labels for these agents.

This was an experimental approach looking for a new benefit for ESAs and this was not reflected in clinical practice or the labeled indication for these agents.

Since the first meeting about safety with these agents at ODAC in 2004, safety concerns have been prominently highlighted in the labels.

[Slide.]

Data from these studies has taken time to mature. A number of these studies were identified at ODAC in 2004 as informative because they do look at survival and progression

outcomes although in a superiority manner as that was the hypothesis that was being tested.

These data sets were presented in interim format at ODAC 2004 and, following that meeting, a timetable for submission of these data was agreed. The timetable for that data submission had been adhered to and the FDA are now in possession of all of this data in primary electronic format.

These studies required long-term follow-up and, thus, the data were not available at May ODAC 2007 because they were not completed. They have now completed this long-term follow-up and the data is now available and has been submitted on time.

There is now, as you can see, a very large database available to look at the impact of ESAs on mortality in patients with cancer, over 10,000 patients of data has been submitted.

[Slide.]

However, when we look at these survival studies, the hypothesis the ESAs could improve survival has not been substantiated. Safety concerns have been raised by some of these studies and the safety ceiling of 12 to exclude use in the way in which these studies have been performed has been

put in place.

The indication for these agents and the benefits remain avoidance of transfusion. But we have a large database of data and we can interrogate this to see if there are answers to some of the questions which have been raised by these studies.

[Slide.]

Target hemoglobin has been the focus of a lot of discussion, quite rightly, because this is the setting, high hemoglobin targets in which the safety signals have been observed. However target hemoglobin, in and of itself, is a surrogate. It cannot explain the findings itself.

In fact, target drives two different parameters. The first of these is drug exposure, ESAs in this case and, if we are looking for an adverse event, it would be sensible to look at drug exposure as one of the mechanisms, because exposure and adverse event should in some way be related.

Also, achieved hemoglobin is changed in the target hemoglobin study and, paradoxically, these two are inversely related, that is, those patients who achieved the highest hemoglobins, who are responsive to ESAs are dosed with the lowest doses. Conversely, those patients who do not respond

to ESAs received higher doses in target studies in order to try and get them to achieve the target, you drive the non-responder.

This is important because if you lower the hemoglobins at which you are trying to drive people, you may continue to dose non-responders and, in fact, deprive responders of benefit.

We do not know which of these two is definitively associated with the adverse outcomes we are interested in, survival and progression. It could be as exposure, it could be achieve hemoglobin.

These relationships are confounded and when we attempt to study them, we must be very cautious, because these are post-baseline factors and they are interrelated. As I have already said, dose and achieved hemoglobin are inversely related.

To make matters more complex we are also confounded by the performance states, the underlying biology of individual patients, such that those patients who are likely to respond are also those patients who have the best underlying biology. Those patients who are unlikely to respond have the worse underlying biology and therefore the

worse outcomes.

So, in fact, when we look at the analysis of this, what we see is that patients with the worst outcomes are the non-responders, who have the highest exposures, and that leads us to this next slide.

[Slide.]

These observations are not unique to oncology. They have also been in nephrology where we see an increase in thrombovascular events particularly in higher target hemoglobin studies.

High targets require increased drug exposure especially in the poor responders and patients who respond tend to have better prognosis and better outcomes.

Non-responsive patients have worse outcomes and, in fact, this is the basis of a wording within the current CRF label which advises limiting exposure in those patients.

We therefore, based on this, although we cannot draw causation from these associations which we have seen because of the confounding of biology and the interrelationship of these factors, it is sensible to try and reduce exposure in those patients who are receiving the least benefit, the non-responders.

Most patients respond, about two-thirds respond to ESAs and these patients use the lowest doses and avoid the transfusion and, therefore, epitomize the current wording within the label to avoid transfusions using the minimal dose.

However, patients who do not respond, about a quarter of patients, received higher doses, on average 30 percent higher than their responsive counterparts, and receive a high burden of transfusions, about 67 percent of such patients will be transfused.

Thus, they are receiving both ESAs and transfusions and are potentially exposed to risks from both of these. It is therefore sensible based on primary pharmacological principles to limit exposure in these patients and stop dosing them after they have had a trial of the drug for responsiveness.

[Slide.]

To summarize this section, the history of ESA trials has been looking at higher hemoglobin targets to improve survival. This has not been proven by the studies and safety concerns have been raised by some of these studies.

[Slide.]

There is an inverse relationship between achieved hemoglobin and ESA exposure, which is driven by high hemoglobin targets in some studies. To reduce exposure while preserving the important patient benefits of avoiding transfusion, we propose label changes: to initiate below 10, which will reduce exposure in this population overall as less patients have a hemoglobin below 10, below 11 or other numbers; to limit dose escalation; and to discontinue ESA for non-responders who are receiving little benefit and are exposed to transfusions already.

[Slide.]

Next of all, I would like to look at some potential mechanistic hypotheses that have been suggested to underline the signals which have been observed.

[Slide.]

The first of these is that there might be an increased risk of thrombovascular events. Cancer patients have an increased risk of these events just because of the nature of their disease and, the more advanced the disease is, the higher their risk.

TVE is also increased by chemotherapy treatment

for cancer. Autopsy series suggest that TVE is a frequent and occult cause of death in patients with cancer so it is often undiagnosed. TVE risk is associated with hemoglobins and risk factors for TVE in cancer patients are well known and are included in practice guidelines.

One such risk factor is, in fact, the use of ESAs, the fact that ESAs increase TVEs has been well recognized since these molecules were first licensed. In some of the studies which have seen increased mortality, TVEs have been suggested from the data as being the underlying cause.

In Nephrology, also, we have seen higher targets have been associated with higher TVE rates and, in fact, in nephrology, we have the advantage of randomized studies comparing higher and lower target hemoglobin outcomes and we see a difference between these two strategies where lower achieved hemoglobins are, in fact, associated--lower target hemoglobins, pardon me-- are associated with lower TVE rates.

Likewise, in oncology studies, which have targeted higher levels of hemoglobin, some of these protocols have been amended and we have been able to see the TVE rates both before and after the amendment. Those studies have shown

that post-amendment to lower hemoglobins, lower rates of TVEs have been observed.

We understand that there is not enough data within this area and TVEs being more formally studied both within the ongoing EPO-ANE-3010 study and within our new pharmacovigilances study 782 where we will be able to look at mortality, the rates of TVE, and to systematically look for TVE within this patient population.

[Slide.]

Next, I will turn to the potential for tumor progression from these agents. One theory that has received a great deal of interest is that EPO and EPO-receptor interactions might play a role in tumor progression.

Firstly, it is key to say that mortality signals have been observed in both nephrology and oncology. But tumor progression is clearly not the cause of the signals in nephrology, thus, TVE events actually provide a unifying hypothesis for the signals which have been observed.

If chronic exposure to ESAs, as occurs in the renal population, were to promote tumor progression, we would expect both early emergence of cancers and more aggressive cancers when they present.

We have an almost complete database of renal patients that have been treated over many years, and these observations are not substantiated by this observational data.

We can look at the preclinical biology of the EPO receptor all the way from the gene to surface expression of the protein. The EPO receptor does not behave as an oncogene, it is not found in increased copy number, it is not selectively mutated to give growth advantage.

If we look at mRNA levels, we can detect these very specifically with PCR and we find, in fact, that Epo receptor mRNA is present in almost every normal tissue in the body. But those levels are not increased in cancer cells derived from those normal parent tissues.

Published studies on the expression of the Epo receptor are floored by the fact that we do not have specific reagents which are able to detect the Epo receptor reliably.

There has recently been a meeting at which both the sponsors and the FDA were present to discuss the biology of the Epo receptor and a potential role within cancer. It is clear from this meeting that, although an enormous amount

of work has been done, and both sponsors have done an enormous amount of research pre-clinically to look into this and to attempt to make specific antibodies which can help with this question, that more work needs to be done.

Indeed, the sponsors are supporting the NCI and the NIH in doing this.

[Slide.]

if we now turn to the clinical data that is available to address the progression question, within chemotherapy-based studies, there are 20 studies which have measured progression in some manner.

These have used heterogeneous measures, but we have seen inconsistent outcomes in this study. There is not a clear pattern within the data that has been presented. None of these outcomes has been statistically significant, and thus we believe that cardiovascular and thromboembolic events provide a more likely hypothesis for the mortality signals that have been observed.

[Slide.]

One study which has been much misunderstood in this regard is the BEST study. As you can see from the panel on the left, there was indeed a mortality signal in

this study which occurred early whilst the patients were on treatment.

During this study, the investigators reported adverse events which of course included death, and whilst reporting adverse events had the option of ticking a check box which said death due to disease progression, or they could have the option of Other, those were the only two options on the cause of death form.

Not surprisingly, given the advance stage of cancer in these patients, the majority of physicians checked the disease progression cause as the cause of death.

However, when asked the same question formerly within the progression part of the study, the investigators noted the date of progression of these patients. And you can see the results of that analysis on the right-hand panel, the time to disease progression in which no difference is noted between the two arms.

Thus, whilst there is a mortality signal, it is far from clear in this study whether the tumor progression is the underlying cause of that observed signal.

[Slide.]

There are two studies which have looked at

progression in a particularly rigorous manner. The first of these is the PREPARE study, which we will discuss in more detail in a moment. This had a specified interim efficacy endpoint of pathologic complete response.

This was a neoadjuvant study and so this endpoint represents the amount of tumor that is left post-surgery in these patients following chemotherapy. This study was conducted in a homogeneous patient population with regard to both chemotherapy and tumor type and in this study we see no difference in ESA use in the outcome with respect to ESA use.

In the 145 study again, which was presented to ODAC last year, in May, tumor progression was studied in a systematic and rigorous way with regular radiographic assessments. We have recently submitted the centralized read from this data to the FDA as an update to that study.

This was again conducted in a homogeneous patient population and one in which the Epo receptor has been suggested to be expressed. This study did not show any difference in tumor progression between ESA use and placebo on this rigorous assessment.

[Slide.]

There have been two studies which have demonstrated decreased loco-regional control in head and neck cancer studies using radiotherapy alone, targeting a higher hemoglobin.

These studies did not administer chemotherapy at the same time and used clinical and not objective measures of progression. However, in both, failure was seen loco-regionally but wasn't seen distantly, suggesting that this may be a reduced effect of radiotherapy locally.

A lot of preclinical work has been done around this observation also and the suggestion is that high hemoglobins may in some instances interfere with the efficacy of radiotherapy with microthrombi or other radiologic effects within the tumor and the radiation field.

[Slide.]

In summary, we know that cancer patients are at increased risk of TVEs and that ESAs do increase this risk, and this is recognized and labeled risk. We have seen the same signals in terms of TVE in both nephrology and oncology, and so this provides a unifying hypothesis.

The role of the Epo receptor in tumor biology is unclear. We do not know what role it plays and more

research is require.

Tumor progression has not been established in the chemotherapy setting in rigorous studies. Reduced loco-regional control in head and neck cancer with radiotherapy alone may reflect an interference with local efficacy of radiotherapy.

We accept that there is not enough data within this area which is being rigorous to make a final assessment and thus again we have the ongoing EPO-3010 study and our new proposed study which will rigorously address these questions.

[Slide.]

Next, we will look at the clinical data which is available and, in particular, the two new data sets which have become available recently. One of these is from the GOG-191 study, the other is from the PREPARE study. Both of these are high hemoglobin studies targeting high hemoglobins to improve survival in these patient populations.

[Slide.]

The GOG study was in patients with cervical cancer and here, the strategy was to increase hemoglobin to 13 or above with ESAs compared with the transfusion strategy

maintaining above 10. This study was designed to look at progression-free and overall survival.

[Slide.]

It was a high target study and, in fact, in this study, a high rate of TVEs was observed in the EPO arm, 19 percent versus 9 percent, and the study was terminated early with only 114 out of 460 patients accrued.

The initial safety report was submitted to the FDA at the time of the ODAC in 2004, and the study update was unexpectedly published in December 2007 by the GOG group. As soon as those data were presented to Johnson & Johnson, they were forwarded to the FDA in February of this year. That is obviously in the recent time frame and the FDA have not yet had time to review that data.

There have been two analyses. There is an intention-to-treat analysis which I will present. There is also a safety analysis, which shows similar results.

[Slide.]

As you can see here, these are the baseline demographics of these patients with cervical cancer and there are some minor imbalances between the arms. But again it is an incomplete data set and not surprising given the

small number of patients in this data set.

[Slide.]

The patients treated with ESAs did indeed achieve high hemoglobins in this high target hemoglobin study.

[Slide.]

When we look at the progression-free survival, Kaplan-Meier curves, you can see them here. And indeed there is a small number of excess events in the EPO arm, two to be precise.

The log-rank test here shows a p-value of 0.86, which is nonsignificant, and a hazard ratio of 1.06 with the confidence intervals you can see there which span one.

[Slide.]

Likewise with the overall survival, there is a small excess of events within the Epo-treated arm. But comparisons by the log-rank test show a p-value of 0.44, a nonsignificant difference in this study.

[Slide.]

There is another study within a similar patient population at a high target hemoglobin which has also recently been submitted to the FDA as part of our commitment to give them all of the data which is available, and this

has been submitted on time as agree with the Agency.

This is the AGO/NOGGO study, also known as Blohmer, which has recently been submitted for publication. This study again was designed to look at survival and relapse-free survival with epoetin high hemoglobin target of 13, non-ESA control.

[Slide.]

This study does not show a difference between the two arms. There is no statistical difference here although in this case the numeric number of events is less in the EPO arm.

[Slide.]

Therefore, we have two studies, both at high hemoglobin targets, one of which is incomplete, one of which is complete and has mature follow-up data.

Neither of these studies shows a statistical difference in outcomes for patients with cervical cancer treated with chemo-radiotherapy to high hemoglobin targets. But one of them has an increased number of events in the EPO arm and the other one has a decreased number of events in the EPO arm.

It is therefore inconsistent and unclear what the

effect may be in this patient population.

[Slide.]

Next, I would like to talk to the PREPARE study, which is, in fact, a factorial design although the primary outcome of the study is looking at the effect of the chemotherapy regimen on the outcome of neoadjuvant breast cancer patients.

The patients were randomized to a standard chemotherapy regimen before surgery or a dose-intensified chemotherapy regimen. Surgery was then undertaken and long-term follow-up.

Patients in both arms were randomized to receive either darbepoetin or no darbepoetin. This was a high hemoglobin study looking at prevention, so hemoglobin's administration when darbepoetin was started was at less than 13. Patients could enter the study at any hemoglobin but were administered darbepoetin when the hemoglobins went below 13. 733 patients are available for analysis in this study.

[Slide.]

It was designed as a survival study but also with relapse-free survival and remission rate. It is important

to note here that the data set that has recently been submitted to the FDA, as required by our postmarketing commitment, is a final study report for the pathologic complete response which is a specified primary endpoint and this interim analysis. This data has been submitted and is final.

[Slide.]

What happened in this study is that an unplanned survival analysis occurred at the time of this interim. This interim was never designed to look at overall survival and progression-free survival, only at the on-study endpoints of pathologic complete response.

Because this was unplanned, the database was incomplete and was not formally locked for these analyses. The investigators kindly provided us with updated data. So the data that I will show you, which is still an intention-to-treat analysis, will differ from that which you see in the FDA's briefing book, because it contains a high number of patients.

[Slide.]

Here are the baseline demographics of this study showing this to be a high-risk, early breast cancer group

with a number of women with larger cancers and with involved lymph nodes.

[Slide.]

Here we see the results of the pathologic complete response, the formal endpoint analyzed in this interim data set. We can see that there is no difference between the two arms of this study on pathologic complete response.

[Slide.]

In terms of the achieved hemoglobins, again the darbepoetin group maintained their hemoglobin--this was an anemia prevention study--at a level of about 13.6 grams.

I should note at this point that this study originally had a ceiling of 14 g/dl when it started but halfway through altered to 13 g/dl and the baseline hemoglobin you therefore see is approximately halfway between those two levels.

Patients received on average just over 100 mcg of darbepoetin and 27 patients in the darbepoetin arm, who are analyzed in these analyses as treated with darbepoetin, did not receive drug per protocol because their hemoglobin did not decrease below 13.

[Slide.]

These are the results of the relapse-free survival from the updated data set using an ITT approach. You can see that there is an excess number of events in the darbepoetin arm but this does not reach statistical significance.

[Slide.]

Likewise with survival, there is an excess of events within the darbepoetin arm but this does not reach significance, with a p-value of 0.16.

[Slide.]

Likewise with the cervical cancer studies, there is another study which looks at an early breast cancer population which is complete and mature and has 5 years of follow-up and targeted a high hemoglobin with the aims of improving survival.

This is another study carried out by the AGO group in Germany, this time in adjuvant breast cancer rather than neoadjuvant in the PREPARE study. This study randomized patients again primarily to a dose-intensified approach with chemotherapy. A second randomization in that intensified group looked at EPO versus no-EPO to maintain hemoglobins during the intensified regimen.

[Slide.]

These are the five-year follow-up data from that study which show no difference between the two arms. And as you can see, during the study period, there is a period there where the EPO arm is, in fact, tracking above. And I just mention that because at the last ODAC, there was a misunderstanding that these lines were, in fact, in the reverse order. The EPO arm here is, in fact, the blue line tracking above that.

[Slide.]

When we compare these two studies, we can see that they both do not show a significant difference. They both target hemoglobins, they are both in early breast cancer population. Again, we do not see concordance in these results.

There is a trend in PREPARE to adverse outcomes. But this is not mirrored in the Mobus data. Again, both of these data sets have been submitted to the FDA as requested.

[Slide.]

We can now look at the totality of the available data which Dr. Hait has already referred to. You can see that the bulk of the data is within the chemotherapy

setting, either anemia prevention or anemia treatment.

There are two other areas, that of anemia of cancer where patients are not receiving any treatment, and there are 9 studies here. Two have raised concern. This area is now clearly put in the label as not being an appropriate use for these agents, and uses within this area has sharply declined.

If we look at radiotherapy, the same is true. There are two studies of concern. The label appropriately reflects this concern so that use with radiotherapy alone or to the high hemoglobin targets that we used in these studies is now not according to label, which leaves us with the chemotherapy area.

Chemotherapy-induced anemia is still the labeled indication. There are 46 studies here representing 12,034 patients. Four studies have raised concern, two of which we have just discussed and two of which have been discussed at previous ODACs.

[Slide.]

Given this large body of data, a number of study level analyses have been performed. These study level analyses have used slightly different numbers of studies as

they have evolved over time and different analytic methods.

However, all of them have seen overall a slight disfavor to erythropoietins, which has been driven by the off-label uses which I have just highlighted, mainly that in anemia of cancer and that in radiotherapy alone.

[Slide.]

All of these studies have also been concordant when they look at the chemotherapy-alone area and that we do not see a consistent effect within the body of data that is available. This does not negate the safety signals which have been seen in individual studies. But it does mean that we do not see a consistent signal within all studies when we place these together.

We acknowledge the limitations of study level meta-analysis. You cannot look at individual patient factors, you cannot look at hazard ratios or other time-based measures of survival.

[Slide.]

To that end, all three manufacturers of ESAs have submitted their patient level databases in their entirety to the independent Cochrane analysis group. They will be performing a patient level meta-analysis which is ongoing at

this time and results will be available later this year.

This analysis will enable looking at survival in a time-based fashion with hazard ratios and Kaplan-Meier plots and the other things that one would expect. It will also enable analysis of progression endpoints and of TVEs and risk factors for TVEs.

It will also allow the ability to analyze by important patient covariates, such as tumor type, hemoglobin and others which have been mentioned in the FDA briefing book. This analysis will allow that to happen on a very large comprehensive data set and will be informative to our deliberations around these agents within chemotherapy.

[Slide.]

To summarize this section, we have seen recent data from two more high hemoglobin studies greater than 13 in target terms. GOG-191 is a small data set from a study which terminated early. PREPARE for the survival and progression is an unplanned interim analysis of the primary endpoints which will be mature at 5 years of follow-up, which have not yet been reached.

Signals in these studies are inconclusive in the context of other similar studies in similar patient

populations which have mature follow-up.

An independent patient-level analysis with all of the available data is underway, will be informative and will be available later this year.

[Slide.]

I would now like to look at the ongoing pharmacovigilance studies and our new proposed study.

We have a number of postmarketing commitment pharmacovigilance studies.

The first of these is Amgen Study 145 in small cell lung cancer. This data was first presented to ODAC last year. We have updated the data set with the centrally read radiology and this has not changed the outcome of this study.

There is no difference in survival in this rigorous placebo-controlled study in a homogeneous patient population. Follow-up continues with this study.

This GELA LNH-03-6B study continues on accrual with 458 out of 660 patients. I should note that this study does allow the use of erythropoietin at a hemoglobin below 9 as a rescue strategy in the control arm, as is the standard of care in France where this study is being conducted.

The PREPARE study I have just discussed. It is complete in accrual terms but the follow-up is not complete. We are awaiting 5 years follow-up data and that will be sometime yet.

The ARA-PLUS study in adjuvant breast cancer continues accrual with 1,112 patients out of 1,234. This will be an important data set in adjuvant breast cancer.

Recently, the Data Safety Monitoring Committee has met and discussed this study and has recommended that it continue unchanged except that the hemoglobin ceiling be reduced from 13, which is its current level, to 12 to be concordant with the new European label.

The DAHANCA 10 study was discussed at ODAC last year. This was presented as interim data at a scientific meeting in Europe in September last year and will be published in a peer-reviewed journal this year we understand from the investigator.

Finally, the EPO-3010 ANE study continues accrual with 280 out of 1,000. This study in a homogeneous population has been challenging to accrue and following discussions between the sponsor and the FDA, amendments have been made to the protocol to broaden to second-line

metastatic breast cancer patients and other types of chemotherapy to allow accrual in this study to improve and we believe that that will help now that that protocol has been amended.

[Slide.]

I am now going to briefly discuss the new proposed pharmacovigilance study, Study 782. This is a placebo-controlled, randomized study in three major tumor types, namely, metastatic breast cancer, advanced non-small cell lung cancer and metastatic colorectal cancer.

It is randomized 2:1 in favor of the darbepoetin arm. Patients on the study will be receiving chemotherapy per the labeled indication and darbepoetin will be dosed to the safety ceiling of 12 per the labeled indication.

It is specifically designed to address overall survival and progression-free survival in a rigorous manner. There will be regular radiographic review and tissue samples will be collected in some patients for Epo-receptor analysis if and when a reliable agent for detection becomes available.

There will, of course, be a Data Safety Monitoring Committee which will formally and regularly assess interim

data.

[Slide.]

The primary endpoint is overall survival. This is designed and powered to exclude in a non-inferiority design a hazard ratio of 1.15 for each tumor type.

Assuming that we see similar outcomes in each tumor type, there will be the ability to pool these to exclude a hazard ratio of 1.1.

Progression-free survival is a powered secondary endpoint. We will also look at other secondary safety endpoints of adverse events--patients who exceed the safety ceiling of 12, and the sub-study on TVE prophylaxis in high-risk patients.

Other efficacy endpoints will also include transfusion and we are also working to design a patient reported outcome measure which will meet FDA guidance.

[Slide.]

When we look at this study with respect to those factors which have been discussed at previous ODACs as ideal in the design of survival studies, this study almost uniformly addresses those design issues.

The only area in which it varies very slightly is

in the homogeneous use of chemotherapy which from our experiences in EPO-ANE-3010 we need to use broader chemotherapy regimens which will not impact the validity of this study but will allow more rapid accrual.

[Slide.]

Formal feasibility for this study, by which I mean approaching sites to see if they will be interested to take part in such a study, is already underway worldwide. This is a large study and will require a very large number of sites all across the globe.

We are working to finalize the study protocol. But this will be subject to a special protocol assessment and will be submitted to the FDA to make sure that both sponsor and FDA are aligned on the adequacy of this study to address the concerns which have been raised.

It will also need to be submitted to other regulatory authorities worldwide to ensure that they, too, would be satisfied with the results of such a study. Other potential studies are also in discussion with the FDA to ensure that we have a comprehensive pharmacovigilance program.

[Slide.]

So, as we conclude this section, I would like to briefly summarize on the ground that we have covered.

Benefits of ESAs are clear, both transfusion and symptom relief. Transfusions in ESAs are different anemia management strategies, prevention of transfusion with ESAs and rescue with transfusion. Both transfusions and ESAs have known and uncertain risks.

Experimental studies with high hemoglobin were set off looking for survival benefits and some of these have raised concerns which we have acknowledged and been incorporated in labeling.

Primary data from all of the studies that are being considered informative for the survival question have been submitted on time and as agreed to the Agency for their review although much of this has been recent and the FDA have not yet been able to review this.

Target hemoglobin affects both dose and achieved hemoglobin. And it is important when we are looking for an adverse event to be able to distinguish between those two and decide which of these might be causing the problem that we are trying to track down.

Higher achieved hemoglobin is, not surprisingly

given the underlying biology and the confounding that I have described, associated with better outcomes, not worse outcomes.

Looking at such responders, two-thirds of whom are patients treated with ESAs, the benefits are very clear. They received minimal dose, they avoid transfusions. In non-responders, we are proposing to limit exposure in these patients who receive a lot of transfusions and little benefits from ESAs.

A conservative hemoglobin initiation of less than or equal to 10, but allowing discretion for physicians, for patients who may need to have higher initiations due to cardiovascular or other concomitant comorbidities is proposed in order to reduce overall exposure in this patient population whilst maintaining benefit.

Patients with cancer are at high risk for TVE and ESAs increase that risk. TVEs could explain the observed mortality signals and this will be further explored in new studies.

Consistent clinical data with respect to progression have not been seen within the chemotherapy settings. Two further studies have recently been reported

with high hemoglobins designed to assess improved survival and have triggered this meeting.

One is a limited data set in an incomplete study in cervical cancer, the other is an unplanned analysis of an incomplete interim data set in the adjuvant breast cancer in which follow-up continues.

The report which has been provided to the FDA which is final is the interim data set for the pathologic complete response, the formal endpoint for this interim analysis. In both cases, data from other mature and complete studies does not corroborate the findings within those two studies.

Study level meta-analyses have been reported over time and these do have slightly differing outcomes depending on the data set and analytic approach used, however, they have all been concordant in showing that within chemotherapy, regardless of whether the studies are anemia prevention or treatment, there is not an adverse outcome seen in the meta-analyses.

This does not exclude an adverse outcome and does not negate the signals observed but does mean that we have inconsistency, further research is required, and we are

proposing to do that.

A comprehensive patient level meta-analysis is underway and will allow both time-based analysis of survival and looking at patient covariates.

The ongoing PV program is continuing to deliver data and will continue to do so over the next few years. The new proposed study will rigorously answer these questions in three commonly occurring tumor types.

Based on this assessment, we believe that the benefit-risk assessment for ESAs and CIA remains positive when used according to label.

Safety signals have been observed and prominently included in the label but uncertainty remains and there is therefore a need for further data which we will be provided by both the ongoing and proposed pharmacovigilance studies.

Ongoing risk management includes proposed changes to the label to limit exposure whilst preserving benefit, and a comprehensive risk management program that my colleague, Dr. Thomas, will now present, will further enable clear benefit and risk communication to patients and utilization of these agents according to the label.

Thank you.

[Slide.]

Risk Minimization

DR. THOMAS: Good morning. My name is Adrian Thomas and I am here to present the risk management plan and risk minimization action plan on behalf of Johnson & Johnson and Amgen.

[Slide.]

Two key components to our risk minimization plan are, first, label modifications to further enhance the risk and benefit profile in patients with chemotherapy-induced anemia and, secondly, the specific risk minimization action plan to ensure appropriate use.

[Slide.]

I would like to draw your attention to the key tool for primary risk communication, which is the label in the black box warning which reflects the changes recommended at the 2007 ODAC and discussions with FDA.

Importantly, on the top, the warnings of increased mortality, serious cardiovascular and thromboembolic events and tumor progression.

Secondly, the nephrology situation, the risks for death and serious cardiovascular events when administered to

higher target hemoglobin levels versus lower target hemoglobin levels.

Within the cancer indication, the ESAs have been observed with shortened overall survival and/or time to tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers when dosed to a target hemoglobin of greater than or equal to 12. It is also acknowledged that these signals have not been excluded when ESAs are dosed to a target of hemoglobin of less than 12.

To minimize these risks, as well as the risk of serious cardio- and thrombovascular events, those are the events that have been seen across all indications to use the lowest dose needed to avoid red blood cell transfusions.

Use only for the treatment of concomitant myelosuppressive chemotherapy and the need to discontinue these following the completion of a chemotherapy course.

[Slide.]

The sponsors proposed further label changes to further enhance the risk-benefit profile of these products in chemotherapy-induced anemia. The first is a more conservative initiation for transfusion avoidance, which

includes the initiation of ESAs at a hemoglobin level less than or equal to 10 g/dl. As mentioned before, this is a reduction from the current recommendation which is 11 g/dl.

This will avoid exposure by patients to ESAs who may not necessarily reach the new target level of 10 but still preserving the proven benefits in that population as the benefits have been primarily seen in the 10 to 12 range.

Secondly, increasing improvements to dosing guidance to reduce further unnecessary exposure, limited dose escalation, which will be appropriate per the pharmacologic profile of each product, and discontinuing ESA use for non-responders.

By this, we mean discontinuing ESA therapy for patients who do not achieve a hemoglobin of 10 or a rise of 1 g/dl over a period of two months as these patients clearly do not demonstrate benefit regardless of whatever their risk may be.

It also includes a safety ceiling of 12, which reflects the data we have, which is that high target studies above the level of 12 have also not shown a benefit and may well confer risk.

It is important to note that the target range is

between 10 and 11, because physicians do need flexibility to achieve an appropriately meaningful hemoglobin response within the context of real world patients in clinical practice, however, it is our recommendation that the overall goal is to achieve the lowest possible dose to achieve the benefits allowing for clinical flexibility.

[Slide.]

I would like to talk now about the risk minimization plan, acknowledging upfront that following the Food and Drug Administration Amendment Act, this may well migrate in 2008 to risk evaluation and mitigation strategy.

The principles I believe are the same. This is a strategic and specific program within the oncology indication designed to meet the specific goals and objectives in minimizing product risks while preserving benefits.

We will propose tools that are evidence based, that allow appropriate product access, that consider stakeholder input, technology and the complexity of the practice settings.

It is worth noting that there will be challenges for ESAs given the variety of indications including

nephrology and oncology and others, the variety of practice settings within oncology, the community-based centers, hospitals, so-called super clinics.

We need to ensure that we don't raise undue burdens to access or place undue burdens administratively on these clinical settings. The three categories of tools the companies have evaluated include target education, outreach systems, reminder systems and performance-linked access systems, which are really around restrictions of distribution.

The effectiveness of these tools will be monitored and periodically reported to the FDA.

[Slide.]

I will be discussing for ESAs and chemotherapy-induced anemia what should the goals and objectives of RiskMAP be, what will be the appropriate and effective tools following our evaluation, and how we propose to monitor this effectiveness and actions taken thereafter.

[Slide.]

We have identified four CIA risks from our investigational use outside in high target studies that we can mitigate in chemotherapy-induced anemia within the label

usage. The first two on the left are uses that can be modified or risks that can be modified. This includes avoiding high-target hemoglobins, complying with the recommended initiation hemoglobin levels and ceiling levels.

TVE risk--and it is important to note the ESAs are only one incremental risk factor for TVE in patients with cancer. Cancer itself provides an increased risk for TVE. Our recommendation is not specific to ESAs, but we propose to conduct a widespread education program to ensure that these risks are identified and, if necessary, appropriately managed.

I will say that the survival signal has been seen in the nephrology setting and the data from the high target hemoglobin studies in oncology have shown potential mortality issues. We have not seen that issue within label use and TVEs are manageable within the clinical setting.

On the right-hand side, clearly areas where we have not demonstrated benefit, anemia of cancer and radiotherapy only, and also patients who don't respond. Regardless of what we believe about the risks in these patients, if they do not respond with an appropriate hemoglobin response, they will likely require a transfusion

and therefore do not need an ESA.

Although these are all contained within the label and largely within the boxed warning, there is our proposal to incorporate those into a formal RiskMAP to ensure adherence to that label.

[Slide.]

Our specific goals will be to minimize risk while preserving benefit by ensuring appropriate ESA use in specific populations, eliminating inappropriate use.

The objectives, discontinuation in non-responders and following completion of the chemotherapy course, identifying and appropriately managing patients at risk for TVE, eliminating exposure in unlabeled indications, and patients who do not meet the hemoglobin eligibility criteria.

[Slide.]

So what does this look like? This looks like a series of tools that will be applied within a RiskMAP framework to address the identified risks on the top. The tools we have evaluated include targeted education and outreach.

This goes beyond the package insert to health care

provider letters, patient package insert updates, a Medication Guide which will need to be signed that it has been received and delivered, a patient start-up kit addressing risks and benefits. And clearly we have to address the appropriate cultural and technology issues related to educating patients at this stage of their cancer, a continuing education program to ensure that these are effective.

The second, reminder systems--and these are formalized processes and designed to ensure adherence to targeted education outreach and appropriate practice. This includes documentation and agreement by the health care provider and the patient of a discussion of benefit and risk and an agreement to receive an ESA.

This will be documented and placed in the patient file and subject to audit, documented patient receipt of the Medication Guide, and a prescribing algorithm or checklist designed to guide the physician or health care provider to appropriate prescription or product based upon the approved label.

We have also evaluated controlled oncology distribution. And this is an area which will be

challenging. We want to acknowledge upfront potential burdens and barriers to access for patients who have chemotherapy-induced anemia.

There are three broad settings of care as I have described - the hospital-based setting, the super clinics and community-based centers. The majority of patients receive the chemotherapy in community-based settings and therefore we have to ensure that we don't unduly restrict access to those patients who may otherwise have to move to other settings of care to receive treatment.

We do propose to enroll pharmacies and distributors, those who are willing to comply with a risk minimization action plan, and to make sure that we enroll our provider sites--and they also have to agree to comply with our risk minimization action plan.

This is an area that we will evaluate closely in consultation with stakeholders, the FDA, but we would be also interested in the ODAC's input.

[Slide.]

With respect to monitoring, evaluation and reporting, it is critical to demonstrate the success of this plan. We will be contracting this to a third party who will

be responsible for enrolling pharmacies, distributors, provider sites who agree to comply with the RiskMAP.

The third party will maintain a database of these sites and distributors and will conduct compliance and utilization audits. I will share with you some information in a few minutes around utilization.

These audit reports will be provided to the sponsors who will evaluate and report them to the FDA. The intent will be to evaluate and demonstrate the effectiveness of the ESA RiskMAP based on defined process and outcome metrics and to implement whatever strategies at a tool or program level that are required to ensure we are successful and these results will be shared.

[Slide.]

It is important to note that ESA utilization patterns have changed dramatically during 2007 as a result of the label changes, safety warnings and reimbursement changes in the U.S. oncology setting.

Fifty percent reduction in patients in any month exposed to ESAs in 2007 compared to the average of 2005 and 2006.

ESA use in cancer patients with hemoglobins

greater than 12 has reduced from 12 percent to 5 percent. This is clearly an area we can target our risk minimization action plan to improve.

The percentage of patients initiating ESAs in chemotherapy-induced anemia when the hemoglobin level is less than 11 has fallen from 80 percent to 64 percent in oncology clinics.

Although they are not part of an FDA risk minimization action plan, the sponsors are committed to supporting efforts by payers to align coverage and reimbursement policies with the FDA label to reinforce appropriate use as this has clearly been a highly effective mechanism.

These data come from claims data from a large EMI database.

[Slide.]

In summary, the sponsors have proposed important label guidance to reduce ESA exposure while still maintaining benefits for patient with chemotherapy-induced anemia. We recognize that reimbursement policies provide a tool for minimizing inappropriate use in concordance with the approved label.

We are committed to a RiskMAP that ensures appropriate use of ESAs in chemotherapy-induced anemia. We have proposed a variety of tools I have discussed before.

I would also reiterate the sponsors do not intend to use broadcast DTC advertising for ESAs. The RiskMAP effectiveness will be evaluated through third party measures and we will provide regular updates to the FDA and are committed to whatever measures are required to ensure any RiskMAP is successful.

[Slide.]

I would like to now call my colleague, Dr. Paul Eisenberg, to summarize.

Proposed Label Revisions and Summary

[Slide.]

DR. EISENBERG: I will make some summary comments on behalf of both Amgen and J&J.

First and foremost, I want to point out that the sponsors agree with the ODAC 2007 recommendations. There were concerns raised, they needed to be appropriately addressed. We sought to do so. We think additional measures are appropriate and, in fact, believe that the risk minimization and additional activities we are proposing will

assure appropriate use.

The question on the table, though, is obviously more profound and that is, given the signals that have been seen, what does this speak to in terms of potential mechanism regarding the indication, the benefit-risk.

There is no question that the benefit transfusion has not changed and that the impact on the improvement of anemia in patients undergoing chemotherapy for ESAs is different in terms of the treatment of anemia than transfusion and provides a benefit to patients.

It is clear that the signals that have emerged are important, they need to be addressed, patients need to be aware of them, providers need to prescribe understanding them.

We do, however, differ with the explanation being as simple as tumor progression. We have considerable data in the totality of all the studies that have been done with ESAs that suggest, like any other titratable drug, the endpoint is important.

We have learned as we targeted high hemoglobins and used doses to achieve those high hemoglobins, often in patients in whom pharmacologically would not respond to the

ESA, that that was associated consistently with a poor outcome. We believe that should be the primary means of labeling and managing patients within the indication.

There is no clinical evidence that clearly defines tumor progression within the chemotherapy-induced anemia population as a reason for the signals that have been observed and that underlies the strategy that would define use by tumor type.

There is a concern regarding thrombovascular events and we believe that is important and can be managed by using lower hemoglobin targets, managing dosing appropriately and avoiding excess disclosure.

The PREPARE and GOG studies that have emerged since 2007 are part of a very large set of data that we have described. We acknowledge that all of these data are difficult to review in aggregate and, clearly, the Committee's judgment as you look at each of these questions is going to be critical and as you look at each of these studies.

The PREPARE and GOG studies are not compelling. They do not represent the data set that clearly indicates the risk has changed since you evaluated these data in 2007.

We do believe that a comprehensive patient level meta-analysis, independently done, is important to guide further use of these agents.

We are delighted that the Cochrane group has agreed to do that for all of the sponsors and include all of the data. So this represents all of the data in the oncology indication and look forward to being guided by their interpretation and analyses going forward.

We recognize that the results of meta-analysis should not dismiss the importance of signals that have been observed, and we believe that it should guide the labeling as it has to advise the potential risk cannot be completely excluded. But we do not believe the data support further restrictions based on tumor type or support withdrawal of the indication.

We do, however, believe that our response and how we provide guidance on the management of ESAs needs to be robust, aggressive and in a well-considered risk minimization program.

[Slide.]

My colleague, Dr. Thomas, has outlined our program. I won't reiterate his points. But risk assessment

in addition to the studies we have described, the independent analyses, and risk minimization designed to reduce exposure through an aggressive program that ensures that there is controlled distribution of ESAs to providers who understand these risks and agree to ensure that they have a robust discussion with their patient regarding risk.

I would highlight that it is important to recognize that the setting in which this discussion occurs for a patient is a setting of extreme stress, concern at the time of a diagnosis that is life-changing for many patients.

We believe that this should be recognized and should be informed in how to have this discussion at a time when patients can make informed decisions and that those decisions should be documented.

We strongly feel, and both sponsors agree that a third party oversight of the program, regular updates in monitoring are important to transparency of the success of the program. In point of fact, the data suggest in 2007 that we have made strides to have the risk fully recognized and for management of ESA use in chemotherapy-induced anemia to be appropriate.

I want to thank the Committee for your time, we

appreciate your judgment and looking at the data in a balanced manner and providing further guidance to the sponsors and FDA in the appropriate use of ESAs in chemotherapy-induced anemia.

Thank you.

DR. MORTIMER: Thank you.

We are going to take a 15-minute break. So we will be back here at 9:50.

[Break.]

DR. MORTIMER: We would like to resume the hearing, so if people could take their seats. We would also like to thank the sponsors who moved some of their staff members into the overflow room so that others could have seats here. So thank you very much.

The next part of the hearing is the FDA report and I will turn this over to Dr. Juneja.

FDA Presentation

ESAs for Chemotherapy-Induced Anemia and Management of Risks

DR. JUNEJA: I hope everyone had time to refill their coffee mugs and their stomach.

Welcome to FDA's presentation today.

[Slide.]

I am Vinni Juneja, a medical officer in the Division of Biologic Oncology Products. I would like to remind everyone that today's discussion will focus on the ESA oncology indication and not on other indications for ESAs.

[Slide.]

Credits also to the rest of my review team, all of whom have proved that working in the Government is not just a 9:00 to 5:00 job.

[Slide.]

For our presentation today, we will start with the background on ESAs. This background will consist of a regulatory history, the benefits versus risks of ESAs, and oncology trials that have showed decreased survival and/or increased tumor promotion.

Since the May 2007 ODAC meeting on ESAs, we have several updates to present. The two additional trials which showed decreased survival and/or increased tumor promotion will be presented, new analyses on hemoglobin levels will be presented, and current data submitted to, and analyzed by, FDA, by tumor histology, will also be presented.

We will also outline FDA actions since the May 2007 ODAC. We will end with a variety of risk evaluation and mitigation strategies to manage the risk of ESAs given currently available evidence.

We will start a brief snapshot of regulatory history.

[Slide.]

This slide provides an overview of ESAs for the indication of chemotherapy-induced anemia that are available within the U.S. and outside of the U.S. The first ESA to be approved in the U.S. in oncology was Procrit or Epoetin alfa and was approved in 1993. Darbepoetin, or ANE, was approved in the U.S. in 2002. The ESAs Eprex and NeoRecommon are approved for use outside of the U.S. and are relevant because numerous studies have been conducted using these agents.

[Slide.]

This slide offers a timeline for approval dates of Epoetin and Darbepoetin, as well as dates of previous ODACs. Now, the first approval of Epoetin in the U.S. was in 1988 in the indication for anemia related to chronic renal failure.

Epoetin was then approved in 1993 in the oncology indication for use in patients with anemia due to the effect of concomitantly administered chemotherapy.

Darbepoetin was approved in 2002 in the oncology indication and previous ODACs in 2004 and 2007 have been convened by FDA in response to oncology trials showing increased tumor promotion and/or decreased survival.

Now, we will examine the benefits versus the risk of ESAs in oncology.

[Slide.]

The clinical benefits of ESAs, as described in the label, were demonstrated in anemic patients receiving chemotherapy who were able to avoid red blood cell transfusions and their concomitant risk.

At best, 30 percent of patients, or 1 in 3 patients, derived the benefit through the avoidance of transfusion, while all patients incur the risk of ESAs.

[Slide.]

These are the actual benefits of ESAs with respect to reducing the proportion of patients on chemotherapy who are transfused.

Looking at the top table, the 1993 approval of

Procrit was based upon pooled data from 6 studies with 109 evaluable patients. These studies demonstrated that 22 percent of patients were transfused in the Procrit arm, while 43 percent of patients were transfused in the placebo arm.

Now, referring to the bottom table, the 2002 approval of Aranesp was based on a study with 297 evaluable patients and demonstrated that 21 percent of patients were transfused in the Aranesp arm, while 51 percent of patients were transfused in the placebo arm.

The patients in the Procrit approval received both platinum and non-platinum based chemotherapy, while patients in the Aranesp approval received platinum-based chemotherapy. Their ESAs do not eliminate the need for transfusion but an approximately 50 percent reduction in the percentage of anemia patients who are transfused.

[Slide.]

Now, these are effects of ESAs that have not been established with sufficient evidence. Improved quality of life, fatigue and other symptoms associated with anemia in patients with cancer have not been established according to FDA standards in randomized, double-blind, placebo-

controlled trials.

Improved survival or improved tumor control in cancer patients have not been established with the use of ESAs.

The majority of the trials that we will be mentioning today have been designed to detect evidence of improved survival or tumor outcome and none of these trials have definitively shown improved survival or tumor outcome.

[Slide.]

Now, red cell transfusions are the alternative to using ESAs. This slide outlines the most significant risk of red cell transfusion and the incidence of these risks are estimated to occur in 1 per 1,000 units of red cell transfused to 1 per 1 million units of red cells transfused.

Unfortunately, no trial has collected data on adverse events relating to red blood cell transfusion to assess the impact of ESAs on the reduction of transfusion risks in patients with cancer.

[Slide.]

In contrast to the risk of red cell transfusion, these are the risks of ESAs in cancer patients. First, the risk of increased thrombovascular events in both cancer and

in patients without cancer.

Numerous oncology trials have shown an increased risk of thrombovascular events in patients receiving ESAs, so we can regard this as a known risk of ESAs. And this will cause increased morbidity and potentially increased mortality and this risk needs to be weighed against the benefit of reducing the proportion of patients transfused.

Secondly, the risk of decreased survival. And, third, the risk of increased tumor promotion.

[Slide.]

Six studies show statistically significant evidence of increased tumor promotion and/or decreased survival and these studies are listed here.

There is 1 study in breast cancer, 2 studies in head and neck cancer, 1 study in lymphoid malignancies, 1 study in non-small cell lung cancer and 1 study in a variety of tumor types.

Two additional trials showed trends of increased tumor promotion and/or decreased survival and survival results from these studies have been presented to FDA since the previous ODAC in May 2007.

So the first is the PREPARE study in patients

receiving neoadjuvant chemotherapy for breast cancer. And the second is the GOG-191 study in patients receiving concomitant chemoradiotherapy for cervical cancer.

So these first 6 studies highlighted in yellow have previously been discussed in both the 2004 and 2007 ODACs and these last 2 studies now highlighted in yellow, the PREPARE and GOG-191 study will be further discussed here.

[Slide.]

I will now briefly present a timeline of relevant oncology studies and studies with decreased survival and/or increased tumor promotion relative to the 2004 and 2007 ODACs.

[Slide.]

This slide provides a road map of where we have been prior to ODAC 2002, important trials presented at ODAC 2004 and events that have occurred subsequent to ODAC 2004 leading to ODAC 2007.

I will now empty out this map and we will build it back up. At the time of the approval of Epoetin in the indication for chemotherapy-induced anemia in 1993, there was a theoretical concern for tumor promotion.

In the pooled studies that resulted in the 1993 approval for Epoetin were not designed to assess for tumor promotion. After the 1993 approval, the postmarketing commitment study N93-004, which is highlighted in yellow, in small cell lung cancer, was agreed upon between Amgen and FDA to assess the tumor promotion potential of Epoetin.

Now, the BEST and ENHANCE studies, which I have highlighted in yellow, were also conducted prior to ODAC 2004 and both showed decreased survival in patients receiving ESAs, which led FDA to convene ODAC in 2004.

[Slide.]

Now prior to ODAC 2004, GOG-191 study, which I have highlighted in yellow now, in cervical cancer, was prematurely terminated due to an increase in thrombovascular events. The survival results of this trial were not known until December 2007.

Now, three other trials not shown in this slide, in breast cancer, small cell lung cancer and gastric and rectal cancer were also prematurely terminated prior to ODAC 2004, also due to an increase in thrombovascular events.

Now, these studies in yellow that have appeared in the right-hand side of the slide were trials that were

discussed at ODAC 2004. Now, these studies were already ongoing as of May 2004 and, according to Amgen and Johnson & Johnson, were designed to answer questions regarding the potential of ESAs to cause tumor promotion.

Now, we remind the Committee that the majority of these studies highlighted in yellow were not conducted under an IND and were not reviewed by FDA prior to their initiation. After review of the study protocols, FDA has determined that the majority of these studies were not designed adequately to test for and exclude increased risk.

Now, this study that I have highlighted in yellow, EPO-ANE-3010, was proposed at ODAC 2004 by Johnson & Johnson. This is a large breast cancer trial that has had significant difficulties with patient accrual.

Now, I have highlighted two more studies in the bottom of the slide, Studies 103 and 161. Now, these were not studies that were designed to look for safety signals but were studies designed to explore additional indications for ESAs.

Now, to review the timeline of studies with safety signals, worsen survival and/or increase tumor promotion, from the BEST and ENHANCE trials led FDA to convene ODAC in

2004. Now, I have highlighted four different studies in yellow, the 103, 161, CAN-20 and DAHANCA studies.

Adverse findings observed in these four studies led FDA to convene ODAC in 2007. Since ODAC 2007, we now have two additional studies, the PREPARE and GOG-191 studies, with trends to worsen survival and/or increase tumor promotion which are leading us to convene ODAC here today.

[Slide.]

This slide offers a summary of the 8 studies that have shown safety signals of decreased survival and/or increased tumor promotion.

[Slide.]

This table summarizes more specifically each of the studies with safety signals shown in the previous slide, and a similar table appears in the revised label issued last Friday.

The studies are divided into three categories: studies in which patients received chemotherapy, studies in which patients received radiotherapy and studies in which patients received neither chemotherapy nor radiotherapy.

Each of these studies randomized patients to an

ESA versus a control arm that may have included transfusion support. We will start with the studies in patients who received chemotherapy, which is the labeled indication for ESAs.

The BEST study involved patients with metastatic breast cancer and demonstrated worse 12-month overall survival in patients receiving ESAs.

The 161 study in patients with a variety of lymphoid malignancies demonstrated worse overall survival.

The PREPARE study in neoadjuvant breast cancer demonstrates trends to worse, relapse-free and overall survival.

The GOG-191 study in cervical cancer shows trends to worse overall survival.

Moving on to studies that used radiotherapy only, which is an off-label ESA use, the ENHANCE study in head and neck cancer showed worse loco-regional progression-free survival and worse overall survival.

The DAHANCA study in head and neck cancer showed worse loco-regional control and a trend to worse overall survival.

Lastly, two studies involved patients who received

neither chemotherapy nor radiation therapy, which is again an off-label ESA use.

The first, the CAN 20 study in non-small cell lung cancer showed worse overall survival and the 103 study enrolled patients with a variety of non-myeloid malignancies and demonstrated worse overall survival.

I would like to note that each of these trials targeted hemoglobins greater than or equal to 12 and we will be discussing this later on in the presentation.

I have highlighted two studies in yellow, the PREPARE and GOG-191 study, and these have had again survival data that has become available after ODAC 2007.

[Slide.]

I will now briefly present a timeline of these two studies and we will then explore details on both of them.

[Slide.]

Before we talk about these two new studies, I would just like to clarify the hazard ratios that will be presented for the rest of this discussion.

The trials presented in this discussion generally randomized patients to an ESA versus a control arm and, with respect to discussing the outcome of the clinical trial,

such as a survival result, a hazard ratio of less than 1 is in favor of the ESA arm, while a hazard ratio of greater than 1 is in favor of the control arm.

[Slide.]

Marked on this figure are the months since the May 2007 ODAC. Again, in late November and December of 2007, FDA was notified of the results of the PREPARE and GOG-191 studies and clinical study reports and data have been submitted to FDA on both of these studies. Labeling updates incorporating the results of these two studies have been initiated in December 2007.

[Slide.]

Now, we will examine these two studies in more detail. We will start with the PREPARE study in patients receiving neoadjuvant chemotherapy for breast cancer as agreed upon between FDA and Amgen, the PREPARE study with a postmarketing commitment study as of March 2006.

[Slide.]

In a letter in March 2006 from FDA to Amgen, a postmarketing commitment agreement was noted to obtain and submit a final study report including the primary data and analyses of the PREPARE study and the final study report