FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

TWENTY-FOURTH MEETING

OF THE

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE



8:05 a.m.

Friday, July 30, 1998

Versailles Ballrooms I and II
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland 20814



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ALSO PRESENT:

RICHARD CHAMPLIN, M.D.
FRANCES MOTLEY

C O N T E N T S
Morning Session

C O N T E N T S
Afternoon Session

P R O C E E D I N G S

(8:05 a.m.)

MS. DAPOLITO: Good morning. I would like to welcome the committee and all here today to the 24th meeting of the Biological Response Modifiers Advisory Committee.

My name is Gail Dapolito. I am the committee Executive Secretary and designated federal official for today's proceedings.

I would like to begin this morning by introducing the committee members, consultants, and guests seated at the table. I will begin at the far end of the table here by the podium. Dr. Marianne Frieri, State University of New York, Nassau County Medical Center. Joining us shortly will be Dr. Susan Leitman, National Institutes of Health. Dr. Jonathan Arm, Harvard Medical School, Brigham and Women's Hospital; Dr. Charles August, Miami Children's Hospital; Dr. Carole Miller, Johns Hopkins Oncology Center; Dr. Richard Goldsby, Amherst College; Dr. Ellin Berman, Memorial Sloan-Kettering Cancer Center; the Chair, Dr. Julie Vose, University of Nebraska. Also joining us shortly, Dr. Hugh Auchincloss, Harvard Medical School, Massachusetts General Hospital. Dr. Virginia Broudy, University of Washington School of Medicine; the committee Consumer Representative, Ms. Abbey Meyers,

National Organization for Rare Disorders; and Dr. Dean Follmann, National Institutes of Health.

The FDA Center for Biologics Evaluation and Research is represented today by Dr. Patricia Keegan, Dr. Karen Weiss, and Dr. Jay Siegel.

One note: Dr. Frederick Appelbaum and Mr. Michael Katz are on today's roster. They will not be attending today's meeting.

I will now read for the record the conflict of interest statement for today's meeting.

This announcement is made a part of the record at this meeting of the Biological Response Modifiers Advisory Committee on July 30.

Pursuant to the authority granted under the committee charter, the Director of the FDA Center for Biologics Evaluation and Research has appointed Drs. Charles August, Jonathan Arm, Ellin Berman, Marianne Frieri, and Susan Leitman as temporary voting members for the committee discussions on the biologics license application for Stemgen, topic 1.

Drs. Daniel Salomon and Ellin Berman have been appointed as temporary voting members for the discussions on the Xenotransplantation Subcommittee report, topic 2.

Dr. Ellin Berman has also been appointed a temporary voting member for the discussion on topic 3.

Based on the agenda made available and on relevant data reported by participating members and consultants, it has been determined that all financial interests in firms regulated by the Center for Biologics Evaluation and Research that may be affected by the committee's discussions have been considered.

In accordance with 18 U.S.C. 208(b)(3), Dr. Virginia Broudy has been granted a waiver which permits her to participate fully in the committee discussions and vote on topic 1.

Dr. Hugh Auchincloss has been granted a waiver which permits him to participate fully in the discussions and vote on topic 2.

Also, in accordance with the Food and Drug Administration Modernization Act of 1997, section 505, Dr. Broudy has been granted a waiver which permits her to participate fully in the committee discussions on topic 1.

In regards to FDA's invited guests for topic 1 and topic 2, the agency has determined that the services of these guests are essential. Drs. Dean Follmann and Marianne Michaels had no financial interests to report. Dr. Follmann and Dr. Michaels have been invited by the committee Chair to participate in today's topics in a nonvoting capacity.

In the event that the discussions involve

specific products or firms not on the agenda for which FDA's participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record.

Screenings were conducted to prevent any appearance, real or apparent, of conflict of interest in today's committee discussions. Copies of the waivers addressed in this announcement are available by written request under the Freedom of Information Act. With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Dr. Vose, with your permission, I would now like to begin the open public hearing.

DR. VOSE: Yes.

MS. DAPOLITO: Before we begin, though, I would like to ask, in consideration of the committee and others in the audience, that cellular phones be turned off and pagers be put in silent mode. Please step out into the foyer if you need to use a cellular phone.

We have received one request for public comment. I would like to invite Ms. Frances Motley to come forward and address the committee. For the public record,

please state your name, affiliation, and any financial association you might have with firms affected by today's discussion.

MS. MOTLEY: My name is Frances Motley. I own Liaison Services and Patient Advocacy in Hampton, Virginia. During the 1970s I was a researcher for supportive drug therapies at MCV-VCU with Bill Regelson. Most recently I was active in the patient advocacy program Dr. Kessler had for FDA to create a better access for information to patients.

My primary role is to represent people before Medicare, Medicaid, and Social Security for disability benefits.

I have no financial interests in any of the companies here today or that I might discuss.

Each one of you have a printing and I do not see any sense in going through the background.

I am here today to report to you the devastating nonmedical consequences of poor mobilization of platelet progenitors. These patients are left without cancer but exposed to repeated transfusions and in peril for catastrophic consequences for injuries that normally would be minor in nature except for their irreversible platelet depletion problem. As an example, one of my clients has been diagnosed with hepatitis C. Prior to her

transfusions, she was not in a high risk group for developing or being exposed to hepatitis C. I am not here to review how she got it, just that she has got it now and didn't have it before.

Although I am familiar with Neupogen in high dose chemotherapy with cycle compression and dose intensification, I've never had any clients who have ever been mobilized with Neupogen. All the clients that I have were mobilized by Leukine.

All the apparently irreversibly depleted platelet count patients were mobilized by Leukine at private profit-making centers.

When these patients get into the mode of depletion and repeated transfusions, Social Security is, by their new mandate, reviewing them at the three and five year out-date from their diagnosis.

Because they were originally approved for their disability because of their cancer and now their oncologists report them as disease-free or in remission, they no longer are disabled. They must meet the category of disability again. During that period of time, unless they follow some very strict guidelines, they lose their Medicare eligibility and their Medicaid eligibility, which means they lose their medical coverage.

The way patients get referred to me is that

they end up in the charity system looking for some assistance in paying for needed medical care, if they have not met the strict guidelines Social Security establishes for them to maintain their benefits during the appeal period.

So, this has devastating financial consequences to both the medical community, if those who are at major medical centers choose to continue seeing patients who have no insurance, no Medicare, no Medicaid, and no income. I am not aware of any of the profit centers in my area who will see patients who have no benefits whatsoever.

So, if there any product out there -- and from what I have read about the Stemgen, when combined with Neupogen -- if there is any product out there that will prevent this from happening, we need to get it approved and approved as quickly as possible.

If you've got any questions, I'll be happy to answer them.

MS. DAPOLITO: Thank you, Ms. Motley.

We have had no other prior requests for public comment. So, at this time I would like to ask if anyone else present would like to address the committee concerning this morning's topic.

I would like to mention we have scheduled an additional open public hearing to begin the afternoon's

discussion. If you would like to address the committee for this afternoon's topic, please register outside in the hallway.

Is there anyone who would like to address the committee at this time?

(No response.)

MS. DAPOLITO: I see no one.

Dr. Vose?

DR. VOSE: Thank you, Gail.

We have a very busy agenda today, so I would like to keep on time as much as possible. So, I apologize in advance if I appear abrupt in certain circumstances.

We will go ahead and start with topic number 1 and start with an FDA introduction by Dr. Edward Max.

DR. MAX: I'd like to thank the advisory committee coming to assist us in our consideration of ancestim, the stem cell factor that has been submitted for approval by Amgen. So, I am going to just give a very brief introduction.

The CBER review team includes the people listed here who have dealt with product issues, inspection, establishment licensing, clinical trials, bioresearch monitoring, and the whole team has been helpful in reviewing the product.

The next slide just gives an introduction to

some of the background. The stem cell factor protein was first found as a result of mutations noticed in mice, the steel mutation and white spotting. Both of these had a similar phenotype with drastic defects in hematopoietic cell system and also some pigmentation defects. It was determined, as a result of transplantation experiments, that the white spotting defect was intrinsic to the stem cells and the steel defect was intrinsic to the hematopoietic environment. Further experimentation identified the gene that was mutated in white spotting as c-kit, which is a tyrosine-kinase type receptor, and the mutated gene in steel is the ligand for that receptor, c-kit ligand, or most commonly known as stem cell factor.

C-kit itself is expressed on hematopoietic precursors and also on mast cells, and the stem cell factor is produced by stromal fibroblasts and fetal liver primarily, among other cell types.

The primary activities of this protein is that it promoted proliferation of early hematopoietic stem cells in the presence of specific cytokines, and related to this and the key feature that brings us here today is that it has the property of mobilizing these early stem cells into the peripheral blood. It also stimulates mast cell growth, maturation activity, degranulation, and that accounts for the chief side effect of this agent, as we will hear about

later this morning.

The protein is encoded by a gene whose structure is shown here. It has a signal peptide transmembrane region because the protein is initially expressed as a cell surface protein and a cytoplasmic domain with a total of 273 amino acids. There's a proteolytic cleavage site, and so the cleaved product is approximately 165 amino acids or some variability at the C terminal, and the engineered protein, which is produced in E. coli, engineered by the Amgen staff, includes the 165 amino acids of the soluble region plus an N terminal methionine.

This amino acid sequence was reverse transcribed using E. coli codon preferences and placed into a plasmid vector with a temperature sensitive promoter and a termination codon and a number of other elements that facilitated its expression. It was transformed into a production strain and the bacteria were then used to create a master cell bank and a working cell bank.

I will briefly go through on the next slide the production scheme which involves expansion of the cells from a working cell bank: the fermentation, a 150-liter fermenter; induction of the production of stem cell factor by a temperature shift via the temperature sensitive promoter. The cells are then harvested, inclusion bodies

are obtained, and the protein from the inclusion bodies is solubilized and then renatured in a controlled oxidation. Then there are three primary column purification steps involving cation exchange, reverse phase, and anion exchange. The purified protein is then formulated in mannitol, sucrose, histidine, glutamic acid, vialed, and then lyophilized.

Now, I just wanted to briefly go over the perspectives in which FDA has been guided by previous discussions by this advisory committee.

In 1994 we asked the committee what criteria we should use to evaluate agents intended for mobilizing peripheral blood progenitor cells. What this committee recommended is that such agents should demonstrate efficacy, clinical benefit to the patient in either of two categories: either superior time to engraftment or fewer leukaphereses with equivalent time to engraftment. That is the perspective that we have been operating under.

I would like to show the final slide which gives the highlights of the exchanges between FDA and the sponsor. Of course, there have been many communications back and forth, but the salient ones include the BLA application which was submitted in 1997, including final study reports for the phase I/II trial, and phase III studies, and then subsequently there were interim study

reports for four phase II studies, which you will hear about, and a long-term follow-up study.

A clinical complete review letter was sent out by the FDA in January of this year, indicating that further information would need to be submitted for approval, though as a response to this letter -- several responses, but finally in May of 1998, there was a response that answered essentially most of CBER's questions. This included the final study reports for three of the four phase II studies. You will hear about these in Amgen's presentation and our view later this morning.

I think I'll turn over the floor now to Amgen for their presentation.

DR. MORSTYN: Good morning. My name is George Morstyn. I'm Vice President of Product Development at Amgen and Chief Medical Officer. I'd like to thank Dr. Vose and the members of the BRMAC advisory panel and also Jay Siegel and the other members of the FDA for the opportunity to discuss with you our stem cell factor this morning. I'd also like to thank Dr. Max for that introduction.

In particular, I think I'd like to thank those members of the panel who have flown here from the west coast like us and are here at 5:00 a.m.

Now, the issues really that we're here to

discuss and that the FDA is really seeking your advice on I think boil down to two.

The first one is: What is the magnitude of the benefit that patients derive from the greater mobilization of CD34 cells by filgrastim and stem cell factor?

And then the second one is: What is the safety profile of stem cell factor when used appropriately, and do the benefits outweigh the risks? Clearly in our view the benefits do outweigh the risks, and stem cell factor will prove to be an important drug for patients who undergo transplantation.

Now, to help with your discussions, we've invited a number of distinguished clinical investigators from around the country, and I think their value comes in a number of ways, both their experience, but also that they have really treated 379 of the patients that are in the various submissions. So, they have firsthand knowledge of both the benefits and the side effects of stem cell factor.

They are, and I will introduce them briefly: Dr. John Glaspy, who is Director of the Bowyer Oncology Center at UCLA. I will ask him to stand up. Dr. LeMaistre, who is Director of the South Texas Cancer Institute; Dr. Shea, who is Director of the Transplant Unit at UNC; Dr. E.J. Shpall, who is Co-Director of the Transplant Unit at University of Colorado; and Dr. Pat

Stiff, who's Director of the Transplant Unit at Loyola University.

In addition, we've also asked two consultants to help with your deliberations: Dr. Steve Galli from the Harvard Medical School, who is an expert in mast cell biology, and Dr. Gary Koch, a consultant statistician.

The way that we'd like to present to you is shown on this slide. We'll ask Dr. Shea to provide a background for the potential of stem cell factor in transplantation. Then Bill Parker, the team leader at Amgen for the development of stem cell factor, will review its efficacy. Dr. Bill Sheridan from Amgen will review the safety data, and then Dr. Glaspy from UCLA will discuss the risk/benefit equation.

As we've heard, the clinical benefits of stem cell factor arise from its biology. It synergizes with many cytokines by acting on early cells and particularly with G-CSF in expanding early cells and in increasing the numbers of progenitor cells in the circulation.

I don't have time to review the preclinical studies, but they're studies that have been done in rodents, dogs, and primates showing that the cells mobilized by stem cell factor and G-CSF cell-for-cell are as effective as the cells mobilized by G-CSF, and you get many more cells so that one is able to rescue very

effectively animals that have been treated with myeloablative therapy. These preclinical findings led to the clinical program.

In addition, as was just mentioned, stem cell factor has well characterized effects on mast cells and these lead to the adverse events. So, there's nothing unexpected about both the clinical benefits of stem cell factor and the potential adverse effects.

As Dr. Max mentioned, stem cell factor was discovered at Amgen in 1989. An IND was filed in 1991. The initial phase I trials were done in the standard chemotherapy setting, and in that setting, we identified, at the doses that were tolerated by patients, modest effects on hemopoiesis, and also we identified doses that were not well tolerated. The side effects in that setting were due to effects on mast cells.

We then utilized the biology that I've just outlined and the effect of stem cell factor on mobilizing progenitor cells in an extensive phase I/II program, and the objectives of that, as you'll see, were to really define what the minimum effective dose of stem cell factor would be, what would be an appropriate duration of therapy, and to identify both the premedication regimen, and also a patient's selection criteria that would make patients able to benefit from stem cell factor with tolerable side

effects.

The program. As was just mentioned, stem cell factor was defined as an orphan drug because the target patient population is relatively small and this is a very specialized field.

To do a thorough job of the development of stem cell factor, so we could characterize both its benefits and the adverse effect profile, we've enrolled 1,067 patients in various clinical trials.

In 1997 we submitted results, as was mentioned, from 12 of these trials. They involved 64 sites, 250 physicians, and were carried out worldwide.

In response to questions from the FDA, we also then subsequently submitted final study reports on an additional 200 patients treated with myeloma and lymphoma. All the studies, the breast cancer trial, the myeloma and lymphoma trial, were randomized, controlled clinical trials with fairly similar study designs.

So, we have a large clinical database from which to work. As I mentioned, there are over 1,000 patients in these trials. In the early studies, we defined the optimum dose and schedule of stem cell factor, and then we have these three large controlled trials to look at its benefits and, in addition, two exploratory trials. What we'd really like you to look at is the overall picture and

what I think becomes apparent is the very consistent effects of stem cell factor in all these settings.

I think the clinical benefits of SCF really come from being able to achieve an optimum transplant for patients by giving them the optimum number of CD34 cells and also from the reduction in the number of leukaphereses that these patients undergo. The proposed label, which is in front of you, I think really reflects the clinical benefits that you'll hear about.

What I'd like to do now is introduce Dr. Shea to discuss with you the potential of stem cell factor in transplantation. Thank you.

DR. SHEA: Well, thank you, Dr. Morstyn and Dr. Vose, members and guests.

My job this morning is to provide a little bit of background and rationale for use of stem cell factor in mobilizing and acquiring blood stem cells and also a little bit of a background regarding transplantation with the use of peripheral blood progenitor cells as it currently exists.

First of all, the field of autologous stem cell transplantation is a fairly specialized area. There are a small number of highly trained physicians and nurses in the country that are currently undertaking this procedure. Approximately 170 transplant centers as identified by the

ASBMT have been registered and are performing these procedures each year, and there are about 12,000 autologous stem cell transplants performed in the United States each year, so not a huge number. On the other hand, these are for patients who obviously have bad diseases and for whom this is a worthwhile therapy.

Now, in evolving a little bit of the information regarding the current status of the field, I think there are two things that I want to focus on. One is the technology currently available to us for acquiring stem cells, which in fact are the necessary component in order to provide patients the ability to go on to the transplant. You have to get enough cells from them in order to then allow them to be treated with the high doses of therapy. So, in acquiring these cells, we undertake a process called mobilization and that can be utilized with either cytokines alone or with a combination of chemotherapy and cytokines in order to achieve the adequate number of cells that you're targeting.

There are two hematopoietic growth factors that are currently approved for progenitor cell mobilization in the United States. One is Neupogen. The other is Leukine. The trade names are listed up there.

Then lastly on this slide, I've indicated what are the clinical benefits of this. Obviously, there would

be no reason to pursue this therapy if there wasn't some clear benefit to patients undergoing this treatment. There has been clear data suggesting or indicating survival advantage for patients with lymphomas and multiple myeloma from several large randomized trials around the world indicating a survival advantage for patients undergoing high dose therapy. And there are a number of large trials underway in breast cancer with certainly encouraging data regarding how that will play out in the years to come, although the randomized trials have yet to be completed.

So, these are really the three major areas that currently are appropriate for blood stem cell transplantation.

Now, in determining what is an adequate dose of cells to be reinfused, because that really is what is the major factor involved with whether or not people get "an adequate graft," as I think you heard a little bit from Ms. Motley this morning, there are two major components that we look at. One is neutrophil recovery and the other is platelet recovery.

As you can see here, this is a slide that looks at the recovery of neutrophils in patients undergoing blood stem cell transplant as a function of the number of cells that they've had reinfused. The yellow line on the bottom there is patients who have had 1 or less than 1 times 10 to

the 6th CD34 cells. The red line is those who have had 2 or less than 2 CD34 cells. The blue line, the kind of turquoise line, there is for those who have achieved an infusion of 5 or more blood progenitor cells. Then the purple line there is those who get reinfused with 10 or more blood stem cells. This is data that has been provided by Dr. Glaspy in a publication that came out in Blood last year in a number of patients with breast cancer.

The important thing to note here is that neutrophils, i.e., those cells that fight infection, in fact recover pretty promptly and pretty uniformly in all of these patients despite the number of blood stem cells that they're reinfused with. Whether it's as few as 1 or as many as 10, these patients do recover their white blood count, and so infection is not the issue now that it was 10 years ago before we had blood stem cells and before we had growth factors.

However, on the next slide I'll show you that platelets, on the other hand, which are really the better marker, if you will, for true engraftment of the marrow, are a different story. As you can see here, with the same curves, yellow for 1, red for 2, turquoise for 5, and purple for 10, you can see a huge discrepancy in terms of the median time to platelet recovery there.

Also, even more importantly, if you look at the

right-hand side of these curves, there's a big splay in terms of the number of patients who do require transfusions and platelet support even out beyond 21 and 28 days, the point here being that if you give back more cells to patients, not only do their median platelet counts improve, but also more importantly, you bring in these patients who would otherwise be at risk for the long-term transfusion requirements that were mentioned earlier today which really can be quite devastating in a clinical setting because they tie people into long-term follow-up with their medical center even at a time when their cancer may be in remission.

Now, a couple more ways to display this are again data that was generated from the same trial by Dr. Glaspy looking at CD34 cells on the left, less than 1 times 10 to the 6th, 2 to 5 times 10 to the 6th, or greater than 5 times 10 to the 6th. If one looks at the median days to platelet recovery in the middle slide, what you can see there is that for the very low numbers of cells infused, the platelet median times are quite long, 31 days. That means a month's worth of transfusions. The range goes out to as far as 6 months, at least in that study that he performed, with 30 percent of patients requiring transfusions more than a month out from their transplantation.

If you look at the people getting an intermediate number of stem cells, those in the 2 to 5 group, the median comes down much lower. So, in fact that median is the same as even patients who get more cells. But you still have a marked range, 10 to 64 days, so there are some patients getting transfused even out at 2 months following their transplant, and 9 percent of patients are requiring transfusions beyond 1 month. So, again you've got a number of patients who don't fit within the tight framework that you'd like to say they're through with their treatment and they're now out and doing well.

Whereas, those patients who get 5 or more cells in the bottom line there, the median again is 12 days, so quite a short period of time for the thrombocytopenia. But most importantly, there are very few. In fact, in this study there were no outliers who were requiring transfusions out beyond day 28. So, you don't have the poor patients who are stuck out there 2, 3, 4 months still getting transfused with both platelets and red cells.

Now, another way to look at this is what are some of the other clinical and potential economic benefits for the use of more cells that result in more rapid and uniform engraftment. What I've looked at here is the length of stay, days to ANC greater than 500, platelets greater than 20,000, number of platelet transfusions and

red cell transfusions on the left axis. Then the two columns in the middle there are those patients getting less than 5 and those getting more than 5 times 10 to the 6th CD34 cells and then the p values for the difference on the right-hand side comparing the two columns in the middle.

This is two trials, again the one by Dr. Glaspy and another larger trial by Dr. Weaver that was published in the ASH meetings last December. Dr. Weaver's study actually included over 1,000 patients, data from a large multi-center study.

If you look at the duration of time in the hospital on the first line, for patients getting less than 5 versus more than 5, in the left-hand column you see it is 20 days. It drops down to 18 days. In Dr. Weaver's study, it was 14 days and dropped down to 11 days for those getting more cells. You can go on down in every category there and see an improvement in the patients getting a higher number of cells to be infused.

Now, obviously not everybody can get a higher number of cells to be infused, but I think it makes sense to look at this data and say that at least should be a target, and the more cells you can give back to patients, the more likely they are to do well.

The p values are over there on the right side.

The last thing I'll mention is that when we

talk about patients not requiring transfusions, getting out of the hospital and so on quicker, as you can see from Dr. Weaver's data, the savings can be anywhere from $4,000 up to $8,200. Obviously, those can be very center-dependent, but the idea is that you use fewer resources and patients do better.

Now, there are some other benefits that have been accrued to these patients as well, beyond just the issues of getting more cells. That in and of itself is not a benefit. But if you look at these large trials, Dr. Weaver's one, Dr. Bensinger from Seattle, Dr. Ketterer, Remes, van der Wall, Maroto, all of these trials have reported, in addition to more rapid and uniform engraftment, a reduction in the number of transfusions, frequency and duration of hospitalization, use of antibiotics, and so on. So, there's a number of other parameters that go into the supportive care of these patients which are improved by giving people back more cells.

So, in conclusion, I think it is safe to say that patients getting less than 1 times 10 to the 6th CD34 cells as part of their collection generally are considered to be unsafe transplants and most of us would not take those patients on to even single cycles of high dose therapy.

With patients getting the interim number between 1 and 5 times 10 the 6th, there is some safety concern. The majority of those patients will engraft their neutrophils adequately, but some of them, up to 15 percent or more, are going to be left with poor platelet recovery and the issues of prolonged transfusions.

Yet, with patients who get more than 5 times 10 to the 6th CD34 cells, there tends to be much more predictable and rapid engraftment, and perhaps most importantly, resource utilization is minimized and the potential for long-term problems is markedly reduced.

Now, when we talk about how do we get cells, one is how do we mobilize them and the other is how do we collect them. The collection is a process called pheresis or apheresis.

There are several disadvantages from having to pherese people multiple times. It would be ideal if you could do this once or twice rather than 5 or 6 times, and the reason being that people getting multiple phereses tend to have a higher incidence of deep venous thrombosis or catheter related infections, thrombocytopenia requiring transfusions, hypocalcemia, hypotension, and progressive anemia and thrombocytopenia associated with the multiple pheresis attempts. It is quite clear the more times you pherese somebody, the lower their hemoglobin level will

get, as well as their platelet count.

On top of that, there are issues of patient inconvenience. Having this done once is certainly much easier on patients than trying to do it 4, 5, or 6 times.

Transplant center resource utilization. It's quite expensive to set up these machines every time. If you could do it reliably one time, it would make our life much easier and certainly improve the patient's as well because it does not require so many trips back and forth.

Then lastly the cost there. As I alluded to before, if you don't have to pherese people, then potentially there's a substantial cost savings.

Now, we know that there are some patients who don't tend to do very well with mobilization and pheresis, and how do we identify those people up front? Well, we know that people with prior cytotoxic therapy using particular drugs such as melphalan, BCNU, or a drug called busulphan, many of which are commonly used in the treatment of lymphomas and myeloma, patients who get multiple cycles of conventional therapy -- and some people have said more than 6, others have said more than 12. The point is, the more treatment people have had before they come in, the harder it is to get these progenitor cells from them, and people who have had extensive radiation, particularly to the chest as many breast cancer patients have had, or to

the pelvis as people with diseases like ovarian cancer or lymphoma tend to have.

In general, people with a diagnosis of lymphoma or myeloma, owing largely to the fact they've tended to have had more prior intensive therapy, tend to be poor groups to mobilize. Lastly, people who have their marrow involved with tumor also tend to be a group that doesn't tend to do particularly well in terms of mobilizing their cells.

Now, having said that, even if you identify the people who don't tend to do well, it's important to realize that you can't always predict. There are patients who are going to do poorly despite them having all the good risk features, if you will. If one looks at the use of filgrastim or G-CSF alone for mobilization, approximately 20 percent of patients require more than 4 phereses to reach even that minimum number of 1 times 10 to the 6th CD34 cells, and this is data that has been obtained either from studies run by Dr. Glaspy and people at Amgen, but also from the North American Bone Marrow Transplant Registry, information that is provided to them by participating centers.

The next one says that approximately 60 percent of patients require more than 4 phereses to reach their target number of 5 times 10 to the 6th. So, even if we

accepted that as the number that we'd like to get, it's clear that not everybody is going to be able to achieve that even with otherwise good risk features.

In 1996, 13 percent of breast cancer patients, stages II to IV, and 15 percent of lymphoma patients underwent 6 or more aphereses in order to get their adequate numbers of cells, the point here being that this is not an insignificant problem. My guess, from talking to my colleagues, is that is probably an underestimate and if anything, more patients than that end up getting pheresed on multiple occasions, oftentimes more than 5 or 6 times, to get adequate numbers of cells.

So, the next two slides I'll finish up and just summarize. Increasing CD34 cell yields I think would benefit several different patient groups, really everybody who would be otherwise potentially eligible for this treatment. People who tend to be in the good risk categories who are likely to have a good yield with mobilization are the group that is likely to be able to do this with fewer phereses if in fact, you had a higher number of CD34 cells and better ways to mobilize patients.

People in the intermediate group may in fact reach their optimum number with fewer phereses, but also you're going to take some of those patients who would otherwise be below that threshold of 1 times 10 to the 6th

and in fact put them up above the level at which you feel that they are now safe to take on to transplant. So, it actually provides them the opportunity for treatment that they otherwise wouldn't have.

Lastly, the group who is likely to have a poor yield, perhaps the biggest benefit to them is that that really is going to improve the number of patients that are eligible for this treatment because many of them would otherwise have inadequate grafts to even take them on to a marginally safe treatment.

So, lastly, I'll just say that increased CD34 cell yields I think will decrease the number of patients requiring prolonged transfusion support. It increases the number of heavily pretreated patients eligible for transplantation. It decreases the duration of hospitalization and use of antibiotics. In at least one study, the one by Dr. Weaver, there was a reduction in the day 100 mortality in patients who got more than 5 times 10 to the 6th cells versus those getting fewer because of all the complications, as alluded to earlier, about transfusion requirements, et cetera.

So, with that, I'll go ahead and stop and turn it over to Mr. Parker.

MR. PARKER: Thanks, Dr. Shea.

With this, I'd like to spend the next several

minutes reviewing the efficacy data associated with stem cell factor when used in combination with filgrastim for the mobilization of peripheral blood progenitor cells.

As Dr. Morstyn showed you, we submitted 12 studies in the clinical program submitted with the BLA application for stem cell factor. There were three phase I safety trials, four dose finding studies, two randomized exploratory trials, one in myeloma, one in lymphoma which is currently ongoing, and in addition, three large randomized, controlled studies, each with over 100 patients in breast cancer, myeloma, and lymphoma. I'll focus most of my presentation on these three studies.

We've seen a very consistent effect of the addition of stem cell factor to filgrastim for PBPC mobilization, and this effect has been independent of the mobilization regimen, that is, whether it's with cytokines alone or with chemotherapy in addition to cytokines for mobilization. The clinical effects observed due to this increased CD34 positive cell mobilization are an increase in the proportion of patients able to achieve an optimal CD34 positive cell yield and in some patients a minimal cell yield to proceed to transplant, as well as to decrease the number of aphereses procedures required to obtain an optimal cell yield.

This graph shows the dose-response data from

our phase I/II breast cancer study conducted by Dr. Glaspy and other investigators here, Drs. LeMaistre and Shpall, and shows the dose response of stem cell factor when added to filgrastim for PBPC mobilization. I just want to make a couple of points on this slide.

Number one, as shown by the second bar here from the left, this is a group of patients who received stem cell factor alone for PBPC mobilization. As you can see, as a single agent, there weren't sufficient CD34 positive cells mobilized, and indeed 4 of the 5 patients who received this regimen received their backup marrow infusion.

The next point I'd like to make is that 20 micrograms per kilogram per day was selected as an optimal dose of stem cell factor based on a balance between the efficacy -- this was the lowest dose which had a statistically significant difference in number of CD34 positive cells -- balanced with safety considerations in terms of the incidence of serious systemic reactions.

As Dr. Shea mentioned, there are different clinical benefits due to increased CD34 positive cell mobilization depending on that patient population's inherent ability to mobilize CD34 positive cells with patients with high CD34 positive cells, most of whom are able to reach an optimal target for transplant, benefitting

mostly by reducing apheresis requirements, and patients with very low CD34 positive cell yield, most of whom are unable to reach an optimal cell target for transplant, experiencing primarily a benefit of increased proportion of patients reaching a optimal target and in some patient groups a minimal target for transplant. There's also a group of patients with moderate CD34 positive cell yields in whom you can see both of these benefits.

Amgen has performed large randomized studies in each of these three clinical settings. I'll just point out here on this slide that the ability of a patient group to mobilize CD34 positive cells is reflected in the cumulative proportion of patients able to reach an optimal target yield across the days of apheresis. So, for patients with lymphoma in our lymphoma study who were poor mobilizers, heavily pretreated patients, very few of those patients with filgrastim alone -- all of these lines represent patients treated with filgrastim alone -- are able to reach an optimal target within 5 aphereses.

In breast cancer patients undergoing cytokine alone mobilization, about half the patients are able to reach the target within 5 aphereses.

And in a select group of patients with multiple myeloma undergoing chemotherapy plus cytokine mobilization, a high proportion of patients are able to reach the target

yield within the maximum number of aphereses allowed.

This slide shows you in the solid bars here the group in each of these trials who received stem cell factor plus filgrastim. You can see that in every case the proportion of patients able to reach the target is improved with the addition of stem cell factor to filgrastim. You can see in heavily pretreated patients with lymphoma, breast cancer patients, as well as multiple myeloma patients where the difference appears primarily earlier.

I'd like first to discuss the study in breast cancer, which was the first randomized trial submitted to the BLA filing. This was a controlled, randomized, open-label study conducted at 14 transplant centers in the U.S. It was conducted in patients with high risk breast cancer, stage II through IV. In this study, as in all of our studies for PBPC mobilization, we utilized a central laboratory for CD34 positive cell analysis, and this laboratory was blinded to the treatment group.

In all of these studies, we've tried to standardize as many of the methods associated with the PBPC mobilization, collection, and chemotherapy regimen as possible, including this study.

This slide shows you the study design which included a one-to-one randomization to a control group receiving filgrastim at the labeled dose of 10 micrograms

per kilogram per day or to a treatment group receiving filgrastim at that same dose in combination with stem cell factor at the previously defined optimal dose of 20 micrograms per kilogram per day.

Daily apheresis began on day 5 and continued until either the CD34 positive cell target was reached or until a maximum of 5 aphereses were performed. Those patients who collected a minimum yield of 1 million CD34 positive cells per kilogram were then eligible to go on to the high dose chemotherapy regimen. In this case it was STAMP I followed by PBPC infusion and filgrastim support until ANC recovery, and patients were followed through 100 days of post-transplant for engraftment.

The co-primary endpoints of this study were, firstly, the number of aphereses required to reach the target CD34 positive cell yield and, secondly, as a safety assessment, the time ANC and platelet recovery post transplant with this study being powered to show similar engraftment and the protocol-defined clinically equivalent engraftment as less than a 2-day difference in neutrophil recovery or less than a 3-day difference in platelet recovery. Safety was also, obviously, an endpoint of this trial.

There were over 200 patients enrolled in this trial, and the treatment groups were well balanced for

baseline characteristics, including age, disease stage, and number of cycles of prior chemotherapy. The number of cycles of prior chemotherapy was prespecified in the protocol as a covariate for the number of aphereses to reach the target, and it as a highly significant covariate. And good statistical practice dictates that if a prespecified covariate is a statistically significant predictor of the response, in this case the number of aphereses, then it should be included in the analysis whether or not the groups are in balance at baseline.

This slide shows you the results of the co-primary endpoints. There was a reduction in the number of aphereses, in this case the median number of aphereses required to reach the target CD34 positive cell yield, patients on filgrastim requiring at least 6 aphereses; i.e., less than 50 percent of the patients reached the target within 5 aphereses. Patients in the treatment group requiring a median of 4 aphereses. There also was clinically equivalent recovery of ANCs and platelets as defined by the protocol. However, there was a statistically significant difference in neutrophil recovery, which will be discussed by Dr. Sheridan in the review of the safety information.

The protocol specified a Wilcoxon rank sum test which yields a p value of .104. The FDA's analysis

presented in their briefing document shows a p value of .14 based on two primary differences in the analysis.

There was 1 patient who was mobilized with SCF plus G-CSF whom the FDA counts as receiving G-CSF. This patient was initially randomized to the G-CSF arm. However, the study was conducted in 1995. If you remember on the east coast there were lots of blizzards that year, and this patient, due to a snowstorm, was unable to undergo apheresis and was subsequently withdrawn from the study. After meeting the protocol specified inclusion criteria, including being off cytokines for a week, the patient was re-enrolled, re-randomized to the SCF plus G-CSF group, treated with both cytokines and analyzed in that fashion in Amgen's analysis.

In addition, in the FDA's analysis, the patients who don't reach the target are counted as having received 5 aphereses regardless of how many aphereses they actually received. One effect of this is you count patients who reach the target on the fifth apheresis the same as you count patients who have 5 aphereses and don't reach the target.

As I mentioned, the number of cycles of prior chemotherapy was prospectively identified as a covariate. However, due to an oversight, a methodology was not included in the protocol for including that covariate into

the statistical analysis.

In addition, there were 15 patients who stopped apheresis prematurely prior to reaching the target and prior to undergoing 5 aphereses. In the Wilcoxon rank sum analysis, those patients are counted as having received the maximum number of aphereses. However, an alternative way of handling those patients would be to censor them at their last apheresis which makes maximal use of the data provided by those patients.

There are several different ways that you can analyze this data and the first two methods which I mention and the median number of days of aphereses are shown on the top two rows on this slide. An analysis which includes both the covariate and allows for censoring of patients who stopped prematurely was considered appropriate, and we employed the Cox proportional hazards analysis to address this, which yields a p value of .038, with the median reduction in aphereses being the same.

Alternative analysis, such as a Wilcoxon rank sum test, just counting the actual number of aphereses performed on patients within the trial, also yields a statistically significant result, maintaining a difference in number of aphereses of 2 aphereses.

A log rank test, which includes the censoring of patients who stopped apheresis prematurely, also yields

a statistically significant p value, as does the Wilcoxon rank sum test on an evaluable group of patients who had no significant protocol violations.

So to summarize the statistical results of this trial, the addition of SCF to filgrastim always reduces the number of aphereses required to reach the target, with a difference in median from 1 to 3 aphereses in the analysis I just showed you. In this case, means are not used due to the right truncated nature of the data and the need to assign artificial values to patients who don't reach the target which can distort means.

In addition and perhaps most importantly, the reduction in the number of aphereses is confirmed by two additional large randomized, controlled studies in multiple myeloma and lymphoma patients, which I'll discuss.

An observation in the breast cancer study was that there appeared to be a more sustained mobilization with stem cell factor plus filgrastim compared to filgrastim alone, and by that I mean that in later days of aphereses, the patients who received stem cell factor appeared to have a yield of CD34 positive cells which was more similar to their yield on the first-day pheresis. This graph expresses the yields on days 2 through 5 of apheresis as a percent of the day 1 apheresis yield, being 100 percent for the first column. So, this I think

graphically displays this effect of sustained mobilization with stem cell factor.

Now, two of the most clinically important outcomes and clinical problems in PBPC transplantation are patients that either don't collect enough cells to go on to transplant, which most groups would agree is at least 1 million CD34 positive cells, although that seems to be moving to perhaps even 2 million CD34 positive cells, or the incidence, as mentioned previously, of delayed platelet recovery beyond 28 days.

What this slide shows you is whether you employ a methodology of using fixed aphereses -- and this example is from our phase I/II breast cancer trial which used 3 fixed aphereses -- of if you apherese patients to an optimal target CD34 positive cell yield, the addition of stem cell factor to filgrastim improves the incidence of either of these negative outcomes.

Another point, if you just focus on the group receiving filgrastim, is that it's apparent that by employing a strategy of apheresing patients to a target of 5 million CD34 positive cells, you can also reduce the incidence of these negative outcomes.

The next study I'd like to discuss is a study conducted in myeloma patients. This study was conducted at 15 transplant centers in Europe and included patients with

stage I through III high risk disease and a similar design to the breast cancer trial. An exception is that this trial utilized chemotherapy plus cytokine mobilization, 4 grams per metered squared of cyclophosphamide as the mobilizing chemotherapy.

As you can see, the schema for this trial is very similar to the breast cancer trial. Again, the primary difference is the inclusion of chemotherapy and the mobilization regimen, the dose of filgrastim being 5 micrograms per kilogram per day, and daily apheresis being initiated when the white count was rising through 4,000 per microliter, and the high dose chemotherapy regimen being that which is appropriate for myeloma patients.

The primary endpoint of this trial, as with the breast cancer trial, was the number of aphereses required to reach the optimal target of 5 million CD34 positive cells per kilogram. Secondary efficacy endpoints included measures of progenitor cell yield as CD34 positive cells, granulocyte macrophage, colony forming cells, or mononuclear cells.

Again, there were over 100 patients enrolled in this trial and the treatment groups were well balanced for baseline characteristics. I'll just point out that the number of cycles of prior chemotherapy was quite small in this group of patients, a median 3 cycles in each treatment

group, and that chemotherapy was primarily VAD chemotherapy rather than melphalan-containing regimens which tend to be more stem cell toxic.

The results for the primary endpoint, number of aphereses, showed a statistically significant reduction from 2 aphereses in the group receiving filgrastim alone to 1 in the group receiving stem cell factor plus filgrastim. In addition, all of the secondary efficacy endpoints, the progenitor cell measures, were also statistically significant for the yield on the first apheresis and all aphereses, despite apheresing patients to the target. You can see the difference in CD34 positive cell yields on the first apheresis is almost threefold.

As I mentioned, all of the measures of progenitor cells in the first and overall aphereses showed statistically significant increases, including the GM-CFC and mononuclear cells.

The next study I'd like to talk to you about is the large randomized study in lymphoma patients, but before I do that, I just wanted to share some data from our dose finding study in lymphoma patients that was conducted at Memorial Sloan-Kettering and Loyola, which Dr. Stiff is here, as well as other centers.

In this study, looking at the subgroup of heavily pretreated patients -- and in this study a

definition of heavily pretreated was developed, which I'll share with you in a moment -- you can see that these patients had very low CD34 positive cell yields. However, there were higher yields in the patients who received SCF plus filgrastim, and in this study this did lead to a reduction in time to ANC recovery and time to platelet recovery in these patients.

However, this study was done quite early and the field was progressing, and the reliance on CD34 as an indicator of graft quality was becoming more and more universal and transplant physicians were becoming unwilling to transplant patients who had yields below 1 million CD34 positive cells per kilogram. So, for this reason we focused in future studies of trying to get more patients to an optimal level for transplant rather than trying to show engraftment differences by transplanting patients with low CD34 cell yields.

The lymphoma study had a design very similar to the breast cancer study. The primary differences included that it included patients with intermediate to high grade non-Hodgkin's lymphoma as well as patients with Hodgkin's disease, and all of the patients enrolled met protocol-specified criteria for being heavily pretreated.

These criteria, as I mentioned, were developed in a phase I/II trial and included patients who had 2 or

more cycles of various stem cell toxic agents, most of which Dr. Shea mentioned, nitrosoureas, such as BCNU and melphalan being primary among them. Also patients who had received prior high doses of Ara-C, as well as 10 cycles of any prior chemotherapy or radiation to significant areas of the bone marrow.

The study design is virtually identical to the phase III breast cancer trial with the main difference being the high dose chemotherapy regimen was appropriate for lymphoma patients.

The primary endpoint in this study was the number of CD34 positive cells in the first apheresis procedure. The reason this endpoint was chosen is at the time, as you saw from the phase I/II study, it was apparent that very low CD34 positive cell yields may be expected and it was uncertain how many of these patients we would be able to get to an optimal target. So, we included the clinical endpoints of proportion of patients reaching an optimal target, proportion of patients reaching a minimal target, and number of aphereses required to reach an optimal target as secondary endpoints within this study.

There were over 100 patients enrolled onto this trial. Again, the baseline characteristics were well balanced, in this case with the exception of prior radiation therapy which appears to bias against the group

of patients who received stem cell factor plus filgrastim.

The primary endpoint of the study: CD34 positive cells in the first apheresis. You can see here there was not a difference in the number of CD34 positive cells in the first apheresis. However, we did observe a similar phenomenon to the breast cancer study where there was a sustained mobilization with SCF plus filgrastim which resulted in more CD34 positive cells being collected over all aphereses.

The secondary endpoints of the trial I think reflect that increased CD34 positive cell collection. Firstly, there was a statistically significant increase in the proportion of patients able to obtain an optimal yield for transplant: only 17 percent of patients in the filgrastim alone group versus 44 percent of patients in the group receiving stem cell factor.

In addition, there was a statistically significant reduction in the number of apheresis procedures required to reach this target, although there was no difference in the median number of procedures. If you look at the 25th percentile, there was a reduction of at least 3 apheresis procedures.

Another endpoint was the proportion of patients reaching a minimal level for transplantation, and you can see that there's a difference, although it doesn't reach

statistical significance, with 26 percent of patients who received filgrastim alone unable to achieve a level to proceed to transplant versus 16 percent of patients who received stem cell factor plus filgrastim.

This slide just illustrates the sustained mobilization phenomenon observed in this study, similar to the breast cancer study.

At this point I'd like to just make a few comments on the FDA reviewer's conclusions expressed in the briefing document which was provided to the panel.

The first conclusion was that G-CSF and G-CSF plus SCF both mobilized sufficient numbers of CD34 positive cells for engraftment, and the conclusion went on to state that although this was true, there was no difference between the treatment groups where the SCF group fared better in terms of reaching a minimal level to proceed to transplant.

On the next slide, I'd just like you to consider the data which I've already shared with you both in the two breast cancer studies in terms of improvements in mobilization failures -- patients were unable to reach their minimal level for transplant -- or what we call engraftment failures here, patients with delayed platelet recovery. Although these differences between the two groups here are not statistically significant, we think

that they show important trends, as does the data from the lymphoma study which I just showed you, where 26 percent of patients mobilized with filgrastim were not able to proceed to transplant based on low CD34 cell yields versus 16 percent of patients who received the combination.

So, our response to the first conclusion would be that the studies were not designed nor powered to show statistical significance of these outcomes. However, there were three studies where we think clinically important trends are observed for both of these important clinical problems in transplantation: delayed platelet recovery or not collecting enough cells to undergo transplantation.

The FDA reviewer's second conclusion stated that the addition of SCF to G-CSF has a small to negligible effect on the number of aphereses to reach an optimal target of CD34 positive cells.

In making that conclusion, the reviewer has made a few assumptions which I just want to share with you.

The first is that the mean is an appropriate measure of central tendency, even though the mean can be distorted by artificial values which are assigned to patients who have not reached the target of CD34 positive cell yield.

A second assumption is that if you don't reach the target and you stopped early for any reason, you should

be assigned to the maximum number of aphereses allowed within the study.

A third assumption is that no one would ever undergo more than 5 aphereses. Now, the data that Dr. Shea showed you is that currently about 15 percent of both breast cancer and lymphoma patients are undergoing more than 5 aphereses. One of the effects of counting things this way, as I mentioned before, is that you end up counting patients who don't reach the target in 5 aphereses the same as you count a patient who has 5 aphereses and reached the target on the fifth apheresis.

The reviewer's result -- and I apologize on the slides you have, this table didn't come through, but the results from the reviewer show a mean difference in number of aphereses in the three large randomized studies that ranges from .4 to .6.

Alternative assumptions can be made about this data. Number one is that the median is the most appropriate measure of central tendency when you have, the statisticians tell me, differentially right truncated data sets since the median doesn't require that you assign artificial values to patients who don't reach the target.

In addition, we have made no assumption about the maximum number of aphereses. If a target is not reached within 5 aphereses, we censor those patients at 5

which essentially allows for them having any value greater than 5 aphereses.

A third assumption that Amgen made is basically that no assumption about the number of aphereses is required if a patient stopped their apheresis early. We censored them at whatever apheresis that may have been with the exception of patients who experienced adverse events related to stem cell factor. In that case we did assign those patients the maximum number of aphereses as a penalty to the study drug.

As you can see, based on those assumptions, there's a difference in the median number of aphereses to reach the target, and in all studies where a median can be calculated -- and this data is actually provided in the briefing document which Amgen provided to you as appendix 1 for all studies -- there's a difference ranging from 1 to at least 2 aphereses in all of the studies shown.

So, in response to the FDA's conclusion number 2, I think firstly it's important to note that in all studies SCF plus filgrastim patients had more CD34 positive cells collected per apheresis, and when looking at the medians, patients save from 1 to at least 2 aphereses.

A third conclusion made by the FDA reviewer in the briefing document is that adding SCF to G-CSF may modestly increase the proportion of patients achieving a

target of 5 million CD34 positive cells per kilogram. We agree that with SCF you can improve the percent of patients reaching that target. We would argue that that's not a modest effect, particularly in the lymphoma patients where the difference is 17 percent of patients who received filgrastim versus 44 percent of patients who received stem cell factor. We think that's a clinically important difference, particularly in that study.

In addition, the reviewer's conclusion went on to say that based on a small amount of data, it did not appear that stem cell factor could improve patients' ability to reach targets higher than 5 million CD34 positive cells per kilogram, and I'll just share some data relevant to that.

This conclusion is based on an exploratory study in heavily pretreated patients with multiple myeloma where a target of 10 million CD34 positive cells was used in order to support two transplants. In this group of heavily pretreated patients, few patients in either treatment group were able to achieve such a high target. However, if you look at groups of patients who are what we call good mobilizers and have high CD34 positive cell yields, such as in the myeloma study, which I just showed you, and also in our dose finding studies in chemo-naive breast cancer patients and ovarian cancer patients, there

are statistically significant improvements in patients' abilities to reach a target of 10 million CD34 positive cells per kilogram.

So, in response to this additional conclusion number 3, we would say that in patients with high yields, further increasing CD34 positive cells with SCF may give more of these patients and opportunity for novel transplant procedures which require higher doses of CD34 positive cells such as tandem transplants or multi-cycle chemotherapy or graft manipulation procedures.

The FDA reviewer's fourth conclusion is that it's too soon to make conclusions about the effect of adding SCF for chemotherapy plus G-CSF. In the briefing document it describes a couple of assumptions that form the basis for this conclusion.

The first is that 10 micrograms per kilogram per day is the standard G-CSF dose for chemotherapy plus filgrastim mobilization.

A second assumption is that the results of the ongoing European lymphoma study are negative and warrant skepticism of the data from other studies.

Some data that needs to be considered in responding to this conclusion are firstly for chemotherapy plus cytokine mobilization, filgrastim doses less than 10 microgram per kilogram per day may be appropriate. There

are no randomized studies reported in the literature which compare doses of filgrastim in the post-chemotherapy mobilization setting. I will show you some data from the literature in a moment from a nonrandomized study which also suggests that doses of less than 10 micrograms per kilogram may be effective. Also, in Europe 5 micrograms per kilogram per day, which is where these studies were conducted, is the approved and labeled dose of filgrastim for chemotherapy plus cytokine mobilization, and in the U.S., based on Amgen's market research data, more than half the patients undergoing chemotherapy plus cytokine mobilization currently receive less than 10 micrograms per kilogram per day.

In addition, I've shown you data from our myeloma study which employed chemotherapy-based mobilization showing pretty significant improvements in CD34 mobilization and the clinical benefits associated with that. As well, there's an ovarian cancer study in our dose finding studies which showed about a threefold increase in the number of CD34 positive cells collected.

I should note, in fairness to the FDA, we haven't submitted this data to the FDA yet, but the latest interim data from the European myeloma study does now currently show that the addition of SCF to filgrastim does improve CD34 positive cell yields in the first apheresis.

I mentioned that there are no randomized studies in the literature. This is a study done by Martin-Murea, et al. and Rainer Haas' group at Heidelberg looking at doses of G-CSF for post-chemotherapy mobilization, and their conclusion, based on looking at peak CD34 positive cell yields in the peripheral blood, are that doses lower than 10 micrograms per kilogram per day may be appropriate for mobilization in the chemotherapy setting.

So, based on this, our response to the FDA's conclusion number 4 would be that sufficient data exist which demonstrate that SCF provides a significant benefit when added to filgrastim for chemotherapy based PBPC mobilization and that this is actually a particularly important use due to the difficulty of using multiple apheresis procedures in this setting.

So, to summarize the efficacy information on PBPC mobilization with stem cell factor plus filgrastim, we've seen across all of the studies presented that there are increases in CD34 positive cell yields. This has been observed independent of the tumor types studied and independent of the mobilization regimen whether it's cytokines alone or chemotherapy plus cytokines.

The benefits of CD34 positive cell increases differ by the patient population being studied, with reduced aphereses being the primary benefit in patients

with higher yields, and increased proportion of patients reaching the target being the primary benefit in patients with lower yields as well as reaching minimal levels, although as I showed you in the lymphoma study, you can also see a benefit in reducing numbers of apheresis procedures.

That concludes the efficacy presentation. I'd now like to turn it over to Dr. Bill Sheridan for safety.

DR. SHERIDAN: Good morning. I'd like to review our extensive safety database.

The FDA's briefing document has addressed two issues with respect to safety of stem cell factor in the setting of progenitor cell mobilization. The first issue is graft quality, and the second is the syndromes that we've observed related to mast cell mediated adverse events.

With regard to graft quality, we now have an extensive database of various types of analyses that one can bring to bear on assessing the quality of the cells collected during apheresis after administration of stem cell factor plus G-CSF. The first set of data concerns laboratory evaluation -- and this can be done in a couple of different ways, phenotypic assays and functional assays, and with clinical evaluation with regard to the acute and chronic engraftment data and long-term marrow function and

immunologic recovery.

I'll start by addressing laboratory assays of graft quality. During our large phase I/II study in breast cancer patients, we analyzed various types of phenotypically and functionally assayable cells. The first is CD34 positive cells. As you can see, the number of CD34 positive cells collected was increased in the groups receiving combination cytokine therapy in this study.

The same was true of myeloid and erythroid clonogenic progenitor cells that one can assay in semi-solid agar, and you can express this information as a cloning efficiency. This is a somewhat difficult type of concept, but it addresses how many of the phenotypically identifiable cells can actually grow and divide in culture. Cells mobilized by SCF plus G-CSF are at least as good in this regard as cells mobilized by G-CSF alone on a cell-for-cell basis.

Another way of looking at this is to put these cells into liquid culture. Dr. Shpall did this experiment with cells mobilized from the same study at her site and cultured them with combination cytokines, and cells mobilized by the combination therapy again are at least as good if not better than cells mobilized by G-CSF alone with regard to the ability to proliferate in liquid culture.

Another way and a very important way of

addressing the laboratory aspects of graft quality is to look at very, very primitive cell populations. One of the ways to do this is to do long-term culture initiating cell assays. This experiment was done in our dose finding study in ovarian cancer where patients received chemotherapy with 3 grams per square meter of cyclophosphamide plus 5 micrograms per kilogram of G-CSF, and we escalated the dose of SCF in cohorts. The frequency of these cells per mononuclear cell collected was assayed in Dr. Dexter's laboratory in Manchester and rose from about 1 in 10,000 at the 0 dose of stem cell factor to 1 in 2,500 at the 20 microgram per kilogram dose. So, there's a fourfold improvement here in the frequency of long-term culture initiating cells.

This group found similar results of phenotypic assays for primitive cell populations, both CD34 positive 38 negative cells and CD34 positive 33 negative cells.

So, I'd like to turn to the FDA questions that were provided for the panel to consider today and paraphrase this by saying that this issue of graft quality that the FDA has posed has arisen because of a slight delay in recovery of neutrophils to 500 observed in two of the studies that Bill Parker has mentioned. The question addresses are these cells mobilized by the combination cytokine therapy as good on a cell-for-cell basis.

So, let's turn to clinical data with respect to this neutrophil recovery issue. I think the first point to point out here is that when looking at the aggregate data, neutrophil recovery in these studies is remarkably rapid. Certainly compared to the days of autologous bone marrow transplantation, this is a very uniform and predictable event after mobilized progenitor cell transplantation, as mentioned by Dr. Shea. Most of these patients recover within 10 to 12 days to get to a safe neutrophil count.

There is a statistically significant difference of 1 day or less with a 95 percent confidence limit around that of 0 to 1 day in two of these studies. However, it's worth noting that in the breast cancer randomized study with over 200 patients, we prespecified that the clinically relevant difference to try to detect here was 2 or more days for neutrophil recovery and 3 or more days for platelet recovery. So, we can be confident by the result and by the 95 percent confidence limit around the difference that we have excluded a clinically significant delay of 2 days or more.

Nevertheless, because there is this apparent delay of 1 day, it is worth looking at what are the potential clinical consequences of a delay in neutrophil recovery. I'll go through to share the data in the form of Kaplan-Meier plots and we'll look at that clinical data.

This is the Kaplan-Meier plot of neutrophil recovery in the breast cancer study. The curves are overlapping, and the difference arises for two reasons. One is that there is a difference in about 20 percent of the patients in the SCF group recovering at a 1-day longer duration, but the main reason is because the distribution of the data is so tight. As you'll see later, when the distribution is wider with similar differences in a reverse direction, we don't get statistically significant differences.

One of the things to look at here is what is the pattern of neutrophil count after recovery. Interestingly in the combination cytokine mobilized patients, the neutrophil count on the day of transplant is twice as great as it is in the patients mobilized by G-CSF alone. This translates into a delay in the onset of severe neutropenia which balances the delay in recovery of severe neutropenia so that overall duration of severe neutropenia here is equivalent. We can analyze that by counting the number of days of severe neutropenia and comparing them.

We can also look at all of the clinical consequences associated with severe neutropenia. As you can see here, the duration of severe neutropenia was 7 days in each group. Days of fever were equivalent. There were a very low number of days of febrile neutropenia, and this

is consistent with the literature on transplantation in this patient population. Antibiotic use was equivalent and days of hospitalization were equivalent. None of these clinically important parameters associated with prolonged durations of severe neutropenia are statistically different.

A way to think about this is to think about what is the effect of CD34 cell dose and is there an interaction of CD34 cell dose with the type of mobilization regimen on this particular outcome. In the FDA's question number 1, this was approached by stratifying CD34 cell dose into arbitrarily chosen strata, and we've duplicated those strata here: 1 million to less than 3 million cells per kilogram, 3 million to less than 5 million cells per kilogram and more than 5 million cells per kilogram.

We've looked at here the clinically relevant issue of the duration of severe neutropenia. As you can see, the mean duration of severe neutropenia in all these groups is very equivalent with very minor differences and no statistically significant differences.

So, in the breast cancer study with all of that information, I think we can now be confident that our original assumption that detecting a delay of 2 days or more would be clinically relevant was in fact correct because the delay of 1 day that we did detect was not

clinically relevant by any of these measures.

This conclusion is supported by results from the randomized myeloma study. The curves here are overlapping. Interestingly, if you look at the dotted yellow line which is the combination cytokine group, 20 percent of these patients in the combination group recover a little bit faster than the G-CSF group which is the same proportion as recovered more slowly in the breast cancer study, but there's no statistically significant difference here because the distribution of the data is so wide.

Again, in the randomized lymphoma study, these curves overlap. In this study in particular, there's very prompt engraftment of neutrophils. It's almost like a square wave. So, it would be difficult to actually improve on this.

Again, in the lymphoma study because of the statistically significant delay of 1 day, we looked at the clinical parameters that I mentioned before. Once again, none of these clinical parameters are statistically significant, and in no case is there a reason to believe that the clinical consequences of severe neutropenia are any worse in the SCF plus G-CSF mobilized patients.

So, our response to the first part of the question concerning quality of the graft with respect to neutrophil engraftment is that cells mobilized by the

combination of SCF plus filgrastim are at least as good both biologically and clinically in supporting engraftment of neutrophils.

So, I'd now like to turn to a more sensitive indicator of graft quality and that is platelet engraftment, and I would like to remind you of the information from Dr. Shea and from Bill Parker about the importance of getting a high number of CD34 positive cells. This is not a trivial issue, and the CD34 cell dose is one of the most important determinants of the pace of platelet engraftment. The target of 5 million cells per kilogram was chosen for our large randomized studies following discussion with the FDA and in accordance with the advice from this panel in 1994, and it has now become a fairly commonly used target in transplant medicine. The field has evolved while we've been doing these studies.

As I mentioned, we predetermined in our breast cancer study that a delay in platelet engraftment of 3 days or more would be a clinically relevant difference to show and that we should try to look for that in our safety analysis. So, here's the data from the three large randomized studies: 11 days versus 11 days, 10 versus 9, and 12 versus 12. The p values on all of these are not significant, so there's no reason to believe here that in this type of analysis that the quality of the graft with

respect to platelet recovery is any worse in SCF plus G-CSF mobilized patients.

We can look at that in Kaplan-Meier plots, as we did for neutrophil engraftment. Here's that information for the breast cancer study.

Here's the information for the myeloma study. Once again in the myeloma study, there's a slight improvement, if anything, in the SCF patients, but these curves really overlap and because we are apheresing to a target here, it would be difficult to show an advantage for SCF.

Finally, in the lymphoma studies, the curves once again overlap with rapid platelet recovery in the majority of patients.

Getting to this issue of how do we figure out an interaction or potential interaction between the type of cell mobilized by either a single agent, filgrastim, or the combination of filgrastim plus stem cell factor and the CD34 cell dose, one way to do this is a bivariate analysis.

So, in response to this question we're providing this analysis today. Looking at the mobilization regimen as one factor and the CD34 cell dose as another factor for platelet engraftment in the breast cancer study, as you can see, the CD34 cell dose is a highly significant predictor of the pace of platelet recovery. So, with this

type of information, I think we can conclude that for platelet engraftment now, as well as for neutrophil engraftment, that CD34 cells mobilized by the combination of cytokines are equally effective as CD34 cells mobilized by filgrastim alone on a cell-for-cell basis.

In your briefing document, we did provide an analysis of the delayed platelet engraftment by some arbitrarily selected CD34 cell dose strata, in this case more than 5, 2 to 5, and 1 to 2. There are a couple of important points here. One is that rapid platelet recovery by day 14 is actually improved at very low CD34 cell doses or appears to be improved in the group of patients receiving the combination mobilized cells. In addition, patients receiving combination mobilized cells have essentially 0 prolonged durations of platelet recovery in the breast cancer study. So, this is further support for the concept that SCF plus G-CSF mobilized cells are at least as good as G-CSF mobilized cells on a cell-for-cell basis.

FDA question 1(b) essentially asks the graft quality question in a slightly different way and includes the strata that I mentioned before. So, I think that in addition to the information on neutrophil and platelet engraftment, we have a couple of other variables that we can look at to help us identify the quality of the graft.

One of them is long-term bone marrow function. It is important, obviously, not just to get a quick response and a quick recovery in a patient receiving high dose chemotherapy and get them out of hospital soon, but it's also very important, as we heard this morning, that long-term bone marrow function is very good.

We agree with the FDA reviewer that there's no evidence that SCF and G-CSF mobilized cells have a problem with delayed graft failure. Again, we agree that the stability of graft function is equivalent in G-CSF and SCF plus G-CSF mobilized patients.

We also look at immunologic function in a variety of different assays that were quite comprehensive in a subset of patients in the breast cancer study with multiple T and B cell assays, immunoglobulin levels, specific immunoglobulins, and all of these assays were equivalent long term for immunologic function.

I'd now like to turn to the second topic, and I think this is a topic that we've learned a lot about in the progress of the studies from phase I to phase II to randomized trials. We have a database of 644 patients treated with SCF available to analyze here. 56 of these were in phase I studies which were dose finding safety studies. 493 were in patients in progenitor cell transplant studies, and 397 of those were in cytokine only

mobilization studies. That's important because that allows us to look at side effects of the cytokines without confounding effects of chemotherapy.

So, I'd now like to turn to the phase I chemotherapy studies. These were dose escalation studies. We started off with a dose of 50 micrograms per kilogram, but learnt this was not well tolerated.

We then looked at lower doses. We saw that in nearly all patients there were injection site reactions. These are erythematous wheal and flare responses for the most part.

We also saw that there was a high rate, 23 percent, of more systemic effects of mast cell mediated release. We have referred to these in your briefing document as allergic-like or anaphylactoid reactions. 13 out of 56 patients had these events, and 12 out of 13 were seen at doses of 25 microgram per kilogram a day or more.

Because of these events, we took several measures to cope with this. As I mentioned, the doses were high. We were not giving premedications at that time, and the patients were not being screened for a history of allergies. We therefore instituted lower doses of SCF, a standard premedication regimen which I will describe, and exclusion of patients with a severe allergic history. In later studies, we've been able to expand the eligibility

and include patients with a history of mild allergies.

This has worked. The frequency of these systemic reactions has fallen from 23 percent in our phase I studies to 3 percent in our progenitor cell transplant studies, and overall in the 644 patients, including the phase I's, the incidence is 5 percent.

Now, the second bar from the left interestingly displays the incidence in other studies outside the progenitor cell transplant field, and these are mainly chronic administration SCF studies in bone marrow failure states where the drug has been administered for up to 2 years daily subcutaneous injection. The incidence is about 7 percent.

The premedication regimen we chose was chosen to make it as simple as possible. The medicines are very well understood medicines that are widely available with a well understood profile for antihistamine prophylaxis. We included H1 and H2 blockers, a bronchodilator, and early on pseudoephedrine which we subsequently dropped. The event rate with this premedication is about 3 to 4 percent.

We've subsequently moved to a simplified regimen of a once-a-day later generation antihistamine, plus two other agents both once a day, and the event rate is similar in more than 100 patients.

What are these events? The majority are mild

to moderate local skin reactions, and these local skin reactions occur in the majority of patients given SCF. They're not a clinical concern. There were respiratory symptoms that occur in up to 11 percent over the control arms and distant skin reactions that occur in up to 15 percent over the control arms. The most serious systemic events occur in 3 percent.

In our cytokine only mobilization studies, we looked at the pattern of severity of these mast cell mediated type of events. It's very clear both for respiratory symptoms and, as you'll see in a minute, for cutaneous symptoms, that most of these events are either mild or moderate, and the minority in both cases are severe.

In the respiratory system, the events can be either upper or lower respiratory tract, most commonly sore throat, cough, shortness of breath, and feelings of throat tightness and a few patients have had symptoms of dysphonia, dysphagia, or wheezing.

The skin reactions can be the local or distant. The distant skin reactions occur in a minority of patients, less than 20 percent overall. Most of these are mild to moderate and a few are severe.

It's worth pointing out that for both respiratory symptoms and for the distant skin reactions

that the vast majority of patients who had mild to moderate reactions did not get treated for these reactions.

The distant skin reactions in the cytokine only mobilization population were rash, erythema, pruritus, and urticaria. In each case the frequency is about 5 percent or so higher in the SCF group.

In the FDA questions for today, there is a question about appropriate measures to include in a package insert and instructions to physicians. The question comes up later in my presentation. One of the issues is the time of onset of the reactions. Here is the number of reactions at different times after the dose of SCF from less than 1 hour to more than 18 hours, and most of these reactions occur within the first 8 hours or so, but there's quite a distribution. The median time to onset is 5 and a half hours, after a median of the fifth dose, anywhere between the first and the ninth dose. And 10 out of 16 of these reactions occurred outside hospital.

These serious reactions were predominantly skin and respiratory tract type symptoms. About half of them included some cardiovascular symptoms, nonspecific chest pain, tachycardia, and in 2 cases hypotension, both of which resolved with intravenous saline in a very short time.

All of these serious reactions were grade 3.

None were life-threatening or fatal. They resolved in all cases. The management was to treat with various medicines that are listed on the slide. In 5 cases, patients were admitted to hospital overnight for observation, and in almost all cases, SCF was discontinued. Most of the medicines were parenteral antihistamines or corticosteroids and in 2 cases epinephrine was used.

I think with this body of information, which is quite extensive, we can address the question of how similar or different these mast cell mediated reactions caused by SCF are to anaphylaxis. Anaphylaxis is an IgE mediated event. It's quite a scary event, and I think that it's worth looking at both the biology and the clinical features to try to reach a conclusion here.

With regard to the biology of the events, mast cells carry the c-kit receptor and SCF is a mast cell growth factor. So, it's not surprising that SCF causes these reactions in a clinic. SCF mediates the reaction by binding with the c-kit receptor. Anaphylaxis is not mediated that way.

The effector cells for anaphylaxis can include basophils. They don't appear to include basophils for SCF.

Prior exposure is required for anaphylaxis, and generally speaking, the extent of mediator release is high and the reverse is true for SCF.

Now, knowing this biology, I think it's not surprising that there are differences between anaphylaxis and SCF mast cell mediated events. Anaphylaxis is a sudden, dramatic, scary event for both the patient and the physician, and both the physician and the patient end up getting epinephrine in one case, endogenous in the other case, administered. So, the clinical features of anaphylaxis are this sudden onset. It's often life-threatening. The relationship of anaphylaxis to the dose of the precipitating antigen is variable.

SCF reactions, as I've shown with the onset, are gradual. They're not life-threatening in any case that we've been able to identify. Very rarely is it required to treat with epinephrine, and most likely this is a dose-related effect from the information from our phase I studies.

So, here's the question with respect to this issue, and the question was posed that if approved, please discuss the period of time that patients should be observed and what are the additional precautions that should be taken in the package insert. In our clinical trials, in our large clinical trial in breast cancer, we specified that patients should be observed for a minimum of 1 hour. So, the information that we have available is that observation for 1 hour is safe.

In our proposed labeling that we included in our briefing document, we propose pointing out that intravenous use is contraindicated, that the dose of 20 micrograms should be adhered to. Premedications should always be used. There should be an exclusion for history of serious allergic disorders and that if reactions do occur, they should be treated with medications appropriate to the severity of the reaction.

We propose including information for patients along similar lines and a pocket laminated card with the same information with instructions. I think that there are two key points here are the importance of the premedications which do reduce the incidence of these reactions and guidelines on what to do in the event of symptoms.

So, here's our proposal with regard to what to tell the patients, and we'd be obviously happy to work with the FDA and the medical community in refining these and making them as appropriate as possible.

Our conclusions with regard to the safety of SCF is that in the context of peripheral blood progenitor cell mobilization, the risks of SCF are modest and manageable.

The mast cell mediated reactions have been very well characterized in our clinical studies and can be

described in detail in the product labeling. The mild to moderate systemic reactions do not appear to be an issue as the physicians in our clinical trials have for the most part not treated them. Systemic serious reactions are infrequent and none were recorded as life-threatening.

With regard to the issue of graft quality, we believe we have extensive data that the graft quality of combination mobilized cells is excellent.

So, with that, I'd like to hand over to Dr. Glaspy who will address this issue of risk versus benefit.

DR. GLASPY: Thank you, Dr. Sheridan.

I think that the key FDA question was part of question 3 where reviewing the safety and the efficacy data, as we have, the question arises, has the risk/benefit relationship been established which would indicate that this drug is suitable for approval? And that is the question that I will address.

To enumerate the benefits that I and my fellow investigators have seen in the clinical trials, you've seen that it varies with setting, but includes an increased proportion of patients who can receive a minimal target number of CD34 cells and have a minimal graft quality, an increased proportion of patients who, rather than receiving a minimal requisite number of cells, received what we're learning is an optimal number of cells, and finally for

patients who would otherwise be excellent mobilizers with G-CSF alone, a decrease in the number of leukaphereses required to achieve that endpoint.

The toxicities that have been encountered have included the local injection site reactions, including hyper-pigmentation, local urticaria, and itching reactions, which have been reported in the majority of patients; mild to moderate systemic reactions, especially systemic dermatologic reactions, in 15 percent of patients; and serious systemic reactions in 5 percent of patients overall and in 3 percent of the patients in the PBPC studies.

I believe that the concern raised by the FDA is relative to this last group of toxicities, and in the risk/benefit discussion, those are the toxicities upon which I will focus.

In terms of the benefits, I want to talk about those benefits in terms of what their clinical impact is because in many instances these clinical impacts are substantial.

First, in terms of the increased proportion of patients who are able to reach a minimal target that allows them to have high dose chemotherapy, in the studies that we've seen presented, in heavily pretreated patients, there's approximately a 50 percent reduction in mobilization failures in the study that you've seen. This

translates into patients that otherwise wouldn't be candidates for high dose chemotherapy being able to receive high dose chemotherapy or, as an alternative, not requiring backup surgical bone marrow harvesting, remobilization with chemotherapy and cytokine, which we'll get to as another alternative, or having suboptimal grafts with the potential risks that have been demonstrated this morning and were articulated by the patient advocate before we began. Those are major improvements for the patients to whom they're relevant.

Secondly, for an increased proportion of patients reaching an optimal target number of cells, in the studies that have been presented, the variation has been between 9 and 37 percent increment as compared to the control groups. It has been observed as a trend at least in all 8 of the completed peripheral blood progenitor cell studies and was statistically significant in two of the three large randomized studies, although it wasn't the endpoint in all those studies. So, I believe that that's a real impact of stem cell factor.

Dr. Shea showed you that there are benefits for patients to be accrued there, decreased transfusion requirements, decreased antibiotics, decreased lengths of stay, and now in two studies that have looked at the resource consumption associated with being above or below 5

million cells where the patients below 5 million cells had median grafts of approximately 3 million cells -- so these were not suboptimal grafts in the comparison group -- there were resource savings of between $5,000 and $8,000 associated with this.

Finally, for the decreased number of leukaphereses, the studies that have been presented, when focused on medians, have shown a reduction in the number of between 1 to more than 2. It has been observed in all five studies where the medians can be determined, and it's statistically significant in all three large randomized studies provided that prospectively identified covariates predicting leukapheresis efficiency are taken into account.

Now, this is not a trivial benefit to patients. There is an obvious resource consumption issue, but leukaphereses have side effects that were enumerated by Dr. Shea and anything that prevents an increment in leukaphereses can be expected to provide that benefit to patients.

Now, there's also an implication that I've seen in some of the questions that while SCF may increase the number of CD34 cells that are obtained in the leukapheresis, that that is a trivial impact and not significant. I've taken this from the appendix 1, a larger table looking just at the fold increase in the median

number of CD34 cell positive progenitor cells obtained per leukapheresis comparing G to stem cell factor plus G and divided it into the patients who are traditionally high yield patients, moderate yield patients, and low yield patients in the same way that Dr. Parker did earlier.

These fold increases vary between 1.2 and 6.4. Those are not trivial in magnitude. They are consistent.

The other point from this slide is that while the benefits to the patients may be different for different categories of patients, the biology is remarkably consistent across these patient groups with similar fold increases in the number of CD34 cells obtained per leukapheresis. Those additional CD34 cells lead to different benefits, depending on which patients we're dealing with.

Those are the benefits that are apparent from the clinical trials to date. It's not hard to see that there are other potential benefits to patients and to the field from having stem cell factor available. Many of the ongoing research endeavors in peripheral blood progenitor cell transplantation and related fields rely upon the leukapheresis of CD34 positive cells as a starting point, and an increase in the number of available CD34 positive cells will be important in enabling these technologies to move forward. Also the availability of human clinical

quality stem cell factor is important for many of the cocktails that are being used ex vivo in the treatment of cells for ex vivo expansion of progenitor cells and even for generation of dendritic cells.

In terms of the risks that have been articulated that have raised concerns on the part of the FDA with stem cell factor, I believe Dr. Sheridan has addressed the issue of the 1-day delay in neutrophil recovery. I don't believe that tells us anything about the quality of the graft. It clearly did not, if present, lead to any change in the clinical outcomes for patients. Lengths of stay were not different in the two groups and it does not reflect a poor graft quality.

Secondly, serious allergic-like reactions are a major issue. I want to repeat that these have only happened in 3 percent of the peripheral blood progenitor cell patients now that we have learned how to premedicate patients, how to choose them, and what doses of stem cell factor to use.

Secondly, we have learned that the biology is different than anaphylaxis. These patients, while we used very conservative scoring criteria for scoring the toxicities, have not had fatal reactions. We're learning better how to manage these things when they do occur.

I have treated personally 187 patients with

stem cell factor. 2 of my patients have been scored as having systemic serious reactions. 1 of them was a patient who had had a distant urticaria on two prior doses of stem cell factor and had generalized intense urticaria on a third dose which occurred the evening after the administration. She was taken off study, treated with antihistamines, and resolved and never had respiratory symptoms. That's a different thing than anaphylaxis. That patient was receiving 30 mic's per kilo which is above the dose we're proposing.

The second patient was a patient who had, after her fifth dose of stem cell factor, within 15 minutes, abdominal pain, diarrhea, throat pain, and throat tightness, but had no change in her physical examination or vital signs, was treated with antihistamines and went to leukapheresis an hour later, obtained enough cells, and we didn't have to make a decision whether to restart the medication. Those have ended up scored as these serious adverse reactions.

I think it's important that the other clinicians who have extensive experience with the molecule have a chance to comment on this because I think safety is a major issue for everyone. Dr. Shpall from the University of Colorado also has some strong feelings about the enabling technology, and she'll comment on that.

DR. SHPALL: Thank you, John.

I was asked to describe my experience with the toxicity from the perspective of a clinician who has administered SCF or enrolled over 100 patients on this trial, and of those 100 patients, 2 developed what were scored as grade 3 toxicity. The first patient, after her fifth injection in the afternoon, developed a rash in her chest. Over a gradual 3 to 4 hour period, this progressed to involve the trunk, arms, legs, became intensely pruritic. I gave her a dose of steroids, watched her overnight, two more doses of benadryl. The entire rash resolved. But it was systemic and so scored as severe.

The second patient, after her seventh injection, developed a tickle in her throat, and again gradually over 3 to 4 hours, this progressed to throat tightness and a cough. She came immediately to clinic where, on exam, she had some swelling of her uvula. She was not wheezing or stridorous, had no other respiratory compromise, actually at no time had any compromise of her airway. Although I admitted her overnight for observation, gave several doses of steroid, the entire syndrome resolved in the morning.

So, the first point to make is that these toxicities are eminently manageable, in fact, could be considered quite trivial compared to the side effects of,

say, taxol, ATG, amifostine, which we're giving to our patients on a daily basis and which are really much more complicated. I think in the right setting with sophisticated transplant personnel, this really is not going to be a serious problem.

As I have hoped you've heard today, there already clearly are benefits to SCF in terms of patients who might not otherwise be transplantable getting transplants and those who get transplants having safer transplants. But this group of patients who are going to perhaps benefit over the next decade from technology that's not ready I would be uncomfortable or unfortunate to have the possibility that SCF will not be available for this type of strategy. And these are many.

Purging in the autologous transplant setting is being employed with increasing frequency, both with devices such as the Cellpro column, which are approved by the FDA, and with many other different devices under IND or IDE at this time. Many of these procedures, particularly the one when they're combined which make better purges, are associated with a substantial loss of CD34 cells.

Trials are planned now with large numbers of patients, whereby if we can't get more CD34 cells to start with, the loss of 34 may preclude their entry into study or their ability to get purged grafts and therefore identify

this potential strategy as a therapeutic benefit over the next several years.

Ex vivo expansion is another one in cord blood transplantation, for example, a source of increasing frequency being used for patients who don't have donors. These transplants are characterized by profound delays in engraftment and graft failure of very high rates. In static culture systems with SCF, we have very impressive expansion ex vivo, which we haven't been able to produce with any other growth factor available today. That kind of ex vivo expanded cord blood may allow safe transplants for those who otherwise won't get them.

Finally, for dendritic cell therapy, the addition of SCF increases dendritic cells between 100- to 200-fold above the TNF, GM-CSF-type cocktails that are being used now.

And for gene therapy, it's clear. Both David Bodine in mice and now Sumi Dunbar in primates has shown systemic SCF mobilization increases transduction efficiencies independently of the ex vivo exposure to SCF, both improving gene transfer in these settings.

So, we hope the panel understands that given these potential benefits, the manageable toxicity and the already confirmed benefits described earlier today, that SCF should be a drug that our patients have at our disposal

for the next 5 years.

Thank you.

DR. GLASPY: Dr. Fred LeMaistre from San Antonio is a clinician who also has a lot of experience. He has been involved since the phase I/II studies, and I wanted him to comment on his experience.

DR. LeMAISTRE: Thank you. It's always hard to follow Dr. Shpall because she leaves so few things unsaid.

(Laughter.)

DR. LeMAISTRE: We have been involved since the phase I/II studies on through the phase III studies in non-Hodgkin's lymphoma in breast cancer. I guess the principal theme of that experience has been that stem cell factor has done what you might predict from the preclinical studies. It does stimulate mast cells and causes a spectrum of mast cell manifestations that are easily recognizable and managed in a transplant center like ours, and I will underscore some of the previous comments about how I would gladly trade managing some of these side effects in favor of having to manage some of the problems associated with graft failure or delayed engraftment.

I think the second observation is it also, in conjunction with filgrastim, stimulates peripheral blood progenitor cells and we are more likely to collect optimal grafts when we use stem cell factor in this fashion.

What has not really come out in this presentation is that this body of data before you is a very impressive body of data that has helped move our field forward over this period of time. These are uniformly selected, treated, and managed patients that have helped define the understanding of what an optimal cell graft is, and an indirect benefit of participating in these trials in my center is that we now in our practice guidelines more routinely require an optimal graft for our patients. As a program director, what this has meant to my program is a dramatic decrease in morbidity and mortality. As a clinician, what it has meant to individual patients I think is reflected by the comments that began this session by the patient advocate in that we have to deal with far fewer of those tragic problems. So, we do go to greater lengths to try to get more optimal grafts for our patients.

Thanks.

DR. GLASPY: Finally, I think lymphoma is one of the areas that many people are going to be interested in applying this drug. So, Pat Stiff who has been one of the principal investigators on the lymphoma studies I think should comment on that.

DR. STIFF: Thank you.

My program treats a lot of patients with lymphoma, as well as ovarian carcinoma, so we're used to

seeing a lot of patients with delayed engraftment and poor stem cell mobilization. So, I was delighted to be able to participate in these trials.

Again, as was mentioned, there were two lymphoma trials. In the first one, patients were eligible if they had chemosensitive relapse. In many patients great efforts were made to put them into second or third remission prior to transplant, and many of the patients ended up with heavy prior therapy. We were amazed that some of the patients at our institution, despite that, they had a very rapid platelet engraftment of 9, 10, 12 days.

So, we prospectively then went into the second trial focusing on this patient population and again the endpoints are clearly elucidated in the presentation. There are more patients meeting the 5 times 10 to the 6th CD34 target. There are more patients meeting the minimum safe target. The overall yields are higher in this patient population. In contrast to prior years, we saw predictable platelet engraftment and patients had a short stay in the Chicago area.

The availability of this agent will allow us again to treat patients very quickly and get them in and out of their transplant process very rapidly. The alternative to patients who mobilize poorly is to use chemotherapy plus cytokines. This has not been shown to be

of value in patients already in remission for lymphoma and multiple myeloma in several studies. So, the advantage of using chemotherapy plus G-CSF as a mobilizing agent only is something that needs to be strongly considered. It is fraught with complications and side effects, and in some patients it's dangerous and could lead to mortality rates. Again, this needs to be balanced against the rather modest toxicities of the factor in patients under controlled situations.

Thank you.

DR. GLASPY: I think that people who have worked with this drug have a different view of the toxicity than has been taken in some of the review of the data by FDA. We also are real aware of the benefits and want to make sure that you understand these are not trivial.

But we still are left with a risk/benefit balance. In a medical judgment sense, is it appropriate balancing these perhaps refined risks against those benefits? One place to look is, for consistency, at other strategies that are employed in the field in an attempt to augment the harvests with peripheral blood progenitor cell mobilization.

Currently, the only thing other than cytokines to enhance mobilization is the addition of a relatively high dose of chemotherapy and then to harvest cytokine

therapy during the recovery phase of that chemotherapy. This is employed. It's not accidental that it's more frequently employed in the cancers for which poor mobilizations happen than for the ones where it doesn't. This is done more often in lymphoma and myeloma than it is in breast cancer patients. It's also done with the hope that the chemotherapy will have an antitumor effect, but we don't have any proof that that's the case at this point.

That chemotherapy is very toxic, and at least one of the goals of its administration is to enhance progenitor cell yields. This is data taken from Johnsen's review that is not yet published, but we all have similar experience with chemotherapy cytokine mobilization. I think anyone who transplants a lot of patients has patients who have had fatal outcomes from the results of this chemotherapy, and I think that tells us something about how important the field things it is to enhance progenitor cell yields in appropriately selected patients.

My conclusions are that the benefits of stem cell factor in addition to G-CSF for mobilization are not trivial; they're substantial. The biology says there's a consistent increase in the CD34 cells that are yielded which increases the number of patients who achieve targets, reduces the number of leukaphereses that are required by patients, and it represents an enabling technology to help

the field move forward in the future.

I believe that the risks of stem cell factor are modest and manageable, that they are acceptable and will be fully described in the product labeling and educational materials. And the mast cell mediated reactions, because they are well characterized and better understood, are much more easily managed and we have learned that they are different than anaphylaxis.

I want to close with the conclusion that I share with the other investigators who have had experience with stem cell factor, some of whom you've heard from today -- we all believe that the risk/benefit balance of stem cell factor is in a place where it is appropriate for it to be placed in the hands of an informed physician and patient to make the decision, that it's a risk balance and should be balanced at that level.

I'll stop there.

DR. VOSE: I'd like to thank the sponsor and investigators for their discussion and open it up to the committee for questions to the sponsor. Dr. Berman?

DR. BERMAN: Have any patients that received the stem cell factor been premedicated with steroids?

MR. PARKER: I'll just step up here. I don't plan on answering all the questions, but I'll direct them to either my appropriate colleagues or clinical

investigators.

None of the studies which we've performed have utilized steroids in the premedication regimen, at least the studies included in the BLA application. The reason for that is really because we were concerned about possible hematological effects of the steroids and we wanted to make sure that there was no possibility that the steroids would be influencing the mobilization regimen. That's one of the reasons that we chose the premedications that we did in addition to the well-characterized and well-tolerated side effects of the antihistamine medication as opposed to, say, high dose steroids.

DR. BERMAN: Well, I'm not considering high dose steroids, but just form of a low dose of a hydrocortisone is unlikely to have a significant hematologic effect and may abrogate the side effects that you see.

MR. PARKER: That hasn't been studied and it's something that we could potentially study further. But again, we want to exclude any possibility.

Dr. Sheridan?

DR. SHERIDAN: In the studies conducted, we haven't looked at it, but I think it's a very good question and it's something that we could easily look at in subsequent studies post licensure.

DR. VOSE: Dr. Miller?

DR. MILLER: A few questions. Have there been any patients followed long enough to determine the incidence of any secondary myelodysplasia or acute leukemia following mobilization in this patient population?

MR. PARKER: Dr. Sheridan?

DR. SHERIDAN: It's really a survival and long-term complication question. The data provided I think in your briefing document with respect to survival analyses indicates equivalent disease outcome in these patients, and thus far there's no indication of an increase in risk of leukemia or myelodysplasia.

DR. MILLER: Have you seen any leukemia or myelodysplasia in the patients that have been followed up?

DR. SHERIDAN: As far as I'm aware, we've seen no cases of leukemia. Kathy, is that true? 1 patient.

Do you know which study that was in? In an early breast cancer study that was conducted in Australia starting early in the program.

DR. MILLER: The second question is the first discussion about the increasing in people able to get the minimum. In any of the studies, was there a statistically significant increase in arriving at that minimal number of stem cells?

MR. PARKER: No, I don't believe any of the

studies showed a statistically significant increase. However, as I mentioned, the strategy employed was to try to get patients to an optimal target, and studies weren't designed or powered to prove that endpoint.

DR. VOSE: I have one question. I'll take the prerogative.

In discussing the quality of the graft again, another measure of that would be to look at any differences in CD34 density or to look at the CD34 subset analysis such as 33 negative, 38 negative. I know that there were some studies that were quoted in the briefing document. Were any of those analyses performed on any of these patients to look at the subset analyses?

DR. SHERIDAN: Yes. The study in ovarian cancer patients included phenotypic analysis of the CD34 positive, 33 negative subset and also the CD34 positive, 38 negative subset, along with the long-term culture initiating cell assays that I mentioned before. In all three cases, they were statistically significantly more -- each of those primitive subsets in a dose-related way with increasing doses of stem cell factor up to the 20 microgram per kilogram dose.

That was a study conducted in the United Kingdom and the assays were done at Michael Dexter's lab. The results have been published and it is one of the trials

conducted in our trial program.

There were also some assays done in Dr. Shpall's laboratory of various phenotypic results. Maybe Dr. Shpall would like to comment.

DR. SHPALL: In the phase I/II study -- this was presented at the ASBMT in March -- we did a subset analysis on 34 positive, 38 negative, 33 negative, and thy 1 positive. There was absolutely no difference in any of the groups except for the S plus G arm had higher percents of the CD34 positive, thy 1 positive, and the DR positive, 38 negative.

MR. PARKER: The slide is up here which shows the results.

DR. SHPALL: CDW90 is thy 1. So, the 34 positive, 33 positive, and 13 positive, so the myeloid progenitors were identical. There was no statistical difference in those, but there was a higher proportion of the more immature or primitive 34 positive, thy positive, and HLA-DR 38 negative favoring the S plus G arm.

DR. VOSE: One additional question. I know that there was information presented as far as engraftment at some early time points. Do you have any information on engraftment at a little bit later time point such as 6 months or even up to 1 year, if there is any information available on that, for sustained engraftment?

DR. SHERIDAN: The sustained hematologic engraftment was studied by protocol up to a 9-month time point. The data collected at that time was the incidence requiring transfusions and the stability of the graft, and it was collected in a sort of short case form type analysis. There was no indication of a difference between either arm. I'm not sure that we looked at time points later than 9 months.

MR. PARKER: Most of the studies were designed with a 100-day follow-up which had been suggested by the committee, and there was no difference at that point. In addition, as Bill Sheridan mentioned, for the phase III trial we had more extensive follow-up and indeed are following patients continuously on long-term follow-up studies. So, we'll have further information in other tumor types as well.

DR. VOSE: But at this time there's no difference in the --

MR. PARKER: At this time there's no difference in the incidence of graft failure between the two treatment groups at later time points.

DR. VOSE: Additional questions? Dr. Leitman?

DR. LEITMAN: In our briefing document, it's mentioned that the SCF was given in a b.i.d. dosing regimen, but that's never mentioned again. Were all the

doses given b.i.d. or once a day?

MR. PARKER: SCF was given as a single daily injection in the morning. That must have been an error in the briefing document.

DR. LEITMAN: Since there's a requirement for intravenous prophylactic anti-allergic medications, as well as --

MR. PARKER: Actually all of the prophylactic medications are oral administration, including the inhaled bronchodilator. So, some of the therapy which has been used to treat the reactions have been intravenous antihistamines and steroids.

DR. LEITMAN: At the current time are you recommending giving the first dose under observed circumstances and the remaining doses the patient may administer at home then?

MR. PARKER: No. At the current time all doses are given with a 1-hour observation, or all doses in the later studies were given under a 1-hour observation. In the initial phase I/II studies, we did observe patients overnight in the hospital for the first dose, with subsequent observation for variable periods of time depending on the particular protocol, but 4 hours initially was kind of a standard observation which we cut back when we went on to the phase III and other randomized studies.

DR. LEITMAN: I just bring that up because there's a cost differential in giving observed doses in hospital or in clinic as opposed to G-CSF alone which is usually given the by the patients by themselves.

I have a second question. There was no mobilization data presented either this morning or in the packets we received, so there's no data on the increase in circulating progenitor cells in the blood prior to apheresis. Your endpoints were the yield of progenitor cells in the apheresis product, but that's often confounded by difficulties in apheresis, the type of device that's used, the length of the apheresis procedure. So, a more direct measurement of efficacy of mobilization would have been CD34 in the peripheral blood.

And that brings up the very important point which is the number and percent of patients who don't mobilize. It's easiest to see that if you look at increase in CD34. I would like to ask whether you have some data that you didn't present on, for example, percent of patients that did not achieve a peripheral blood count of greater than 10 CD34 per microliter after 5 days in the two arms.

MR. PARKER: The data we've presented has been the apheresis yields, as you mentioned, we as felt that was the most clinically relevant measure since that's what the

patients are going to be receiving back as part of their graft.

In addition, in cytokine only mobilization, as you know, you end up with a very high background white count, and the accuracy of CD34 measurements in the peripheral blood in that situation becomes somewhat less. We did present that information in the study reports for the phase I/II studies, both in cytokine only mobilization, as well as in post-chemotherapy mobilization studies, and we'd be happy to provide that. I don't think we have any slides of the peripheral blood mobilization data, but there was a dose-related increase in peripheral blood levels. I couldn't tell you the percentage of patients who had below a specific threshold level of CD34 positive cells.

But I guess in that case I would still go back that the apheresis product yields are what's most clinically important. And in our studies we did try to standardize some of the things that you mentioned as far as the apheresis machines used, the volume of apheresis, and those types of variables.

DR. SHERIDAN: Perhaps I can comment also. Another set of populations to look at in the peripheral blood are the functionally defined cell populations of myeloid, erythroid, megakaryocytic type colony forming cells. We did look at the myeloid and erythroid colony

forming cells in an early dose finding study in Australia, a breast cancer trial, and there was a dose-related increase in peripheral blood levels of those cells which are easier to define in the setting of a high white cell count. They certainly were at that time. We had a lot of trouble with CD34 positive cell assays under those circumstances at that time. And there was a dose-related increase and the pattern of kinetics was defined as well.

DR. VOSE: Dr. Goldsby?

DR. GOLDSBY: Rates of bone marrow replication are not uniform throughout the 24 hours of the day. How did you determine that 8:00 a.m. was the best time to give the boosting agent?

MR. PARKER: As far as the administration of stem cell factor?

DR. GOLDSBY: Maybe 1:00 a.m. is better or maybe --

MR. PARKER: We chose it as a clinically convenient time for the transplant physicians giving the doses in the morning, especially on the days of aphereses where the patients are coming into the center. The apheresis procedure itself takes on the order of 3 to 4 hours in general as well.

DR. GOLDSBY: Have you considered experimentally the possibility that determining the best

time might produce a better result?

MR. PARKER: We haven't considered it yet, but we'd be willing to look at any proposals that you might have in that regard. It's an interesting question.

DR. VOSE: Dr. Miller?

DR. MILLER: I'm looking for sort of a proof of principle outline. Sort of go along with me in this review.

In a retrospective analysis, greater than 5 million CD34 cells improves engraftment, and your target in these studies was that number. The patients could get up to 5 phereses and then you stopped. Then independent of whether you reached that target, the patient went on to the transplant. Therefore, you would expect that if in fact more than 5 -- so, in a percentage of patients, whether or not they got that 5 million, they went ahead to transplant.

Is it that the studies were underpowered then to show whether or not you got that number, you had improved engraftment? Because none of the studies showed improved engraftment. Is it all in numbers and if you put it all together, can you see that?

As a clinician, my question is, yes, the retrospective studies show that more than 5 million makes a difference. However, that's clouded by potentially other covariates as well. That includes patients who would never

mobilize or have other reasons why they didn't get to more than 5 million.

But in these studies is there any evidence that actually achieving that 5 million goal made a difference for the patients?

MR. PARKER: Dr. Sheridan?

DR. SHERIDAN: Yes, there is. If we can go back to my slide of the outcome, 28-day failure rate. It was towards the end of my safety section. While we're finding that, perhaps I could address some of your other questions.

You are correct. These studies were not prospectively designed or powered to show a difference in those outcomes. They were prospectively designed and powered to show a difference in the number of aphereses required to reach a target CD34 cell dose which was the endpoint recommended by the panel and discussed and agreed to with the FDA at the start of the trials.

With regard to the actual number of CD34 cells that you get, especially in the breast cancer setting, what we end up with is slightly more than 5 million cells and slightly less than 5 million cells in the two different patient populations. So, the design of the study actually biases the outcome against showing a significant difference to some of these clinical endpoints.

MR. PARKER: There are two factors there I guess. One of them is just the statistical power and the numbers of patients to show the difference and then the second, which Bill is alluding to, is the study design itself wherein you don't allow patients with less than a million cells to go on to transplant and you're targeting patients at 5 million cells. All patients are within the same range of CD34 positive cells that are transplanted.

DR. SHERIDAN: With regard to the answer to the last part of your question, this is I'm sure not statistically significantly different, but it does point out that if you just look down the columns and ignore the cell dose, so overall there is an improvement in outcome with respect to delayed platelet engraftment in the randomized breast cancer study.

Also, if you look across the rows, especially the last one, there's an important point which is that even at a low cell dose, so even in people who failed to reach the target, SCF and G-CSF mobilized cells appear to be doing better here. But again, the studies were not designed prospectively or powered prospectively to address this issue.

MR. PARKER: I think looking across all studies is an interesting question, but it's very difficult to do in these different patient populations who are receiving

different high dose chemotherapy regimens which have different inherent engraftment profiles as well. So, although we haven't really looked at it, part of the reason we haven't looked at it is because it doesn't seem to be likely to be fruitful given those differences in engraftment kinetics and different patient groups and different high dose chemotherapy regimens.

DR. MILLER: The reason this may be important is also because of the difference between yours and the FDA's view of how to analyze the greater than 5 or 5. In fact, if you believe that greater than 5, if you kept pushing greater than 5 could make a difference, then your analysis of saying the mean is 4 versus greater than 6 makes more sense. In my view looking at it, I don't know whether in any case going to 5 makes any difference. I don't think there's any real data that if you don't have it at 5, that going to 13 makes a difference.

So, given that, I think the FDA's view of looking at the median number of phereses, the actual number that were done, 5 versus 4, because that's what you've used and basically you showed no difference in engraftment with what was clinically done. So, saying 6 or greater when nobody got 6 or more but still engrafted doesn't seem to me a very reasonable way of looking at the data. I think that's the way the FDA reviewers looked at it. Can you

just respond to that?

DR. SHERIDAN: Yes, certainly. I think there are two parts to the question. One is a clinical one and the other is a statistical issue.

With regard to the clinical question, if we can sort of lower the lights, we might be able to look at this a bit better. But getting to a target of 5 doesn't have much of an impact on the median time to platelet recovery if you look across halfway up the charts. I'm sorry for the small print. The more important clinical parameter here is the proportion of patients who are still platelet dependent a month after the transplant. For both G-CSF and SCF patients and for G-CSF patients, there's an improvement hitting 5 which is the green line. Almost all the patients have recovered in the SCF group if you hit a target of 5.

I agree with you. There is insufficient data at present to know whether getting 10 million or 20 million or 30 million cells is going to give a better outcome than 5. But certainly hitting a target of 5 does give the better outcome.

With regard to the statistical point of what is the appropriate way to look at this complex data set, especially in the breast cancer study, perhaps Dr. Koch could make some comments.

DR. KOCH: Well, with this data, there's a

number of difficulties about how you describe or interpret it. The difficulty with the mean, as you've already noted, is that even if you went beyond 5, there may be patients who would not attain the outcome. Now, the variable you're trying to describe is the number of aphereses that it actually takes in order to have the outcome occur. When you assign values for whom the outcome never occurred, that can be very misleading. So, the use of a mean is misleading from the point of view of whether or not people reached the outcome.

Now, the median is more helpful because at least the median tells you a value of aphereses that 50 percent of the patients required in order to reach their target.

Now, the median isn't that helpful either necessarily because it doesn't tell you necessarily how many aphereses were necessary for 70 percent of the patients to reach target or 90 percent of the patients to reach target because again you may not necessarily be able to increase them to do that.

Now, there is another measure which actually uses the real data without assigning fictitious values to people who did not reach target, and that's on the incidence density slide. Here what we do is basically say how many aphereses were done and how many patients actually

reached target. The word "event" corresponds to achieving target.

Now, if we look at the breast cancer study, 385 aphereses were applied to the patients in that study with respect to the G group, and of them, 47 reached target. So, the number of aphereses that are necessary for a patient to reach target is on average 8.2. In other words, you're doing 385 aphereses to get 47 to reach target or basically 8.2 aphereses per patient who reaches target. And in the S plus G group, it's 5.6, and the difference between those is 2.6. And if you take the ratio of them, it's 1.45.

In the myeloma study, basically more patients reached target sooner, and so basically it's 2.9 aphereses per patient meeting target in the G group, 1.9 in the S plus G group. The difference is 1.

Now, the advantage of this analysis is there's no fiction. You're using basically the data as they are.

Now, this came up in discussion last night. I regret that you didn't get it sooner, and it came up because there's been a lot of debate about whether the mean is useful or whether the median is useful.

The mean is not useful. In order to have a mean, you would have had to basically observe all patients up until they all had gotten the target, and basically

trying to come up with fictitious values for the number that would have been required for people who never reached target isn't useful.

The median is helpful. It is a fair value. It is based on real data. Half the people did, indeed, achieve target when you have an observable median, but it doesn't tell you about the other half.

This particular analysis basically tells you how many aphereses were done, how many reached target, how many aphereses per reaching target you have, and then you can look at those the way they are. But because of the data, you have to look at it several different ways and then decide what helps you with interpretation most readily.

DR. VOSE: Dr. Follmann?

DR. FOLLMANN: Yes. I'd like to make a few points.

First, related to the earlier discussion, I think that when we're considering the targets here, it's important to keep a few things in mind. One is that the target, whether it is achieved or not, is dependent upon the method to mobilize it. So, if you achieve target with stem cell factor, that might produce a yield which is larger perhaps, but the benefit might not be the same because it's mobilized using a different agent. So,

whether you meet a target or not might make sense if patients were all treated the same way. They're not, and so we can't confound performance of the dose that they received with the method they get it. So, looking at target just in that way I think is a little misleading.

The second point I'd like to make about target is that the patients get the dose that they provide themselves, and so you don't have patients getting arbitrarily or randomly assigned doses. What you have is patients confounded with the cell yield that they provided. So, it could be that a patient who gives 5 with stem cell factor would have given it in 3 without stem cell factor, and because this patient has a certain amount of health, that he has a certain ability to reconstitute his blood cell production, he would have had the same time of engraftment even though he got different yields with the two methods.

Another thing about the yield is that I think we should downplay to some extent the importance of the absolute value of the yield which I think was being commented on earlier. If we could raise this from 5 times 10 to the 6th to 10 times 10 to the 6th, could we really reduce the time to engraftment much below 8 days or 7 days? It seems like from the data I've seen here, there's basically a minimum time to engraftment, and you can't

really go much below that. So, if you keep on increasing yields, I don't know that you're going to get that much of a benefit in terms of time to engraftment.

Finally, I'd like to make a comment on this discussion about the mean versus the median. In my mind, if there were no problem with what I'm calling censored observations, that is, patients who stopped being pheresed before they met target, the mean would be the more important and relevant statistic to use because it would give you a precise description of what the average difference between the two groups is. Use of a median for data like this has the effect that the median difference between these two groups would generally be 0 or 1. So, it's going from nothing to something kind of substantial. The mean is a much smoother varying measure of tendency, and so if you have a modest effect, it might be .4 or .5 rather than hopping over to 1. So, that's purely a characteristic of these two methods of estimation for data of this type. So, if there were no problem, I would prefer the mean.

The median has some argument for it in this case in my mind because of the fact that there's a problem in assigning scores to people who don't achieve target. But in my mind the practical implication of that for this study is pretty minor. There were I think about 7 or 5

percent of the patients in each arm that dropped out or couldn't meet the target and weren't pheresed to 5 phereses. So, the practical implication here is that for a small percentage of patients replacing the observed number of aphereses, which might be 3, with 5. So, I don't think that's going to have much of an impact upon the mean. So, all in all, I think the mean is perhaps a better way to look at these data than the median.

DR. VOSE: Dr. Siegel?

DR. SIEGEL: I'd just like to make a procedural suggestion, which is that this is time allotted for questions for Amgen and we have time allotted for discussion. We need to have discussion of these issues, but I think some of the confusion may be clarified. I fear some may be further increased.

DR. VOSE: I think it's going to be worse.

DR. SIEGEL: But some may be clarified. I certainly intend to make some remarks that will clarify some of the confusion that now exists. But I think as a matter of process, it would be best to have questions of fact and then have discussion of issues in the discussion period.

DR. VOSE: Okay. Why don't we hold especially the statistical questions until later and try and hold just to questions for the sponsor.

I think Dr. Auchincloss was next.

DR. AUCHINCLOSS: No. It actually turns out my comment was more in the category of discussion.

DR. VOSE: Okay. Never mind. You're not next.

Dr. Broudy?

DR. BROUDY: Can I just make two brief comments?

DR. SIEGEL: You can do what you'd like.

DR. BROUDY: Thank you, Dr. Siegel.

(Laughter.)

DR. SIEGEL: I don't want to gag anybody. I just want to help the process.

DR. BROUDY: The first is just to briefly comment on what you said about 5 million versus 10 million. I don't think the purpose of trying to get 10 million CD34 cells per kilogram is that we expect that it would engraft more rapidly. I think it is for other experimental manipulations down the road such as tandem transplants or tumor purging or things like that. I don't think anybody has a goal of significantly more than 5 million CD34 cell per kilogram with the expectation of faster initial neutrophil platelet engraftment. It's more to allow other experimental techniques to be developed and furthered.

A second comment is an actual question for the sponsor, and that is, if one were to read your proposed

application on page 6, it doesn't say anything about autologous versus allogeneic transplant, whereas all of the data are on autologous transplant. Could you comment on that?

MR. PARKER: We've only studied and we're only recommending stem cell factor for use in autologous transplantation.

DR. BROUDY: I guess my comment is perhaps that should be really strongly stated in the proposed application because one could read this and think that one can do better with an allo donor with stem cell factor and G-CSF, and I know that is not your intent or would any of the data support.

MR. PARKER: We'd be happy to state that specifically in the labeling.

DR. VOSE: I think you were next, Dr. Frieri.

DR. FRIERI: To move into the allergy side for a moment, I'd like to know what was the allergy screening, how were patients screened.

Number two, was there consideration in the role of opiates in pain medication in these patients since opiates can degranulate mast cells and also lead to reactions?

And number three, was there a consideration in patients that are health care workers that have had

multiple surgeries that are more at risk for latex allergic reactions which can confound some of these reactions?

MR. PARKER: I think Dr. Sheridan can address the allergy screening criteria. I do know that we didn't exclude the use of opiates such as morphine for these patients, and there were a few patients who did receive them, but I don't believe it was a very large number of them.

DR. SHERIDAN: With regard to allergy screening, there's a three-part history here. In the phase I studies, we did not have exclusion criteria based on allergy screening. Once we saw the events, we introduced it. In the back of your handout of slides, there is our first edition 1992 version of a toxicity scale that we developed to help us manage these things, and around about the same time, we developed a set of allergy exclusions that are listed here. We also excluded initially people with allergic rhinitis and other mild allergies, and as the program evolved and we gained more experience, we dropped that and wound up with the list that you see here. In I think two of the studies, we've tracked the number of people that were actually excluded on the basis of one or other of these prior histories, and about 10 percent of the patients that were otherwise eligible were excluded on this basis.

Does that address your question?

DR. VOSE: Dr. Arm, did you have questions?

DR. ARM: Again, in terms of the allergy reactions, have you made any attempts to determine which mediators are released? You're assuming it's histamine related, but I wonder if you tried to measure urinary prostenoids or leukotrienes and whether you've considered premedicating with nonsteroidals in addition to antihistamines?

MR. PARKER: I think I'd like Dr. Galli to address that question.

DR. GALLI: Yes. Actually in the phase I studies, there were attempts to measure two mediators. One was histamine which was measured as methyl histamine in a 24-hour urine, and that showed in a small group of phase I patients, I think about 10, that there was about a 44 percent increase. This was taking all the individuals together, those that had just skin test reactions and those that had more severe reactions.

In addition, a mediator that's more specific for mast cells, tryptase, was measured in some of the patients, and using the commercially available kit which in normal individuals does not detect any tryptase in the serum, which has a lower limit of detection of 1 nanogram per ml, only 1 or 2 of the patients registered above the

lower limit and it was only slightly so. One of those was a patient that had one of these severe systemic reactions. So, even the severe reactions as classified by the sponsor produced a very low level of tryptase. To put that in context, orders of magnitude higher levels would be seen in patients with IgE dependent anaphylaxis if they're measured right after the event.

It's an interesting suggestion to measure additional mediators. That hasn't been done. It could be done prospectively in additional studies, but what the investigators who have used the agent clinically have learned is that the group of premedications and post-event medications that have been used seem to have managed completely the events. So, it's an interesting research question and it may result in some modification of the medication of people who get events, but so far they've been managed with the existing drugs.

DR. VOSE: Thank you.

Dr. Leitman?

DR. LEITMAN: I want to return to the question of the true clinical relevance of pheresing to a target dose and then assessing the number of procedures necessary to reach that target dose. In the data that was given to us in our packets, I didn't see it presented this morning, but which we all have seen in our experience, the vast

majority of the progenitor cells are gathered in the first one or two pheresis procedures. So, the last three -- number 3, number 4, and number 5 -- are commonly used as top-off procedures which clinically sometimes is crazy if one has 3.5 or 3.8 or 4.2 million per kilo. But your protocol says you're aiming for 5. You may end up doing one or two more apheresis procedures, and it gets entered into the data as an increase in the mean or the median but adds nothing of clinical relevance probably to time to engraftment.

So, I just want to raise that as a warning in evaluating what the meaning is of an increase in the mean or median of .4 or .6 pheresis procedure in the various clinical groups. Again, it may not have clinical relevance in terms of time to engraftment.

I have a question for Amgen. Do you have data on the number and percent of patients in which transplant was enabled by stem cell factor? That's a minimum dose, not an optimum dose, a difference in those achieving 1 million per kilo so they could go on to transplant with up to 5 apheresis procedures versus those who not achieving that?

MR. PARKER: Right. I think the relevant study for addressing that question is the lymphoma study which I presented in heavily pretreated patients with very poor

mobilization. As I presented, there was 26 percent of patients who received filgrastim alone who were unable to achieve that dose to go on to transplant versus 16 percent. As I mentioned, the study was not designed or powered for that endpoint. The result was not quite statistically significant, but there did appear to be an improvement in reaching the target that was clinically important.

I guess on the other question about the relevance of doing additional apheresis procedures, either Dr. Sheridan or maybe Dr. Glaspy would like to comment on that.

DR. SHERIDAN: Maybe I'll take a first stab at it and then John.

I think that what has happened during the process of the stem cell factor development program is that people have learnt how to accurately measure CD34 positive cells, and they have also learnt that having more than 5 million and apheresing to a target of 5 million actually is important.

I think that's best illustrated by comparison of the bad outcomes in our phase I/II breast cancer trial with the bad outcomes in our phase III breast cancer trial. The phase I/II results are the two bars on the left. The phase III results are the two bars on the right. These populations of patients are very similar, but the results

are very different.

So, instead of a fixed apheresis number, as you've suggested, you can perhaps collect most of these cells in the first few aphereses, which we did in three consecutive aphereses in the patients in the phase I/II. Simply moving from that strategy to a strategy of collecting to a target of 5 million cells has improved the proportion of patients who fail in one way or another in both filgrastim mobilized patients and in SCF plus filgrastim mobilized patients. So, I think that's one aspect of it.

The other aspect of it is that in addition to that, there is a benefit from adding SCF whether or not you have a fixed apheresis strategy, which is the two bars on the left, or a target apheresis strategy, the two bars on the right.

So, I think there is evidence that indicates that having a targeted apheresis strategy is valuable, and it was the advice from the committee in 1994 and in discussion with the FDA that led to this type of trial design. Maybe John can address it.

DR. GLASPY: You're wrestling with all the issues that everybody wrestled with in designing these trials because it's very difficult to figure out how to statistically demonstrate the benefit to patients of a

higher CD34 per leukapheresis yield. You really have two choices. One is to set a target and look if you can achieve it with fewer leukaphereses or to go after an engraftment endpoint. The engraftment endpoint is problematic because moving the median time to engraftment is impossible once you're giving a minimal requisite number of cells. What we're really talking about is decreasing from 20 to 15 to 5 to 3 percent. Here's the Cox proportional hazards model that sort of demonstrates this. Even with 1 million cells, the median time to platelet engraftment, which is the more sensitive to cell dose, is 14 days.

The differences between the curves that are clinically important start to happen in the later part of the curve, and for those of us who transplant patients clinically, this curve goes on forever. We all have a few patients who never recover their platelet counts. Although you can't show those without doing a study with thousands of patients, you can't show a difference in those numbers, those are the catastrophes both in terms of the human dimensions and the cost dimensions of transplantation.

What we're really talking about now is trying, because PBPC has given us flexibility we didn't have with marrow, to optimize the safety of the procedures by helping those 10 or 15 percent of patients that do do better with

higher doses of cells. I agree with you, 5 million is not necessarily better than 4,999,000. In setting an arbitrary number for statistical purposes to do a trial, you are always open to criticism. We've had people say you should have set it higher. People say we should have set it lower.

But consistently in the field, these sorts of data sets are evolving. Dr. Bensinger's Kaplan-Meier plot that was published, Dr. Weaver's all showed the same thing, that the cell dose affects the number of what we are calling outliers, patients who engraft very late and are the real problems that we have the potential to address with higher cell doses.

DR. VOSE: I think you do have to be a little careful about using absolute numbers, though, as comparing different studies because the techniques can be so different and one needs to use standardized methodology for that. So, that is a little bit difficult.

MR. PARKER: Two of these studies, the two conducted in the U.S., had CD34 analysis performed at the same central laboratory.

DR. VOSE: Yes. No, I agree that's very important. I was just commenting on the different studies' aspects.

Dr. Berman?

DR. BERMAN: Yes. I had a question. I believe the lymphoma study showed that the SCF addition really mattered for people who had had prior radiation. Did patients have prior radiation in the breast cancer studies and the myeloma studies? And if so, did you look at the subset analysis?

MR. PARKER: Actually I think in the lymphoma study it showed that at baseline there was a slight imbalance in the amount of prior radiation between the two treatment groups. However, if you adjust for that analysis, the results, as you would expect, since it appeared to be biased against the SCF arm, remained statistically significant.

In addition, prior radiation to areas of bone marrow at least was one of the criteria for patients being heavily pretreated along with a number of other criteria. We did look at prior radiation as a potential -- in an exploratory fashion in the breast cancer study, and it does appear to be a prognostic factor even for breast cancer patients. But we haven't done any of our analyses trying to adjust for that as a covariate.

DR. BERMAN: Did patients receive radiation for the myeloma studies as well?

MR. PARKER: The conditioning regimen in the myeloma study included melphalan or melphalan with TBI, but

I believe the treatment groups were balanced at baseline as far as prior radiation, and I'm not sure exactly how much they received. We'd have to go look at that.

DR. VOSE: I think we're going to stop at this point as far as questions for the sponsor, and I'd like to take a 10-minute break. We're going to start promptly at 11 o'clock with the FDA presentation. Thank you.

(Recess.)

DR. VOSE: If everyone could take their seats, we're going to get started so we can try and maintain our time schedule.

One comment for the committee members is there are slightly new questions that apparently were given out in your packet, if you didn't get them last night, and they're in the middle of this document with all the members on it.

We're going to go ahead and proceed with the FDA perspective on this application, and Dr. Richard Steffen is going to present that information.

DR. STEFFEN: I'll try to make it a little quicker since we're obviously running behind time.

These are just the main studies that comprise the clinical development program. As we've heard, stem cell factor was originally studied as a hematopoietic growth factor to be used following myelosuppressive

chemotherapy. There was one phase I/II study in peripheral blood progenitor cell mobilization, which led directly to a phase III pivotal trial, what Amgen has referred to as the breast cancer study.

This was actually divided into two studies. There was a short-term study that followed patients out to about 100 days following transplant, and then there was a long-term follow-up study. The original stated intent of having two separate studies was so that this study could also enroll patients who were going to be treated in other randomized trials. However, shortly after the long-term follow-up study was initiated, the protocol was changed to make it only patients from the breast cancer study eligible.

Then there were also these four phase II studies, of which we've heard. These studies were all basically similar in design in that they pheresed to a target, but otherwise they were fairly different in that there were different targets, different mobilization schedules, different apheresis schedules, and as we've heard, different endpoints. Two of them were done in the United States and used G-CSF only with or without stem cell factor. Two were done in Europe which used chemotherapy and, as we've heard, a 5 microgram per kilogram dose of G-CSF with or without stem cell factor.

I'll start with discussing the original two studies. One was done in patients with non-small cell lung cancer and one in patients with advanced breast cancer.

These were fairly typical in design of the type of studies we see as the initial studies for hematopoietic growth factors to be used following myelosuppressive chemotherapy. There was one pre-chemotherapy cycle in which the study drug was given alone followed by two post-chemotherapy cycles. The original intent was to study doses of 10, 50, 100, 200, and 300 micrograms. It was estimated on the basis of the basis of the preclinical studies that a dose at least of 50 micrograms per kilogram would be needed to see hematopoietic growth factor-like effects.

The studies actually went on hold shortly after they were initiated because 6 of the first 31 patients enrolled experienced anaphylaxis. The studies were then revised downward to study doses below 50 micrograms per kilogram. As we've heard, patients with an allergic history were screened out and not eligible for this study and an anti-anaphylaxis prophylactic premedication consisting of H1 and H2 blockers and ephedrine was adopted for all patients. This was directly patterned after the prophylactic regimens given to patients who were undergoing radiocontrast media to prevent anaphylaxis in those

patients.

In these two studies, there was a total 61 patients enrolled. A little over half, 33 patients, failed to complete the study. The most common reason that they failed to complete the study was an adverse event. A quarter of all patients failed for that reason. The most common adverse event was anaphylaxis which occurred in 10 patients. 5 other patients dropped out because of other adverse reactions. 10 patients dropped out because of disease progression. 6 patients dropped out for what were termed administrative reasons. On review of these patients, 1 of these patients was a patient who the physician had suspected had had anaphylaxis-like symptoms at home and was afraid to continue the patient on the next cycle and so dropped the patient out. We have considered that patient as a patient having anaphylaxis in our total of the patients.

In addition, there were 4 additional anaphylactoid reactions. As we've heard, they're a physiological effect of stem cell factor. They don't involve IgE. So, technically they're termed anaphylactoid, but I think really you can't tell the difference between the end result which is the clinical syndrome we know as anaphylaxis.

Three of these reactions were accidental

overdoses. These occurred in 2 patients. 1 patient was overdosed twice. At this time, stem cell factor was being self-administered by some patients. These patients were able to tolerate the assigned dose of stem cell factor but, with each overdose, experienced anaphylaxis. There was 1 patient who, in violation of the protocol, was covered with IV corticosteroids for the last injection or so and did manage to finish the course.

This is just the data on anaphylaxis which, as we've heard, was the predicted dose-limiting toxicity on the basis of the preclinical studies. It was dose and route of administration related. I think this shows you very nicely the dose relationship.

This patient here at 5 micrograms per kilogram was a patient who was self-injecting who apparently inadvertently intravasated the dose. When he aspirated back on the syringe, the syringe welled with blood. He did have an anaphylaxis at that dose and it was felt that it was because of the intravenous injection because certainly the preclinical studies show that when given intravenously, stem cell factor is extremely anaphylactogenic.

These are the adverse events seen in that study. As we've heard, injection site reactions were very common, almost universal. There was a large incidence of respiratory symptoms -- cough, dyspnea, dysphonia, and

throat tightness -- which were thought to be due to probably angioedema of the respiratory tract. Again, skin reactions were very common. Generalized urticaria was seen in almost half of the patients and anaphylaxis was definitely the dose-limiting toxicity occurring in about a fourth of the patients.

Because the dose could not be pushed to the level that they thought they would see hematopoietic growth factor-like effects, there was then a phase I/II study done in breast cancer patients to look at the question of mobilization.

The objective of this study was to study the effect of stem cell factor by itself, G-CSF by itself, which was to act as a control, and the combination of G-CSF and stem cell factor on the kinetics of mobilization. Different doses of stem cell factor alone and in combination with G-CSF 10 micrograms per kilogram, the standard mobilizing dose in this country, were to be studied, as were different mobilization schedules and different apheresis schedules.

This was a very complex study. It was a randomized study. There was an unbalanced randomization so that as additional cohorts were added to this study, patients were always randomized to the G-CSF alone cohort which functioned as a control.

The endpoints were assays of the peripheral blood progenitor cells.

This is the anti-anaphylaxis prophylaxis that Amgen adopted for this study. As we've heard, patients with allergic history were screened out. They were premedicated with four drugs starting 24 hours before the first dose of stem cell factor and continuing to 48 hours after the last dose of stem cell factor. The diphenhydramine, ranitidine, and ephedrine were given around the clock orally. The albuterol sulfate was given either by inhalation or orally.

Because of the problems with intravasation and the inadvertent overdoses, a policy of SCF administration by health care professionals only was adopted and continued through all these studies. As we've heard, the first dose of stem cell factor was given as an in-patient. There was a 4-hour observation after subsequent doses.

There was a total of 215 patients who received study drug. 55 patients received G-CSF alone and functioned as a control. 5 patients received stem cell factor alone. As we've heard, all 5 of these patients failed to engraft. The criteria at that time for transplant was mononuclear cells. These patients met the criteria of mononuclear cells, but when the CD34 cell assays came back, they were very low.

There was a total of 16 cohorts studied in this study. Stem cell factor doses of 10, 15, 20, 25, and 30 micrograms were studied, as were 7, 10, and 13-day dosing schedules.

The decision was made to go ahead with the combination of 10 micrograms per kilogram of G-CSF and 20 micrograms per kilogram of stem cell factor. These are the two largest cohorts. These were dosed for a total of 7 days each. So, the only difference between the two cohorts is the addition of 20 micrograms per kilogram of stem cell factor. As you can see, there's an approximate doubling and even tripling of the various progenitor cells mobilized.

These are the engraftment data from that study. These times naturally reflect -- they used the backup marrow that was given to the patients who received stem cell factor alone mobilized studies. There was 9 days median time to engraftment in the G-CSF alone arm and 10 days in the G-CSF plus stem cell arm. Again, this 1-day difference that has been mentioned has been seen in all the cytokine only mobilization studies. There was no difference in platelet engraftment in these two arms.

These are just the adverse events. Again, we've heard this before. Injection site reactions were very common. Cardiovascular reactions were about twice as

frequent in the patients receiving stem cell factor as those receiving G-CSF alone. These were primarily tachyarrhythmias that were thought to be due to side effects of the premedication regimen or possibly, as has been mentioned, other vasoactive substances being liberated from mast cells. 2 patients discontinued stem cell factor because of anaphylaxis in this study.

That study led directly to the pivotal trial, a phase III study, in women with breast cancer for mobilization.

This was an open-label, multi-center trial with mobilization with G-CSF and G-CSF plus stem cell factor. It was conducted in women with high risk stage II/III or stage IV breast cancer, all of whom had received some prior chemotherapy. Up to 12 cycles was allowed. The amount of prior chemotherapy between the two groups was in essence identical.

The study was divided into phases. There was the peripheral blood progenitor cell collection phase consisting of mobilization, apheresis, and cryopreservation. This was followed by a rest period of 2 to 10 days and then the treatment phase where patients received their myeloablative chemotherapy, the infusion of the entire collection of peripheral blood progenitor cells, and were followed for engraftment to day 100.

Patients were randomized to either 10 micrograms per kilogram of G-CSF, the standard mobilizing dose in this country, or the combination of 10 micrograms per kilogram of G-CSF and 20 micrograms per kilogram of stem cell factor, both given subcutaneously. All patients started their study drugs on day 1 of the collection phase. Apheresis started daily on day 5 and continued until 5 times 10 to the 6th CD34 cells had been collected or until day 9. Day 5 I think was always a Monday. That was a Friday. It was a standard 5-day apheresis schedule that we see a lot of in studies of mobilization.

As we've heard, the study had co-primary endpoints. The number of aphereses to obtain the target number of 5 times 10 to the 6th CD34 cells was one, and equivalent engraftment was the other. Equivalent engraftment was defined as time to ANC of 500 or time to platelet count of 20,000. The protocol did reflect that a delay in neutrophil engraftment of 2 days or a platelet engraftment of 3 days would be considered clinically significant.

The secondary endpoint was safety.

The primary analysis was an intent-to-treat analysis.

This is the statistical plan, as we discussed with Amgen prior to the initiation of the phase III trial

and as reflected in the protocol. As you can see, it does call for the Wilcoxon rank sum test to be performed to assess the number of aphereses to achieve the target and it does mention that the number of cycles of prior chemotherapy was a potential covariable.

There was a total of 204 patients enrolled and randomized in this study. 1 patient was subsequently determined to be not eligible and did not receive any study drug, and neither Amgen nor us considered that patient as part of the intent-to-treat analysis.

As we've heard, there's 1 patient who was actually randomized twice in this study, initially to group A where she received her course of G-CSF for mobilization, then did get snowed in, could not undergo apheresis. When she got dug out, she returned to the clinic where she was dropped from the study and re-randomized, this time to group B where she then went through the entire mobilization again.

We did have a question of how to deal with this patient. It is certainly not uncommon at all in randomized trials that patients receive treatment other than to which they were randomized. When that occurs, usually the conservative thing to do is to go ahead and analyze that patient as they had been randomized, not according to the treatment they received. That's the course we chose for

this patient, so our intent-to-treat population differs very slightly from that of Amgen's. We have 104 patients in group A and 99 patients in group B.

Parenthetically I can say we actually did the primary analysis several different ways with this patient. We considered her as originally randomized, as randomized a second time. We considered her as 2 patients as randomized both times, and we eliminated her altogether. And it did not have an impact on the primary analysis.

(Laughter.)

DR. STEFFEN: These are actually the actual data of leukaphereses now for the patients reaching the target. These, as you can see, for the first 3 days -- these are not the cumulative numbers. Those will be on the next slide. For the first 3 days, the number of patients reaching the target is very similar between the two groups, and as has been mentioned, the bulk of patients who reached the target did reach the target early in the course of aphereses.

The only real difference appears to be on day 4 where only 3 patients reached the target in the G-CSF alone arm compared to 11 patients in the G-CSF plus stem cell factor arm. Then the numbers drop off again very abruptly and it does raise a question whether continuing beyond 5 leukaphereses would really get you many more patients to

reach the target or not or whether it would be futile.

This pattern was seen in all the randomized studies that were done with stem cell factor that continued leukapheresis out beyond 5 or 6 days with the majority of patients, in fact the big bulk of patients, who were going to reach the target reaching the target early in the leukapheresis schedule and then the number dropping off and very few, if any, potentially would reach the target following that.

When we analyzed this using the protocol-specified statistical method, the Wilcoxon rank sum test, we found that the difference in the number of aphereses to reach the target was not significant. The p value was .14. When we adjusted for the cycles of prior chemotherapy, the p value minimally changed. It went up to .16.

These are the cumulative percentages.

If you want to go back, I just forgot to say one thing. I want to correct one thing. Mr. Parker said that we assigned values in determining the patients reaching the target for the primary analysis. We did not. We used the exact numbers that you see here. Anybody who did not reach the target, regardless of whether they dropped off during the apheresis schedule or whether they didn't meet the target after 5 aphereses, was considered in a sixth group we just called failures, and it was at a rank

higher than 5. So, we did not assign any values in our analysis of the primary endpoint.

These are now the cumulative percentages. There does appear to be a difference in looking at the proportion of patients who reached the target, with 46 percent reaching the target in the control arm and 60 percent reaching the target in the G-CSF plus stem cell factor arm.

Now, the proportion of patients reaching the target was not an endpoint at all in this trial. It is included in the proposed indication for stem cell factor. So, we did a statistical analysis on the proportion of patients and we found that the difference in the proportion of patients who achieved the target was not significant. The value did approach significance. The p value was .07 whether or not we adjusted for cycles of prior chemotherapy. It didn't affect this analysis at all.

We too struggled with the best way to actually try to quantitate any difference in the number of aphereses to achieve the target. We did it in several different ways. When we calculated the number of aphereses to reach the target, we did not assign any value higher than patients had actually received their aphereses with the exception of those patients who dropped out during the collection phase without reaching the target were assigned

5 leukaphereses. The study was designed only to have 5 leukaphereses, and so we did not assign any values of 6 or greater for those patients who did not reach the target.

There was a problem with these dropouts. There were 15 patients who dropped out and they were maldistributed. 5 of them were in the G-CSF arm and 10 were in the stem cell factor arm. 3 of those were patients who experienced anaphylaxis. So, we penalized those 15 patients which worked out to about 7 percent of the study population. We did not assign greater than 5 phereses to the 47 percent of patients who did not reach the target after 5 leukaphereses.

When we did this, it's our feeling that probably the mean does give you a better impression than the median of the number of phereses. We found that the change in mean was very minimal, from 3.8 to 3.6. There was a 1-pheresis difference in the median.

We then decided, because of this question of the dropouts, to just go ahead and look at the actual number of leukaphereses that were done regardless of whether or not the patients achieved the target. We felt that in practice some patients will drop out during the collection phase. Not all patients will reach the target, and this might give some indication of what might be seen in actual practice.

In this case then, these patients who dropped out had the actual number of phereses that they had. So, the patients who dropped out because of anaphylaxis with stem cell factor were actually considered as successes in a sense because they had less phereses because they didn't complete the cycle.

When we did that, we found it really affected minimally the mean. The mean dropped then in both arms naturally from 3.7 to 3.3. So, it went from a two-tenths difference to a four-tenths difference. There was a 2-pheresis difference in the median.

Now, this is actually the Kaplan-Meier curve of the patients who had the actual number of phereses. So, again, these are the actual number of phereses. As you can see, the curves are really superimposable in the beginning and the end, and really the main difference you see is right at the median where there appears to be a median difference of 2 phereses, although obviously they're a patient away from a median difference of 1 leukapheresis here. But if you use other commonly used indications, such as the 25th percentile or the 75th percentile or the 90th or 10th, you see that there's no difference then between the two arms.

These are the CD34 cell yields in this study. There was a slight difference which did not achieve

statistical significance. A little less than 5 times 10 to the 6th was the median in the control group and a little more in the stem cell factor group, but again we wouldn't expect much of a difference since both arms were apheresed to a target of 5 and then quit.

These are the engraftment data from the pivotal trial, the breast cancer study, as has been mentioned. There was this 1-day difference in the time to neutrophil engraftment which was statistically significant. There was no difference in the time to platelet engraftment.

We realize that this difference is not clinically significant, but to us it did raise the question that the stem cell factor cells might not contribute as much to engraftment as G-CSF alone cells, that there might be some problem with the stem cell factor mobilized cells.

We did then a series of exploratory analyses where we just arbitrarily divided the yield into between 1 and 3, 3 and 5, 5 and 6, greater than 6 and so forth. These are just the Kaplan-Meier curves for looking at those patients in both arms who had a yield of between 3 and 5 times 10 to the 6th CD34 cells per kilogram, and as you can see, there does appear to be a slight difference in these two curves. Again, there is this 1-day difference in the median favoring the control arm. This picture was seen for essentially all the subset analyses that we did.

This did raise the question then, would we accomplish the same thing if we just leukapheresed with G-CSF to a lower dose than 5 times 10 to the 6th. This is obviously an exploratory analysis and we're not dealing with randomized groups at this point, but we looked at that group of patients who achieved the yield of between 3 and 5 times 10 to the 6th CD34 cells per kilogram for the G-CSF arm and those who achieved a yield of greater than 5 in the G-CSF plus stem cell factor arm. As you can see, the curves are very similar, essentially superimposable, which does at least raise a question that you could reduce the number of phereses by using G-CSF only and apheresing to a lower target. This is actually a little even more dramatic if we actually looked at those who had more than 3 in the G-CSF arm.

These are the adverse events that were seen in the pivotal trial, the breast cancer study. Similar picture again. The injection site reactions were exceedingly common. Respiratory symptoms were more common in the stem cell factor arm. There was a high background also in the G-CSF arm, but when you looked at the actual symptoms, there was a different distribution in the symptoms between the two arms. There was also a difference in the assignment of causality between the two arms. Most of the symptoms in this arm were felt not to be study drug

related. Most in this arm were felt to be study drug related.

Again, we do see a difference in skin manifestations and various types of skin rashes. These are not all generalized urticaria by any means. I think we have to remember with this study, as with the other studies, these patients are getting four drugs around the clock to suppress manifestations of mast cell degranulation. We really don't know how that affects the clinical presentation of those symptoms.

Again, cardiac symptoms were more common in the stem cell factor arm, and again these were mainly tachyarrhythmias.

5 patients discontinued stem cell factor in this study. 3 had frank anaphylaxis. 1 was coded as having urticaria, dysphagia, and throat tightness and 1 was coded as having allergic-like reaction. As the clinical trial program was in progress, Amgen stopped reporting patients as having anaphylaxis and started using this term we've heard, the "allergic-like reaction."

This is the proposed indication for stem cell factor. It's kind of a complex indication which has actually three separate components. Stem cell factor is to be used in combination with G-CSF for providing a sustained increase in the number of peripheral blood progenitor

cells, increasing the proportion of patients reaching a target, and reducing the number of aphereses required to collect the target.

Now, none of the studies actually dealt with the question of the duration of mobilization. In our letter of January, we asked Amgen about this and in their reply, they said they don't want this considered as part of the indication anymore, but we have not yet received an actual revised indication from them.

As we can see, the proportion of patients in the pivotal trial who reach the target was borderline significant, but didn't quite reach significance, and the number of aphereses was not statistically different between the two studies. So, we like Amgen decided to look at these randomized phase II studies to see if we could get any additional supporting data.

These are the randomized studies that were done. 940190 is the pivotal trial. Again, the p value approach did not reach statistical significance.

These are the two studies being done in Europe. These apheresed to a total of 3 and a total of 4 aphereses. Both of these studies used chemotherapy in addition to the 5 microgram per kilogram dose of G-CSF.

This study is currently in progress. An interim report was submitted, and as you can see, there's a

decided trend in this study against the stem cell factor arm with 47 percent of the patients achieving the target as opposed to 31 percent. This difference was not statistically significant.

This is the study that was referred to as the myeloma study, and as you can see, in this study most patients achieved the target. There was a very slight trend, 78 percent to 85 percent, in favor of the stem cell factor arm, but this was not statistically significant.

In these two studies which are being done in the United States and used only cytokines, G-CSF with or without stem cell factor, this study did apherese to a total of 5 aphereses. This study apheresed to a total of 6 aphereses. As you can see, this is the study that was referred to as the lymphoma study. There was a statistically significant difference in the proportion of patients reaching the target with only 17 percent reaching the target in the control arm and 44 percent reaching the target in the stem cell factor arm, and this difference was statistically significant. This study really is quite close in design to the phase III pivotal trial.

This study which is a study that used a higher target, 10 times 10 to the 6th, there was no difference between the two arms. The proposed indication is not specific for a target. It just leaves it open to any

target.

We actually looked at the number of patients in this study who would have achieved a target of 5 times 10 to the 6th, which was the target in the other studies. It was 33 percent in the control arm and 50 percent in the stem cell factor arm. This difference obviously was greater and suggestive, but also looking at the target of 5, the difference was not statistically significant.

These are the data on the total number of aphereses overall. When we did this particular analysis, we are now actually penalizing those patients who dropped out during the collection phase without reaching the target. Again, we assigned just the number of phereses that the rest of the patients had. We did not assign any higher values to those who did not meet the target.

Again, this is the pivotal trial, the breast cancer study. In doing this, as you remember, there was just a two-tenths difference in the means and there was a 1-pheresis difference, but using the Wilcoxon rank sum test, the arms were not statistically different.

In the study that's ongoing in Europe, the means and medians are essentially identical. In the myeloma study, which the difference was statistically significant using the Wilcoxon -- we just decided to use the Wilcoxon rank sum test throughout just for consistency

-- there was a .6 difference in the means and a 1-pheresis difference in the medians. Remember, in this study now, more than half in both arms reached the target. So, these would be the medians regardless of what you assign to the patients who didn't reach the target.

This is the lymphoma study. Again, this difference was statistically significant in this study. In looking at the means, there was a .6 difference in the mean. There was no difference in the median. Again, neither arm achieved the target in over half of them. So, again, the difference in the median does not depend on what you do with those patients who didn't reach the target.

Then finally in the study with the higher target, there was no difference whatsoever between the two arms.

This is just the overall summary. Again, these are the patients who had cytokine only mobilization, and these are only the patients who received 20 micrograms per kilogram of G-CSF.

We see the same picture. Injection site reactions obviously are very common. Respiratory symptoms, again there's about this 10 percent difference, but there is a difference in the assignment of causality for most of these. Skin manifestations, there's about a 20 percent difference between the two arms. Cardiac rhythm

disturbances, there's about a 10 percent difference between the two arms. Again, these were primarily tachyarrhythmias thought to be due either to the premedication regimen or possibly other vasoactive substances. Then there was a 5 percent difference roughly in cardiovascular symptoms. These were mainly blood pressure changes that were really fairly moderate to mild.

As we've heard, I think certainly anaphylaxis is the major concern with stem cell factor. The overall incidence in all the studies was about 6 percent. It was about 6 percent, as has been mentioned, too in the studies that were done in other INDs if you look at it overall.

If you look at only the phase II and III randomized studies which are the studies in which all patients got 20 micrograms per kilogram -- they weren't diluted out by patients who got less, and they weren't artificially higher by patients who got more -- all of the patients in the phase II and III studies had 20 micrograms per kilogram and had the prophylaxis regimen. The incidence was about 4 percent.

Certainly the anaphylaxis is dose and route of administration dependent. There does appear to be a fairly steep dose toxicity curve with stem cell factor. If we look at those patients who just got 5 micrograms per kilogram more, these are all patients who did receive the

prophylaxis. We see that the incidence of anaphylaxis just about triples from 4 percent to 14 percent. So, there does appear to be a fairly steep dose toxicity curve.

Then as we've heard mainly on the preclinical studies, when given intravenously, stem cell factor is highly anaphylactogenic. About 30 percent of the reactions occurred on the first exposure to the drug or a particular dose in the case of the three overdoses.

The median time to onset, just by my calculation, was about 3 hours. I'm not sure of the criteria that Amgen used for theirs. I just put my best guess as to where somebody might have diagnosed anaphylaxis. But I think both the 3 and the 5 and a half hours are in the same ball park, that these reactions are not immediate.

75 percent of the reactions were judged as severe. It is true that none were judged as life-threatening, but the protocol definition of life-threatening was quite strict. There were five criteria mentioned. They were cardiac arrest, respiratory arrest, respiratory stridor, cutaneous necrosis requiring surgery, and exfoliative dermatitis. None of the patients had those, although respiratory stridor was certainly described in the clinical description, but none of them were coded as respiratory stridor. So, none of them did qualify as being

life-threatening.

The conclusions, which have already been given by Mr. Parker and Dr. Sheridan. I think it is important to realize that both G-CSF and G-CSF plus stem cell factor mobilize sufficient number of peripheral blood progenitor cells for engraftment. The minimum number in most of the randomized studies was a million. In the pivotal trial, 96 percent of the patients in the G-CSF arm and 97 percent in the G-CSF and stem cell factor arm did have a million cells mobilized and did successfully undergo engraftment. And it has been mentioned in none of the randomized trials was there any statistically significant difference between the two arms in the number of patients who achieved the minimum for myeloablation and engraftment.

As has been stated, we feel that adding stem cell factor to G-CSF does have a small to negligible effect on reducing the number of aphereses to reach the target. If we look at the means, the mean reduction was from 0 to about .6 maximum. In the pivotal trial, it was .2 or .4 depending on whether you look at the actual number of phereses or penalize the patients who dropped off the study. If you look at the medians, the median ranged again from no difference to a maximum of 1.

Adding stem cell factor to G-CSF probably does modestly increase the proportion of patients achieving a

target of 5 times 10 to the 6th. As I said, in the trial that looked at a higher target of 10, there was no difference, but certainly the proportion of patients does look like the trend is definitely in favor of the stem cell factor arms.

I think at this time it is too soon to make conclusions about the effect of adding stem cell factor to chemotherapy plus G-CSF for mobilization. There are two studies looking at this. The one study that's completed does suggest that there is some advantage, but when we look at the other study which is ongoing, the trend is distinctly in the opposite direction. I think we'll have to wait really until that study is concluded, which shouldn't be too long, before we draw any conclusions about any advantage of adding stem cell factor to G-CSF.

I think the other problem, as has been mentioned, is the dose of G-CSF used was 5 micrograms per kilogram. Certainly in the license application for G-CSF for mobilization, when you doubled the dose of G-CSF from 5 to 10 micrograms per kilogram, you doubled the amount of CD34 cells that were mobilized, so that even if stem cell factor looks like it might add something to 5 micrograms per kilogram of G-CSF, I don't know that we can say that it would add something to 10.

The one thing we do see in all the cytokine

only mobilization studies -- it's actually the most consistent finding throughout the randomized studies -- is the addition of stem cell factor for mobilization does delay neutrophil engraftment by probably less than a day, but it is certainly real. It was statistically significant in the two largest studies and the difference was there in the other studies also. So, we would agree that it's probably not clinically significant, but it is a real difference and it does raise the question about the quality of the cells mobilized with stem cell factor.

I think mast cell degranulation is almost universal. Almost all the patients do show at least local evidence of mast cell degranulation, and in a few it is more generalized. I think without a doubt anaphylaxis is the major toxicity of concern with stem cell factor. The use of this premedication regimen certainly does seem to have at least lowered the incidence of anaphylaxis. In reviewing the actual case reports of these patients, there's a disturbing number of these patients who seem to be tolerating stem cell factor relatively well and then they omit one dose of the premedication regimen and anaphylaxis occurs. It's anecdotal evidence, to be sure, but there is a disturbing number of these that really suggests that compliance could be a major problem with this regimen and that the omission of a dose or so very well

could tip the patients over who seem to be in a fairly precarious balance since they all show some degree of evidence of mast cell degranulation.

So, I think with that I'll conclude. Dr. Siegel wanted to make I guess a few comments.

DR. SIEGEL: I'll just make a comment from here. I don't have any slides. I have illegible scribbles. Since I've yet to find time to get bifocals, I may have some trouble figuring out what I wrote down, but I want to try to clear up some areas of confusion, four or five such areas, that I'm afraid we may have contributed to that seem to be part of the issues here so that people can understand clearly at least how we or, in some cases, how I see these data or these issues.

The first is this confusion about how to count leukaphereses. This discussion about mean and median has in some cases been off target. I hope Dr. Steffen helped clarify that and Dr. Miller's question did to some extent and Dr. Follmann's comment.

But the reason I consider it off target is because what hasn't always been clear is that we're talking about two different endpoint. The primary endpoint of the trials in most or maybe all cases -- I'm not sure -- was the number of leukaphereses to reach a target. I personally agree and I think we agree that in those cases a

mean is quite problematic because, as somebody noted, the data are differentially right truncated, meaning different numbers of patients didn't reach the target to translate into simple terms, and you do, to calculate a mean, have to assign some number and there is no number that one can comfortably, with assurance that there's no bias, assign what number it would have taken those patients to reach target.

We did in our analysis, as Dr. Steffen pointed out, count the people who failed to reach a target by 5 in a group that was larger as doing worse than those who did reach the group by 5 in calculating that number. And the differences between the values of .1 and .14, .04, whatever did not depend on that. They did depend on some of the earlier dropouts and the 1 patient who was switched over. Our perspective at the FDA has been not to focus, at least in recent months, too much on that. The p value, after all, gives you the likelihood that something happened by chance.

We do not think those results arose by chance. We think the database is quite consistent that this factor causes more CD34 cells to show up in the leukapheresis product and the almost unavoidable outcome, if you have more in each leukapheresis, is that in some patients you're going to get to a target sooner. So, regardless of the p

value, those are real and consistent effects.

But we've also presented a different outcome, an outcome of the number of leukaphereses the patients actually received. There, there's no fictional data, as somebody suggested that we may have used. There's no censoring of data. There's no problem at all with the use of the mean.

The question I would like to address is why look at that number. And the answer I would give is that we believe that number to be a very useful, probably most useful measure of clinical benefit.

The basic conceptual design of these trials is that the studies compared patients on one of two management paradigms. Either they received G-CSF or G-CSF plus stem cell factor. At that point, regardless of the arm, they were leukapheresed to either 5 million CD34 cells per kilogram or to 5 leukaphereses, whichever came first. That's the nature of the design. Then provided they had more than 1 million cells, they were transfused.

The design was in some sense arbitrary. The target was in some sense arbitrary, but it was designed to roughly reflect what the investigators were doing, what's done in the community. One can quibble as to whether 5 million should have been higher or lower, and there's no broad consensus. But I would agree with the company that

to do this sort of study, you need to have a plan or a design. You can't just let each physician use their judgment as to when to stop. I think they made a reasonable choice, an acceptable choice.

So, you do that design. You transfuse. Then the plan is to demonstrate equivalence and engraftment and fewer leukaphereses as a measure of benefit.

Well, in terms of what really does measure the benefit, the people who received 5 leukaphereses and had 3 million cells, say, did not have any more leukaphereses than the people who had 5 leukaphereses and got to 6 million cells. They had 5 leukaphereses. They may or may not have theoretically engrafted as well. They may have been worse off, but that's a measure of engraftment and we measured engraftment and there's no difference between the arms in engraftment. And furthermore, there's no difference between engraftment of people who got 3 million cells without stem cell factor and those who got more than 5 million cells with stem cell factor.

So, if you wanted to measure the leukaphereses, if you are sitting there as a physician saying, okay, my paradigm is something like or close to leukapheresing to 5 million cells or 5 leukaphereses, whichever comes first, what will be the difference it will make to add stem cell factor to the regimen. The best estimate of that over a

number of patients is that the expectation is that you'll do a half a leukapheresis less. If you're telling a patient to measure what the benefit is of following that paradigm versus the other paradigm in leukaphereses, the expectation for that benefit is that on average in the largest trial he'd get 3.7 if he doesn't get stem cell factor and 3.3 if he does get stem cell factor.

You're telling your hospital administration how much money they're likely to save and you're following that paradigm, you're likely to do 3.7 leukaphereses per patient if you don't use a stem cell factor and 3.3 if you do use stem cell factor based on that one trial. In some of the other trials, it was .6 instead of .4 or perhaps smaller, but most of the means fell there.

But that is why we've looked at that, not that the other measure is not something also worth looking at for other purposes, the number to reach the target, but reaching the target per se is not a direct measure of clinical benefit. I'll come back to that in a moment.

There has been a lot of confusion regarding this delay of 1 day in neutrophil engraftment. We concur -- I think the sponsor and the agency largely concur -- that this is not of great clinical importance. That's what the committee has advised. I don't know that we'd say it's clinically insignificant, but it's not of great clinical

importance. But it is critical to the validity of the study design and the inference of clinical benefit from this study design.

Let me give, for example, a hypothetical. Suppose you had a drug that increased the number of CD34 cells by a factor of 3. Now, we know -- this committee has advised us and we still know, and several members sitting on both sides of the room, several scientists in this field have told us -- that CD34 is far from the perfect marker for what will give rise to good engraftment. Some CD34 cells may have less potency, maybe further committed down one differentiation path and so forth. The potential of reproducing stem cell is probably a subset of CD34 cells, probably even a relatively even a small minority. There are a lot of people in the room who know a lot more about the specifics, so I won't risk saying any more.

So, if you had this drug that tripled the number of CD34 cells but, say, in the extreme had no impact on engraftment, what would you expect to see? You would expect to see more CD34 cells. You would expect to see fewer leukaphereses to reach a target.

What might the impact be on engraftment? Well, we've tried to address this issue using other data in question 1(b), which will be read shortly I assume, but let me ask you to turn to slide 83 from the Amgen presentation.

In this slide there's a comparison in one of the studies of patients who got 1 million to 3 million cells versus those who got greater than 5 million cells. Well, greater than 5, of course, can be considerably higher than that. Some of those patients got 6, 7, or 8, and it's roughly in the ball park of 6, and 1 to 3 is roughly in the ball park of 2. So, there's roughly a threefold difference.

If you look at either the mean or the median -- and disregard now which arm because there's not too large a difference between the arms -- in the group that got 1 to 3, there's a 7-day median and in the group that got greater than 5, there's a 6-day median. If you look at the means, it's about 6 and a half versus 7 and a half.

So, the point is that this target of 5 million is not particularly sensitive to cell number. If you fall substantially short of the target, if you gave only one-third as many cells, you'd see a 1-day delay. So, you would see more CD34 cells, fewer leukaphereses, a 1-day delay. These are what we saw in this clinical trial. I'm not suggesting that the numbers, the threefold or whatever, or the 1-day delay may be a little less. I'm not trying to be precise about the numbers. I'm trying to get across the concept that the fewer leukaphereses can theoretically arise from creating CD34 cells that lead you to stop leukapheresis regardless of whether those help engraftment,

and if that's the case, you'll see only a very modest decrease in the number of -- increase in the length of days that it takes. Even if two-thirds of the cells are ineffective, you'll see a 1-day increase, something like we saw.

That's why we're asking the question as to whether this trial has the validity to say that there is equivalent engraftment and with that benefit of half a leukapheresis because the half a leukapheresis may not be a true benefit of the drug but an artifact of the trial design, or it may be a true benefit. That's why later in the questions we ask about the risk/benefit of a half a leukapheresis.

Just a little more. I'm almost done.

DR. VOSE: Yes, sure.

(Laughter.)

DR. SIEGEL: You know me too well.

DR. VOSE: Yes, I do.

DR. SIEGEL: A little more about what is of benefit. Better engraftment is a benefit. Fewer leukaphereses with similar engraftment is a benefit, and that's what this committee told us, not the same individuals, but that's what this committee told us four years ago, that those are benefits.

We do not see a higher number of CD34 cells per

se as a benefit, nor do we see increased number of patients reaching the target per se as a benefit. These depend, first of all, on whether the CD34 cells are truly active and helpful and even, to some extent, there are questions that can be raised even if the cells are not active or helpful. There's a great deal of data showing -- and much was summarized, much was done by people here -- that people who get 5 million cells engraft better than people who get less than 5 million cells. That's a known fact. But those studies, for the most part, perhaps in their entirety, were not done by randomizing patients to get 5 million cells or less than 5 million cells. For the most part, those data come from looking at patients who got either 5 million or less than 5 million, and they're quite confounded by many other variables.

Patients who get fewer cells typically get fewer cells because they get, as someone said, what they give. They get fewer cells from their leukapheresis. The patients from whom you get fewer cells at leukapheresis most typically are patients who receive substantial prior chemotherapy. That's why they have lower yields. They probably have impaired bone marrow reserves.

It is quite arguable or possible, based on those data, that those patients simply not only have fewer cells but have less effective cells. It is quite possible

that for those patients who were characterized as the outlier patient or the problem patient by other speakers, that if it were possible to keep leukapheresing them to get 5 million, which may not be possible, that they still wouldn't engraft well because they don't have good cells and good bone marrow.

It's quite possible that the patients for whom you get 5 million cells, if you only gave 1 million or 2 million cells, would look very different and much better than those patients who got only 1 million or 2 million cells because that's all you could get.

So, even beyond the issue as to whether the cells work, there are some questions about whether per se getting more cells out of a given patient will make a difference.

So, the benefits then are fewer leukaphereses with similar engraftment, better engraftment. They're not higher numbers. They're not increased numbers reaching a target. They're not fewer leukaphereses to reach the same target per se unless engraftment is equivalent. And certainly some of the other potential benefits regarding other uses of this are potential benefits that need to be studied that are not benefits shown.

So, the benefits that have been shown are, if you accept the validity of the study, one-half fewer

leukapheresis.

Finally, I'd like to say regarding the toxicity to explain our concern regarding the risk/benefit, that we can have some and we've had some discussion as to how bad the worst toxicity is. Was there a stridor or not? Was it life-threatening or not?

But one issue that hasn't been discussed that I'd like to point out that really underlies also our concern in the last question about whether these patients should be monitored is, if you accept that there is not yet -- there are certainly not fatalities nor life-threatening toxicities. If we accept these all have been reversible, the database of patients is in the neighborhood of 300. That leaves our knowledge, our confidence -- if you were to look at a 95 percent confidence interval, we could be pretty confident that things we haven't seen haven't occurred at an incidence of greater than 1 percent or so, don't occur.

Now, given that we're seeing wheezing, chest tightness, perhaps stridor, whatever, there's certainly the concern in that that there's some incidence that may occur on a more severe basis than we've seen. So, I would ask the committee just to keep in mind, as we think about this and particularly as we look at the last question, that part of our concern is not just what we've seen, but whether we

have yet to see the full spectrum of severity of the toxicities that we have seen.

Thank you.

DR. VOSE: Thank you, Dr. Siegel.

We'll open it now to questions and comments. Dr. Auchincloss?

DR. AUCHINCLOSS: I want to take exception to Jay in two areas. One has to do with the quality of the stem cells that they produce, and I came down here with that as my principal concern because of the 1-day delay in engraftment. I thought that that was, as you've pointed out, a very serious concern.

But during the course of the morning, if you want to turn on your slide page number 94, I said to myself, how would I address that question? I would take the patients who received the most marginal number of stem cells and measure the most sensitive index of failure of engraftment, and so I'd go for patients between 1 million and 2 million stem cells and look at platelet engraftment. So, I was really struck by the numbers in the bottom right-hand portion of this slide, that in fact the stem cell mobilized CD34 cells were in fact doing beautifully in this, what I would have taken to be the most sensitive area for demonstrating a poor bone marrow supply or stem cell supply.

What do you think about that, Jay?

DR. SIEGEL: What I think is we would concur that there doesn't appear to be a problem with platelets. There may appear to be benefit. I don't think these findings are statistically significant. They're certainly suggestive.

But I would not concur necessarily that that's the most sensitive indicator of whether stem cell factor-induced cells engraft well. The fact of the matter is that's the most sensitive factor in many of the -- that's what you see goes first in some of our cell selection devices. That's where we see the most concern. But seeing every trial show a difference in neutrophils, and some statistically different, and not in platelets, I think one has to say it's not the most sensitive factor here.

And why would that be different? Well, there are any of a number of reasons. Stem cell factor, for example, may promote differentiation away from the myeloid series and toward the megakaryocyte and the platelet lineage so that you could see benefits in one series and harms in another series. I think you have to look at each series and I think the data are quite consistent and significant that there is an impairment, and it's not in the platelet series. You're correct.

DR. AUCHINCLOSS: I agree. And there may well

be an impairment of exactly the sort that you're suggesting in the neutrophil line, but if it's total sum is 1-day delayed engraftment and not showing up anywhere else, i.e., in terms of late graft failure or delay of engraftment, et cetera, et cetera, and failure to engraft in a large proportion of patients, then that becomes clinically insignificant compared to the important clinical variable, which is when do you get your platelets back and how many patients do.

DR. SIEGEL: Well, that's what I was just trying to say, that the concern is less than a day delay is clinically important as that it may well suggest that the achievement of a half a fewer leukapheresis, while observed, may be an artifact of the fact that the drug is just increasing numbers.

DR. AUCHINCLOSS: Okay.

So, now let me come to my second point on which I want to take exception with you, and that has to do with the endpoints that you think are important here.

Now, this committee -- perhaps none of us, maybe some of us, not me -- said four years ago that there were two things that they thought would be good to measure. One would be superior time to engraftment and the other would be fewer aphereses with equivalent time to engraftment.

Now, personally I think in 1998 those two endpoints look silly, and I would not think, if I were the company, that they would be either ones that I would want to try to achieve necessarily as being useful to clinical patients. You're not going to get superior time to engraftment, and who cares really whether you have 2 or 3 phereses per patient or 2.3, whatever.

What I would take is the marker that you don't believe in, which is the percentage of patients that achieve a target. Now, that's not perfect for many reasons that you mentioned. I think in fact the proof that any of these targets is, A, relevant and, B, relevant for a stem cell population that you've mobilized in a different way remains to come, but it would be the endpoint that I would use as a surrogate marker at this point.

Actually I was kind of impressed at how well the company walked a tightrope between, oh, my God, we've got these two endpoints that we've got to prove, we can't do one of them for sure, we'll struggle to prove the other, but we really don't think that either of them are relevant. What we think is relevant is getting enough people to a certain target so they can have a transplant at all.

DR. SIEGEL: Well, you know, I think maybe we need to have further discussion with the current committee as to what the right current endpoints should be. And

there are certainly a lot of flaws -- and we recognized them at the time -- with the approach of four years ago.

I would say, though, that the flaws of the number of leukaphereses to reach a target as an endpoint are highlighted by the finding with this drug that you can decrease that number. You can get more cells. You can reach the target better and with those more cells and with more patients reaching the target better, you nonetheless see statistically significant impairment of engraftment twice. That highlights I think the potential problem because the next drug could also reach that target.

DR. MORSTYN: Could I just sort of bring up sort of a trivial point? There are a lot of issues we could take up. I just want to throw one more thing on the table that we realized as we went through the data, and that is, in the absence of chemotherapy, the number of cells that we infused, when we collected them from G plus SCF arm, was much greater than the number of cells that were infused. You can see that from the curve that Dr. Sheridan showed. This tiny phenomenon on neutrophils was only seen when we infused cells that were collected without chemotherapy mobilization, and there is a potential trivial explanation.

Basically what happens is the curve shifts slightly. The duration of neutropenia is the same and

there is a possibility that the filgrastim which these patients are also getting to enhance neutrophil recovery is somehow being metabolized by those high numbers of neutrophils.

So, there are other possible explanations, and particularly you have to think about something like that because the cells mobilized with SCF, G, and chemo in the myeloma model worked perfectly on time to recovery of neutrophils, as well as platelets. So, I think we agree -- and certainly all our consultants agree -- platelets are the best indicator here and there may be a very trivial explanation and not the profound one that you're suggesting for the neutrophil recovery day or less-than-day difference.

DR. SIEGEL: I'd just like to say I can't speak to whether it's in fact correct that -- one of these studies is still ongoing -- with chemotherapy you don't show the delay in neutrophils.

But I would like to note that the implications of having equivalent neutrophil engraftment, if that is the case with the chemotherapy plus lower dose G-CSF regimen, are significantly different from a regulatory perspective. Chemotherapy has no regulatory approval for mobilization of stem cells, nor am I aware of, although there may be, studies comparing the full dose of G-CSF to the partial

dose of G-CSF plus chemotherapy. So, it could be that in fact that the reason for that equivalence is that the chemotherapy plus the lower dose G-CSF is in fact slower by a day. That is something I don't know. We've not certainly had any such data submitted.

But I think quite appropriately, when a design for a marketing approval is based on equivalency, it ought to be fundamentally founded on equivalency to an approved regimen.

DR. VOSE: I'd like to make a few comments and then I'm sure Dr. Broudy would as well.

I think from a clinical transplanters standpoint, that the 1-day difference at that particular time point day, 9 versus 10, is not clinically significant. Now, if that 1-day time point was day 25 versus 26, the patient could have more potential for infectious complications at that that point, so I think clinically that's not significant. But I understand your concern about the cell equivalency at that particular time point.

I have to disagree a little bit, but I do think the number of aphereses is a good outcome to look at because it is costly. It does have side effects for the patients and it's not trivial.

However, I think the question in this particular circumstance is not that so much as the benefits

ratio that we're talking about with the side effects. There's no such thing as decreasing it by a half an apheresis. You can't do that. So, it's either one, none, or more.

DR. SIEGEL: You can decrease it by one in half the patients.

(Laughter.)

DR. VOSE: But for any one patient, obviously it's either an all-or-none phenomenon. So, I think that's more of an issue as far as looking at the risk/benefit ratio to any one particular patient in this particular analysis.

To analyze it as far as the real number of aphereses that the patients received, I think is the most appropriate way to do it because that's what happens to the patient, after all. There's no 3.78 phereses. So, I think that is an important outlook, and to look at the ratio, we really need to understand that that is what is important to the patient in the end.

Dr. Broudy?

DR. BROUDY: I'd like to also respond to one of Dr. Siegel's comments, and that is, what I think we can most safely conclude is that the cellular composition of the pheresis product, whether mobilized by G-CSF or by G-CSF plus SCF, differs somewhat, that the cellular

composition is slightly different in these two populations. However, both populations are capable of quick engraftment and of sustained neutrophil and platelet engraftment and, certainly in the data that was presented, in sustained T cell and B cell function when studied late on.

So, I agree the two populations are different and CD34 is an imperfect marker, although it is the best marker that we have at the present time.

I'd also like to bring up one of the graphs that was shown I think in the Amgen folder of data that we got suggesting -- I think I remember this correctly -- that there was a 1-day later drop in the neutrophil count in the G-CSF mobilized patients. So, the actual duration of neutropenia less than 500 was actually no different. They went down later and they came back later. I'm sorry. The G-CSF plus SCF group. So, the actual duration was really no different. It was just shifted a day.

DR. SIEGEL: Yes. That's a correct observation. I was interested in some input from this committee on that, as we have in many drugs and treatments and trials looked at time to neutrophil recovery and time to platelet recovery as the outcome for transplantation approaches. I don't know of the data that exists as to whether dropping faster or slower or whether during those 2 or 3 days before you're under 500 you're at less risk

because you're over 500, even though you've just received ablative therapy, than if you were under 500. We don't know those data. They weren't designed into the endpoint. So, it has been a little bit difficult to assess what, if anything, that means.

Is it your perception that in fact those patients probably on their way down are at less risk if they're still over 500 and that we should look at duration of neutropenia?

DR. BROUDY: Yes. I think the data would suggest that it's the total period of time that a patient is below 500 or below 200 or whatever number you wish to choose in addition to how severe their mucositis and all that is. That puts them at higher risk for severe infection.

DR. SIEGEL: I would just comment again, although I don't want to get to be a broken record, that that is addressing the issue as to whether these patients have a longer period of danger. We're not trying to emphasize that we believe that they do have -- even if it is a day longer or not, that that's significant. Rather the issue at hand is that the drug is -- and this is I guess confirmed by what you see on the down side -- changing the pattern which calls into question the implications and specifically is leading to larger numbers

of stem cells at the time which is leading to fewer leukaphereses. And these data would suggest, no matter how you look at them, that those larger numbers are in fact not causing shorter times to engraftment as one would have guessed because it's not just that they're getting the same numbers in both arms, they're consistently getting larger numbers. Yet, it's not shorter. It is in fact longer which even if that's compensated at the other end suggests that they're getting a larger of something different.

DR. VOSE: Dr. Champlin? First we have to disclose your conflict of interest.

DR. CHAMPLIN: Okay.

DR. VOSE: Just do this first.

MS. DAPOLITO: As a guest of the FDA, an observer today, Dr. Champlin has been screened for conflict of interest. We would like to disclose that he does serve on the Medical Advisory Panel for Amgen and Searle. He receives research support from Amgen and Immunex and consulting fees from Searle and Amgen.

Thank you, Dr. Champlin.

DR. CHAMPLIN: Just reflecting on the discussion, I just wanted to raise a few points I think that hadn't been emphasized perhaps as much as they might have been.

Now, the design of these type of trials are

very difficult because again you're trying to assess mobilization in a way that still protects the patient. So, you want to be sure the control group gets a good cell dose and that they would then recover well. So, this study was again designed to let the control group have a full dose even if it took more phereses. Their analysis that they presented indicated that the recovery per CD34 positive cell infused was the same and again it's a cell dose effect that was seen.

The real benefits are not again on neutrophils. So, again, none of the studies that have looked at cell dose and neutrophil recovery have found a very dramatic effect, but it is platelets that benefit the most.

Again, it's not the median that we keep discussing. It's the outliers, the people that never recover their platelet count. So, the one phenomenon that is seen, again in studies that look at cell dose and outcome, is a much tighter distribution of recovery, and so you're cutting down the number of patients that are at risk for prolonged transfusion support and prolonged use of medical resources. So, I would focus on that as a potential benefit.

The other thing is that I think there's a fundamental biologic effect of stem cell factor that is different than G-CSF, in that you don't see again the short

up and down mobilization of cells, you see a more prolonged sustained mobilization of cells, making the additional aphereses even more effective in terms of getting meaningful cells for transplantation. So, I see it as again a biologic effect that is desirable and at least that aspect is quite positive.

DR. VOSE: I'm not sure the data really support that. It looks like most of the -- the first three aphereses were really the ones that counted and after that, even --

DR. CHAMPLIN: They may have some slides maybe they can show again.

DR. VOSE: But the FDA analysis, even in the later aphereses, really for the most part, didn't add a lot to that.

DR. CHAMPLIN: They can comment but at least the previous publications would suggest that a different pattern of --

DR. GLASPY: I think there are two issues here. One is whether the cells that the patient is able to mobilize are still there and whether the patients who get out that far without achieving the target are good or bad mobilizers. And those patients are not, and so the proportion achieving a target each day you would expect to go down and the power on the study to see differences to

fall off, unless you had 800 in each arm in those latter leukaphereses.

So, the way that we chose to express the data was looking at each patient's proportion of day 1. We all are used to seeing day 1 predict day 2 and day 3 in all patients and then after that with G-CSF alone it falls off. These data are from the breast cancer study showing that when you normalize it to their day 1 value, there does seem to be more -- a closer to a 100 percent of their day 1 value present in the combination patients. That's number one.

Number two, the data that was talked about but not presented was that we actually in the breast cancer study started out with the leukaphereses taking place on days 11, 12, and 13, and on those days the yields were the same as we saw later when we did day 5, 6, and 7, suggesting that really the mobilization is sustained in leukapheresable quantities out that far in the patients who are good mobilizers.

DR. VOSE: Yes, but that data wasn't presented today.

DR. GLASPY: Correct, but I think it's in your packet.

DR. VOSE: Do you have any additional comments? Carole?

DR. MILLER: I have a comment about the basic question that we're going to ask about what is measures of clinical benefit. I agree with Hugh, but I want to sort of go one step further.

I think one of the issues that have come up here and spoken about by some of the clinicians is that it's not just the number of leukaphereses, but what we now want to do with the CD34 positive fraction. If we believe the data that this will increase the number of CD34's regardless of how many leukaphereses you may need to get there, that may be an additional important endpoint, especially in the people who are good mobilizers, and that you may be able to then do tandem transplants, et cetera, or whatever. So, I think that we also have to consider, even though it wasn't in the 1994 discussion, how important we feel that is as a measure of benefit in these patients.

DR. VOSE: Abbey?

MS. MEYERS: I'm trying to understand this as a layman. First of all, I watch TV at night. Every few weeks you hear an announcement about another drug being withdrawn from the market because it caused severe side effects, it killed people, et cetera. In the last year alone, I read in the newspaper that more drugs have been removed from the market by FDA than in the previous 10 years.

So, this discussion about a drug that obviously has very severe side effects in terms of what we've learned in recent years is that if you have a life-threatening disease and you don't have any other adequate treatment, then maybe it's appropriate in many instances for FDA to say, we approve a drug that's going to cause 25 percent of the people who take it to go into anaphylactic shock. I mean, if it was Huntington's disease, I would say, sure, do it because there's no other chance to live.

But here all of these patients are doing very well on the one drug. So, the question is, should the second drug be added? What is the advantage?

I'm trying to figure out, for example, the statement that was made in the beginning that this would save money because it would save on one leukapheresis. I think it was the amount of $4,000. But does it factor into that the cost of treating anaphylactic shock? I know, for example, there are women who go into the hospital for a mastectomy in the morning. They're thrown out in the afternoon because the insurance wants to save money. I mean, what's the cost of staying overnight in the hospital for anaphylactic shock?

And also, was the cost of whatever you're going to charge for the drug factored into the $4,000? Are you really saving money from using this?

If you're looking at the two questions that FDA is supposed to address, which ordinary citizens like me want to know that the FDA is out there guarding us, there are two questions they have to ask. Is it safe? Is it effective? And what we know from your data is that, number one, it is not safe for a large number of people, and I'm amazed to find that in the study you've screened out all the allergic people first so that you only studied it on the people who didn't have obvious allergies to drugs or didn't have a history of anaphylactic shock. So, you studied these healthier people and yet they got shock.

And the second question is, is it effective? And the data doesn't seem to say that it's effective and that it's worth the risk.

DR. STIFF: I'd like to comment on behalf of patients with lymphoma. If you have a lymphoma that relapses after conventional chemotherapy, intermediate and high grade lymphoma, you are incurable and will die of your disease without a transplant. The bottom line is transplant is the only effective therapy for that group of patients.

If, as we standardly do in the United States, you get two cycles of chemotherapy with what we call a salvage regimen -- we use a variety of different regimens. Two of the most common are DAP and ESHAP -- use of those

regimens would have made you eligible for the trial that was presented, the randomized trial in lymphoma. Fully 26 percent of the patients that got that chemotherapy for relapsed lymphoma did not hit a minimum safe target of 10 to the 6th CD34's per kilogram in the group that just got standard mobilization with G-CSF alone.

Now, if you take those patients and say, what am I going to do with you, if you then go in the second line and give them chemotherapy and G-CSF to try to collect an additional amount of stem cells, you run the risks of fatal complications. And that actually happened with my last patient who we couldn't get enough cells with just standard mobilization. He died of complications of that second or third line chemotherapy trying to collect cells so we could give him the curative therapy. So, sometimes the treatments to collect stem cells are very toxic. No patient has died having been administered SCF.

Finally, the percent of patients that were actually screened out, at least in the lymphoma trial, turn out to be only about 10 percent of patients, those with asthma, those with severe urticaria, those with bee sting type/venom reactions. So, 90 percent of the patients that are eligible for transplant are eligible to receive this drug.

DR. VOSE: Dr. Shpall, a very short comment.

DR. SHPALL: I just want to allay your fears. This is not anaphylaxis. This is not shock at all. It is totally different.

DR. VOSE: There were a couple of people that had hypotension.

DR. SHPALL: There were two instances of hypotension, but they were not scored as serious. The serious patients had wheals, flares, urticaria, all of which responded very quickly.

Granted, if we had patients going into anaphylactic shock, it would be a problem, but this is much safer than many of the medications that we're using. It has been controlled in every case and resolved within 24 hours. So, I think you're overestimating the real danger of it.

MS. MEYERS: I wonder if somebody from FDA can address that. Was it anaphylactic shock or anaphylaxis?

DR. VOSE: Dr. Steffen or Dr. Siegel, do you want to comment?

DR. STEFFEN: First of all, it was coded as anaphylaxis most, until they stopped using the term "anaphylaxis," but it sure looked like anaphylaxis. I was reading the clinical descriptions that came in.

DR. VOSE: Do you want to describe what you would call anaphylaxis for Abbey?

DR. STEFFEN: Well, they had respiratory symptoms consistent with obstruction, generalized urticaria. Some of these patients really had problems mobilizing enough air to talk for several hours after they were treated. Like I say, it sounded like anaphylaxis. It's true that nobody died and no blood pressures went down through the floor, but like I say, it certainly sounded like anaphylaxis and Amgen called it anaphylaxis.

DR. MORSTYN: I'd just like to correct the record. As far as I know, we've treated over 600, 640 patients with SCF. We have not coded a single episode as anaphylaxis. We starting coding them as allergic-like reactions. We then thought of them as anaphylactoid reactions. We feel this is a different syndrome.

The only way that you're really going to get a feel for what this syndrome is is to talk to the clinicians who've treated 379 of the patients. I haven't treated a single patient. He hasn't treated a single patient. These doctors have treated 379 of the patients. They're trying to describe what they saw, and I think it's really their description that counts in the end.

DR. SIEGEL: It's certainly not worth, although it may be necessary if there were labeling written, for example, getting I think too into the semantic aspects of whether it's anaphylaxis, anaphylactoid reaction,

anaphylactic reaction. It's not an allergic phenomenon. It's a phenomenon of histamine release. I think it's well defined what histamine release can do. We can talk about whether this is a more severe histamine-like reaction or a less severe one. Histamine can cause shock.

Shock specifically, Abbey, refers to a rather profound dropping out of blood pressure, and one saw blood pressure effects in some of these patients, but nothing that would probably be categorized as shock. So, it would be correct to say there was not anaphylactic shock.

As I indicated before, we don't know if we've seen the most extreme of what might occur, but certainly in 300 patients we've not seen anything like that.

I hope we don't waste a lot of time on the terminology. I think we all --

MS. MEYERS: In writing the labeling for this drug, would you say that one of the side effects is anaphylaxis, if not anaphylactic shock? What would you say?

DR. SIEGEL: Well, my staff tells me that whereas anaphylactic reaction and anaphylactoid reaction have etiological implications, anaphylaxis describes a syndrome and this does fit that syndrome. However, I'd want to check into that more and figure out what would be the best way to describe what it is.

DR. GALLI: Could I make a comment about the question of Ms. Meyers?

Anaphylaxis, as most clinicians use the term, refers to something that is a life-threatening reaction that occurs very rapidly, and the stories people are familiar with are kids who eat something that's got something with peanuts in it. They're allergic to peanuts, and within 30 minutes or an hour, unless they get epinephrine, they're dead. That's what both lay people and physicians often typically think of as anaphylaxis.

Strictly speaking when immunologists use the term, it means it's an allergic reaction with an IgE antibody, for example, against peanuts. So, you have to have been exposed, and then the next time you eat it, you can get the reaction. Or a bee sting.

It often occurs to many medicines, although the incidence is low. So, you can develop an IgE reaction to a medicine. Penicillin is perhaps the best known example. You take penicillin, you get an anaphylactic reaction, and it can kill you.

Now, Amgen knew early on, because my group was the group that discovered that this drug, when used in a certain way in vitro, could induce mast cells to release their mediators, that this was a potential problem. What wasn't known was how it was going to act in human beings

given the way it's being given in this setting. It may have been that it caused a severe reaction or a mild reaction or no reaction because the animal studies aren't always predictive of human results.

So, the initial patients, when they reacted at higher doses, got lower doses. These reactions clearly are related to mast cells releasing mediators which also happens in anaphylaxis such as to penicillin or to bee stings. An example with diarrhea. You can have diarrhea of the garden variety where you don't treat it, and you can have diarrhea related to cholera which can be fatal if it's not treated. This is not, to pursue the analogy, the cholera type mast cell release reaction. It's something that these clinicians have been able to treat with relatively simple interventions.

DR. SIEGEL: A point of information.

DR. GALLI: Yes.

DR. SIEGEL: Is the time course identical for the early patients who weren't premedicated? These patients all received two types of antihistamines and beta blockers. It also occurs after 3 or 5 hours.

DR. GALLI: I believe that's true. Unlike anaphylaxis to penicillin or to peanuts in sensitized individuals which can happen within minutes, this is a very delayed time course. It's delayed in two senses. It

doesn't start to happen until typically a later period after the injection, and also the symptoms aren't there suddenly in full-blown characteristics. They gradually increase, and that gives the patient time to call a physician and so forth.

MS. MEYERS: Right, but it also makes me wonder if a drug gets out on the market and the average person who was using it is home or happens to go to sleep and this happens during the night. There's much more danger out there out on the open market than there is in a clinical trial where they're warned to watch out for anything and call the doctor immediately and get back to the hospital immediately.

DR. GALLI: Yes. The sponsor has struggled with this and discussed this with the FDA. They're looking for an indication which will be in highly specialized centers. All of the physicians and nurses administering the agent will be trained to appreciate this potential risk. They've already developed an experience in how to manage these patients.

So, I think I shouldn't be misunderstood. There is an issue of risk, but I think it has already been demonstrated in the patients studied that it's a manageable risk, considering the potential benefit to this group of patients.

DR. VOSE: I think Ms. Meyers does have a point, however, that this is a delayed reaction and the patients aren't going to be in the hospital when this happens, and so education will be very important.

What I'd like to do is actually go to the questions because I think many of the things we're discussing are actually in the questions. I think all the committee members have it. It's in the middle of your packet there. We can revisit many of these issues.

For question number 1, in all studies comparing mobilization with SCF plus G-CSF to the approved regimen of G-CSF alone, the SCF arm mobilized more CD34 cells but took slightly longer to achieve neutrophil engraftment, and that was 1 day in two of the studies. This would suggest that on a cell-for-cell basis, cells mobilized with SCF are less effective in supporting rapid neutrophil engraftment. Please comment.

Dr. Broudy, would you like to comment further on that?

DR. BROUDY: I'm willing to reiterate my earlier comment that basically I think what this means is that the cellular composition of the cells obtained with G-CSF and those obtained with G-CSF plus SCF differ somewhat, but I think both do engraft promptly and also offer sustained engraftment of both neutrophils and

platelets. So, I think that's what we can say. They are different populations of cells, and it doesn't surprise me that since they're different populations of cells with different probable percentage of stem cells, progenitor cells, precursor cells, that the CD34 content would vary somewhat. So, this is not a grave concern of mine that there was a 1-day delay in neutrophil engraftment.

DR. VOSE: Dr. August, do you have a comment?

DR. AUGUST: I would echo Dr. Broudy's comments. I think that to me as a clinician, the neutrophil reconstitution and its translation into clinically meaningful infections, with all that that implies, is really kind of trivial. There really is no difference, and when the neutrophil count is rising, the number of infections I think declines basically to 0.

The thing that is impressive I think that I have carried away is that the number of individuals who can undergo this therapy seems, particularly in the lymphoma groups who mobilize poorly, is increased substantially. I think it makes a big difference whether 17 percent of a group of lymphoma patients can mobilize sufficiently to be treated in this way and then be offered a chance at being cured versus 46 percent.

I think the other parameter that is impressive and outweighs the neutrophil issue is sort of the closure

of the number of patients who require platelet transfusions for prolonged periods of time. The 0 percent needing platelet transfusions after a month is impressive versus, admittedly, 8 percent, but if we're talking about hundreds or even thousands of patients potentially receiving this sort of therapy, an 8 percent residua who require prolonged platelet transfusions, that I think is an important clinical as well as personal issue for the doctors involved and the institutions that have to get the transfusions and, of course, for the patients themselves.

DR. VOSE: I'll just reiterate what I said as well, that I don't think the 1-day difference in platelet engraftment is a problem, but there is a slight difference probably in the makeup of the cells that needs to be looked at. The platelet engraftment issue is probably one of the most sensitive issues, but it was not statistically significant.

DR. SIEGEL: Dr. August, those numbers you cited in terms of more patients getting an engraftable number --

DR. VOSE: I don't think those are correct numbers.

DR. SIEGEL: I think they was percent meeting target.

DR. VOSE: Yes. That was percent meeting

target.

DR. AUCHINCLOSS: It's page 55 and you're right. It's numbers getting to target. The difference wasn't significant for those reaching a million. It was 84 percent versus 74 percent.

DR. SIEGEL: Again, we don't know for sure how those somewhat under a million --

DR. VOSE: Right. So, that's not a percent of people being able to be engrafted, but percent meeting target.

DR. AUCHINCLOSS: I'm sure there's no statistical significance to this one either. This is page 42 of yours, the absence of reduction in negative outcomes. But it's always consistent in the right direction.

DR. SIEGEL: Right, and might be meaningful if you believe, as it sounds like many of you do, that if you were to be somewhat under a million without stem cell factor and somewhat over a million with stem cell factor, that not only are you therefore getting engrafted, but there's good reason that you're therefore getting engrafted because you have better cells and a better chance. That is implicit in any endpoint using just a target number as the endpoint.

DR. VOSE: Dr. Weiss?

DR. WEISS: I just wanted to just clarify that

I don't think anybody here thinks that a 1-day delay, 9 versus 10, has any clinical significance. I just want to make sure that that is on the record. It's more I think an aspect that goes into question 1b which is the validity of the study design because here you've got maybe different populations and maybe it's telling you different things and somewhat of a spurious thought that those lead to some benefit. I just wanted to go on the record and say that none of us feel that at the ranges that you're talking about, that there's a clinically significant difference.

DR. VOSE: Any additional comments on question 1?

DR. AUGUST: I misread the graph on page 32 and I stand corrected for the record.

DR. VOSE: Okay, let's move on to question 1b, and this is concerning the study design. The design of the efficacy studies was to mobilize with or without the study drug, leukapherese to a target number of CD34 cells, and demonstrate efficacy by showing fewer leukaphereses with equivalent engraftment. The validity of this design is highly dependent on establishing that the cells engraft equally well. If a new drug mobilized CD34 cells which are less effective or ineffective at promoting engraftment, the higher cell count would, nonetheless, lead to fewer leukaphereses but drug benefit would be uncertain. A

similar reduction in leukaphereses with a similar impact on engraftment might be achievable by leukapheresing to a lower target and not adding a new drug. That was the issue that Jay talked about.

In the pivotal trial, patients on the control, G-CSF, arm receiving 3 million to 5 million CD34 cells per kilo achieved neutrophil engraftment more rapidly than those on the SCF plus G-CSF arm who received greater than 5 million. Had patients on the control arm been leukapheresed to the target of 3 million per kilo rather than 5 million, the reduction of leukaphereses would have been greater than that associated with hitting a target of 5 million with the addition of SCF. If, as suggested by the data, the engraftment and leukapheresis outcomes on the study arms could have been matched or surpassed by choosing a lower target on the G-CSF alone arm, they do not clearly establish that the study drug provides benefit. Please discuss whether a benefit has been established.

Dr. Berman.

DR. BERMAN: I find this a somewhat theoretical question because in fact the target was 5 and not 3. But I would just go back to what Dr. August said and what we saw just there on the slide that a higher number of people hit the target that was chosen and therefore an effect was seen. That seems intuitive. Obviously not.

DR. MORSTYN: Could I just say one thing for the record? In the 3 to 5 group, the average number of CD34 cells is 4, and it took up to 5 aphereses. Filgrastim is clearly a wonderful drug and we make it. In the other group, the average is 6. So, what you're really asking is can you show, with this post hoc subset analysis, a difference between an average of 4 times 10 to the 6th CD34 cells and 6 times 10 to the 6th CD34 cells, and that obviously is impossible from the graphs that you've seen. This isn't an outlier analysis.

DR. SIEGEL: We weren't asking to show a difference, though. In fact, although they are post hoc subsets, if you compared the 4 in the one arm to the 4 in the other arm, those are not randomized. So, what it means I don't know, but the p values are at about .001 and you see that 1-day delay. No. .01.

But if you compare the 4 to the 6, it's not a question of statistics. It's just a question of the curves really overlap and similarly if you compare the 1 to 3 to the 3 to 5 in the other group, the curves overlap. If you compare the 3 to 5 in the control, the greater than 5, they overlap almost entirely. When you compare any like groups, they don't overlap, and if you do the only statistically valid comparison of the total randomized groups, it's statistically significant.

I don't want to make too much. I agree, these are post hoc subsets, but they only highlight the question that we're trying to ask, which is since you can also get leukaphereses by increasing the number of cells, even if they don't work, and since this assay is not highly sensitive to cells that don't work, if you were to give 6 million cells and only half of them worked, you'd have 3 million cells that would engraft just as good, except you would stop leukapheresis sooner because you had a higher number. Then the question is can we attribute that benefit of the half a leukapheresis to the study drug. Obviously, a lot of people who think you can and some who think you can't. We'll take that advice.

The other question that we're as much or more interested in is whether that benefit is worth the overall risk/benefit assessment, given the impacts on other variables.

DR. VOSE: Dr. Follmann.

DR. FOLLMANN: Yes. I just wanted to say in response to the question posed in 1b, I thought this was, as had been said before, kind of a post hoc discussion of an arrangement of the data. It sort of describes an interesting trial that might have been done or could be done in the future, but I don't know what strong evidence or how much this should sway us in our decision about the

product.

In terms of that, the dint of this is whether a benefit has been established. I would like to pick up on the discussion a little bit that had been going around before as to what's the important thing to look at.

In my mind both target and yield are in some sense surrogate endpoints. What are the clinical endpoints more in my mind are the number of times they've been apheresed and whether they engraft. I think we agree that the engraftment isn't an issue and that the remaining one is the number of aphereses that they received.

In my mind Dr. Miller made a comment I believe about how it would be good if you could really achieve higher cell yields, maybe 10 times 10 to the 6th or something like that, that that would be a good thing. I think perhaps that was because she was imagining different therapies that might be possible, maybe repeated regimes of chemotherapy or something, but I would say that we need to focus on what the study was that we're looking at here, not what benefits might happen with increased mobilization.

So, I want to stick to aphereses and engraftment rather than targets and cell yields.

DR. VOSE: Do you have any further comments about the statistical methodology over what you talked about earlier, the mean versus median or anything else you

want to discuss?

DR. FOLLMANN: No.

DR. VOSE: No?

DR. FOLLMANN: No, no.

DR. MILLER: Can I just answer back his comment about the question about the number of actual CD34 cells?

We've had a lot of discussions at this table over the last year since I've been on about getting a CD34 population and then leaving the clinical for the research groups to figure out what best to do with that. This I think is another tool, just like the other tools we discussed, the different machines that we use to collect a better CD34 population to allow the investigators to do with what they want and to prove clinically. So, that's sort of where that came from, not that I just thought that up because we've had lots of discussions about is that useful, and I think we've decided that it is.

DR. VOSE: But, nonetheless, we need to really utilize the study that we have on the board today as far as approving this drug. That's what our task is supposed to be.

Dr. Broudy?

DR. BROUDY: I think the biggest benefit that I've seen so far today in my own interpretation is the addition of SCF seems to increase the proportion of

patients that achieve the target number of cells that one wants to harvest. I think Hugh may have made this point earlier. I think the issue of whether it takes .4 or .6 or 1 fewer pheresis is in some ways irrelevant. That's an issue of patient convenience really and some modest issue of cost.

What I would recommend is that we consider recommending that they drop the claim that this decreases the number of phereses because that has been very controversial the way the data are analyzed by the company and by the FDA. That's really an issue of patient convenience, and .6 or .4 difference in number of phereses doesn't impress me.

I would recommend that we stick with the claim that the addition of SCF increases the proportion of patients who achieve a target peripheral blood progenitor cell harvest. I think that is supported by the data but drop the phereses --

DR. SIEGEL: I have some policy and legal problems with that. Except where we have validated surrogates, as Dr. Follmann noted, the number of cells and the proportion reaching a number are surrogates for benefit; they're not real measures of benefit. We have trouble in laws and policies regarding writing indications and how they relate to clinical benefit.

What is the proportion who reached the target a surrogate for? If you are saying more people reached the target, it can only be a surrogate for better engraftment. The concern lies in that they haven't shown better engraftment and in fact, although not clinically important, the time to neutrophil engraftment was marginally longer. So, we could hardly say that is validated to show better engraftment. So, now I don't think we can do that. I don't think we can give an indication for that.

DR. VOSE: The other possibility would be that it's a surrogate for decreasing leukaphereses which is obviously a contention here. I agree with you. That's a problem.

DR. BROUDY: But I think using G mobilized cells, a number of different investigators, including Bill Bensinger at the Fred Hutch, have provided data that the number of CD34 positive cells is important for speed of engraftment and also for decreasing the proportion of patients who remain platelet dependent. Even though, as I've said, I think this is a different population of cells, I think that's probably going to hold true here too, and I feel uncomfortable giving approval to decrease the number of phereses when it's .4 or .6 fewer pheresis and some question about the statistical differences and when I also think decreasing the number of phereses in this day and age

and given also the risk/benefit of the anaphylactoid-like reactions that have been brought up by Ms. Meyers, that's really more of an issue of patient convenience. Whereas, increasing the number of patients who can then go on to transplant or increasing the proportion of patients who can then have some of the other types of studies that Dr. Miller has alluded to, such as tandem transplants or purging studies, that may really be a benefit.

DR. VOSE: But that's an implied benefit that we don't have data for here. That's the problem.

DR. SIEGEL: Yes. It's a benefit assuming that the increased number of cells really means an increased ability to undergo those things. First of all, we don't have a trial showing whether those things benefit, but it also carries the implication that since we can't tell from these studies whether cutting the number in a third would make any difference larger than a day. We can't tell that doubling the number, which this has done, in fact shows that the patient who was at .8 million and now is at 1.6 million is in fact more engraftable at 1.6 than he was at .8 or whether the fact that he's now engraftable is just an artifact of the fact that people set the limit at 1. I think that will apply whether it's 10 million for cell selectior or anything.

So, there are two issues. One is whether those

cell selection things are indicated, approved, or effective, that we don't have data on them, and whether the number per se is going to be the issue.

DR. VOSE: Dr. Leitman?

DR. LEITMAN: I also agree with Dr. Broudy, but for a different reason. There's an inadvertent bias in the way all these studies were designed because, as Dr. Champlin said earlier and as we all know, with G-CSF there's a very brisk rise and a fall. If you don't get what you want in 2 or 3 phereses, you're very, very unlikely to get it in 4 or 5 because the CD34 in peripheral blood rapidly drops to baseline. So, if you don't get it by 3, you're just adding procedures with absolute minimal likelihood of getting you to a target dose. You increase the phereses. And that's not true for the combination, G plus C, where the CD34 and the peripheral blood stays up at a plateau for a while, and you are much more likely to achieve a dose with a fourth procedure and not have to go to a fifth.

DR. VOSE: I don't know that it's much more likely. It was what? 3 versus 11 percent I think.

DR. LEITMAN: 11 percent versus 3.

DR. VOSE: Versus 3.

DR. LEITMAN: But the pivotal trial got you from 46 to 60 percent.

DR. VOSE: At the end of 5.

DR. LEITMAN: But I think looking at the number of leukapheresis procedures is artificial and there was some inadvertent, just the way the drugs work, bias in that.

I would agree then with the other comments with proportion of patients achieving a targeted dose and with an optimal and a minimal dose as being very important but not necessarily the number of leukaphereses.

DR. VOSE: Dr. Arm, did you want to --

DR. ARM: As others have said, it seemed to me that perhaps that the greatest benefit in engraftment would have been seen in the lymphoma study where there's low yields in the first place where we're looking for a platelet engraftment. I don't think we've seen the data on whether there were reduced platelet transfusions and fewer outliers in that study, patients who have continued to be platelet dependent. I wondered if that data was available. We've seen it for the breast cancer study. I don't think we've seen the data for the lymphoma study.

DR. VOSE: Does the sponsor have that data available for the lymphoma study?

MR. PARKER: We showed the data from the Kaplan-Meier curve for platelet recovery, but I don't believe we have the transfusion data. There was no

statistically significant difference in the number of platelet transfusions between the two treatment groups. However, we did use a cutoff of 1 million CD34 positive cells and there were more patients in the SCF plus G-CSF who were eligible to go on to transplant and included in the engraftment analysis.

DR. ARM: The reason I asked that is just going back to Dr. Siegel's about what is the number of CD34 positives a surrogate for. Ultimately you want to see some clinical benefit which one would expect to see in those sort of clinical outcomes. That's why I asked that question.

DR. VOSE: There's the graph. They don't have the number of transfusions though.

DR. MORSTYN: No, but I think it's really important to realize that we did show you in the study that led to the lymphoma study which was practice at the time -- at that time G-CSF was used in a standard way and the heavily pretreated patients got .28 CD34 cells as an average and they had very prolonged platelet engraftment. The patients who got G plus SCF had 1.6 CD34 cells and got very rapid engraftment.

We could have gone on and done a phase III trial there and shown what you're asking for, but we decided that this was not a reasonable thing to subject

patients to. Obviously, the clinicians wouldn't do that. So, we then introduced the 1 million cutoff.

What we found in the next study was that almost twice as many patients on the G arm had to be taken out of the study because they didn't get enough cells to go forward. So, all you're looking at then is you're looking at more of the G plus SCF patients having their transplant than the G patients, and that's really the benefit. There weren't enough patients to put a statistical p value on that, but it was really building in that safety factor that makes it addressing directly what you're asking very difficult.

DR. VOSE: Dr. Auchincloss?

DR. AUCHINCLOSS: It seems to me, Jay, that's a real clinical benefit that has occurred on the basis of an absolute target number of CD34 positive cells. So, I would have thought the CD34 positive cells was one of the best validated surrogate markers that I can think of.

DR. SIEGEL: I'm sorry. Which real benefit?

DR. AUCHINCLOSS: This was the benefit of number of patients who actually got to go on to their transplant.

DR. SIEGEL: Well, yes. But you see, the problem with --

DR. AUCHINCLOSS: I understand.

DR. SIEGEL: -- that's an indirect surrogate. If I were to have a therapy that gave you inactive neutrophils which 10 or 12 years --

DR. AUCHINCLOSS: Jay, I understand --

DR. SIEGEL: Let me finish the thought please.

If I had a therapy which gave inactive neutrophils which 10 or 12 years ago we wondered about some of the now approved drugs did, then sure enough, when people reached 500, they would no longer have episodes of febrile neutropenia because the count is over 500. They'd go home from the hospital faster, whatever. And those are real clinical benefits. You go home from the hospital sooner. You don't get antibiotic coverage, whatever.

But they're artifacts of study design if you don't know that you have -- so, yes, more people get transplanted if they hit a minimal target of 1 million, but that could be an artifact of study design. If the same thing is achievable just by lowering the target because if more cells are not meaningful.

DR. AUCHINCLOSS: I understand that entirely, but you're asking for a clinical benefit and you're saying that this doesn't have one, but it clearly does at this moment. I personally think that CD34 will turn out to be important, and I think it ought to be studied. But you're sitting there saying, no, we can't use that because our

laws wouldn't allow it because there's no real clinical benefit. The fact is there is real clinical benefit.

DR. SIEGEL: Well, I would take some exception with your saying it clearly does. I don't believe we've seen yet any statistically significant data regarding increasing the number of people who reach a million.

DR. AUCHINCLOSS: That is a true point because I've been going through all --

DR. SIEGEL: I suspect that will turn out. The trends are there.

DR. AUCHINCLOSS: The trends are so powerful that I basically do believe it, but you're absolutely right in that statement. The only place where there's a statistically valid conclusion has to do with the target, the 5 times 10 to the 6th -- they have not hit it for the 1 times 10 to the 6th. So, I agree with that point.

Let me just finish on 1b. It seems to me you are kind of playing a game with the company here.

Your analysis actually convinces me that there is no benefit in number of aphereses. I actually believe that you're correct on that.

But, boy, if I were the company and I was working in a situation where the guidelines said show a decrease in the number of aphereses with equivalent clinical engraftment, and that was the endpoints that the

committee had told me four years ago, and I do a study and I show it with equivalent clinical engraftment, and you come back to me and play some games with it, I'd go berserk. I'd say, come on, you can keep changing the rules on me every time.

Of course, you know how I feel that that's not the relevant endpoint anyway. I think the relevant endpoint is how many CD34 cells you can get out of this product, but it does seem to me you are playing some games with the company here.

DR. SIEGEL: Let me address that because that's an important issue. It gets to the heart of what one means by equivalent. When we do equivalency trials, we set margins not based on what we consider clinical inferiority, but based on what we consider to be clinically acceptable. So, if you have a new thrombolytic and you want to compare it to TPA or streptokinase, you have to rule out the possibility that you're half as good, that you're less than half as good. But if in fact you ruled out that you were less than half as good, but you had such a precise estimate that you also knew you were worse, we wouldn't say, well, it's clinically acceptable because you're half as good.

It's rare that you see an equivalence trial which is inferior but meets the margin and that's because it's rare that the power is there to have a confidence

interval which you get here because the data were so tight at day 9, 10, and 11, that that 1-day shift was consistent enough that it comes out statistically significant. Now here, unlike mortality, we're not concerned about the clinical importance of that.

But the point I'm trying to make is that the margin of 2 days was set as, well, you need to be sure -- if you show there's no difference and we're comfortable that you can exclude a margin of 2 days, we'll be able to presume there's no difference. It's hard to presume there's no difference when there's a statistically significant difference.

So, now we believe there's a difference. We've been very careful to say 100 times we don't think that clinically matters. The question on the table is whether that difference matters because of its implications regarding the study design.

Yes, you could say it's a second guess. Alternatively, you could say in order to do a design which shows equivalent engraftment and fewer leukaphereses, which is the design that was chosen, you need to have a drug that truly provides equivalent engraftment. If it doesn't, even if -- our concern is and our question is, as you know, whether that lack of equivalence makes it impossible to attribute the benefit of decreased leukaphereses. I guess

you said you agreed with that but are looking at a different thing, at a different type of benefit here.

DR. VOSE: Dr. Champlin?

DR. CHAMPLIN: Yes. The 1-day difference of engraftment, in looking at neutrophil counts, again we all talked about we don't think it's clinically relevant, and I agree. I'm not even sure it's statistically accurate because again you're drawing the blood once a day. You don't really have much precision in that. It's like a one tube dilution in a serologic test. Even though the p value was impressive, it biologically doesn't necessarily mean anything.

So, my impression from all the data that I understand is that one cannot conclude, at least with this factor, that there's biologically a difference with the CD34 positive cells. The cell recovery, the recovery post transplant, is related to the number of cells that you've given.

So, what can you use as a gold standard that's really a hard endpoint here? The field needs to have some number. You say you hit this number, you got your target, now you can do a transplant. One can discuss what that number should be. Should it be 1 million? Should it be 3 million? Should it be 5 million? But you can set your parameter. I have been impressed that you can hit whatever

endpoint that you want more reliably with the combination with this drug. So, that again I think is a powerful positive that's been presented today.

I think you have to use the clinical practice sort of as one of the fundamental patient benefits here. Again, it's a standard of care to use CD34 numbers as a decision maker for transplants. Even though we have all of the biologic issues that you discussed on the quality versus quantity of cells, still that's the best thing that we've got today. So, being able to hit a CD34 target I think is a realistic surrogate endpoint. Albeit not perfect, it's the best we've got.

DR. SIEGEL: I invite you to be there. I hope you will. As you know, we're regulating stem cells as a product and moving into that field, and we'll have some public hearings on the issues regarding quality control. I think your statements about the importance of using the absolute number of CD34 cells as a target will be quite relevant there. I'll look forward to your input.

DR. VOSE: I think all of us who are transplanters would rather have a better thing to use, but at the moment that's the best surrogate that we have, unfortunately. I think we'd all like a better surrogate.

MS. MEYERS: Can I just ask? What about days to engraftment? Isn't that a better marker?

DR. VOSE: Well, the problem in this particular design is that the way they designed it to get the optimum number, there's a plateau and a threshold, and almost all the patients were at the threshold. So, it's designed as an equivalency study. So, it's not going to look at that in the way that you're discussing as far as the way other studies --

DR. SIEGEL: Well, it's not just a matter of design. The logic that the committee followed in 1994 was that engraftment by use of stem cells, and particularly mobilized stem cells, as compared to bone marrow, had rapidly shortened from -- in the neighborhood of a month to in the neighborhood of 10-11 days. There was a general feeling, which I think still exists, that to some extent, barring some miraculous new drug that has activities beyond anything we currently conceive, we are sort of up against a wall. Certainly nobody thought that improved engraftment either faster, fewer days, or a higher percent, as has been discussed -- has always been an acceptable endpoint not sought in either of these trials.

But the committee also felt, particularly given that faster engraftment -- that failure rates were quite low already, that faster engraftment -- that there were enough benefits to be had by maintaining those good findings with fewer leukaphereses, that that was also

acceptable. That's how we got to this design and to where we are.

DR. KOCH: I just wanted to comment on the design issue, what this study was best designed to address. Could I have that one slide back that I showed earlier?

If you look at the data for breast, essentially the discussion has said that patients were basically continuing to get aphereses until they met their target. At one time we're interested in reducing the number of aphereses, and at the same time we're also trying to increase the number of patients who reach target.

Now, if you look in the column that says "breast," you can see that the S plus G group had fewer aphereses. It's 338 versus the G group had a total of 385. At the same time, however, the S plus G group had 60 patients who met target which is bigger than the 47 who met target in the G group. The ratio of these two numbers, the ratio of number of aphereses per patient meeting target is 8.2 in the one case versus 5.6 in the other.

Now, these two numbers are the other way of looking at aphereses relative to target than the simple mean. When you take the simple mean that was talked about earlier by the FDA, the divisor for 385 and 338 is 100, the total number of patients, and only focuses on the concept of reducing aphereses. Their statements about that are

correct. In other words, if you're only concerned about how many aphereses people got and what the average number of aphereses per group were, you would divide the numerator shown here by roughly 100 and you get a difference of about .4.

The other variable that we've talked about is the percent reaching target, and in the one case we have about 60 percent reaching target. In the other case you have 47 percent reaching target.

But if your overall goal is essentially to maximize the number of patients who basically reached target for aphereses, or correspondingly reduce the number of aphereses per patient meeting target, the test treatment does that, and the design, by the way it was structured, was designed to do that. And that's another way in which you can try to look at what's going on.

DR. SIEGEL: Just a quick comment, if I might. I think that both of those two columns of numbers, if you look at them in columns, are quite informative and correct. There's a 47 different leukaphereses over 100 patients. It's true each patient will either not get an extra one or will get a different one, but these data suggest that if you do about 100 patients, you'll get 47 fewer leukaphereses. That's where the .4 comes. There's some rounding here.

Similarly, 13 percent more reach target, although again the higher number reaching target did not show any association of any clinical benefit, a suggestion of the opposite.

I have a little trouble with dividing them because when you divide them, you're counting the aphereses in the patients who didn't reach target and you're considering them per patient who did reach target, which seems to carry the assumption that those patients didn't benefit from the aphereses, that you only had 47 benefit in one arm and 60 benefit in the other arm. But in fact, those patients who got those aphereses did benefit. The vast majority, whether they hit target or not, engrafted perfectly well.

DR. KOCH: Well, I think that's a way of looking at it, but if you're trying to basically identify number of aphereses per patient reaching target, the ratio helps you do that. That's really the only point I was making.

DR. MILLER: Is there a statistical analysis for that?

DR. KOCH: Well, essentially the proportional hazards analysis that the sponsor reported basically tests the quantity like the ratio of G over S plus G at the bottom. So, the 1.45 that you see as a ratio there is very

much like the hazard ratio that came out of their proportional hazards analysis or their log rank analysis because when you fit that kind of model, that's the kind of parameter you address.

Oh, and the p value that went with their proportional hazards analysis was around, I think, .038 or something in that vicinity. It was adjusted for the covariate. This is not adjusted for the covariate. Their log rank test I think had a p value of around .043 or .044, and that would not have been adjusted for the covariate. That would be a p value that would be more or less in correspondence with the 1.45. Of course, as you know, it was not their preplanned analysis. The Wilcoxon was the preplanned analysis.

DR. MILLER: And if people stopped because of toxicity, was that counted in here as having -- they stopped after 1, were they counted as only having 1 pheresis?

DR. KOCH: In this particular database, the patients who stopped were censored as opposed to shifted up to 5, but the same kind of analysis would have applied.

DR. MILLER: So, they get counted as 1 as a success.

MR. PARKER: In the Cox proportional hazards analysis that we presented, the patients who experienced an

adverse event were counted as the maximum number of aphereses, so they were censored at 5, the same as patients who had had 5 aphereses and failed to reach the target.

DR. MILLER: I'm trying to figure on this analysis here.

DR. KOCH: Oh, in this analysis. In this analysis, they would be in the numerator for the number of aphereses they got and they would not be in the denominator. So, they would not contribute to being a success in the denominator.

DR. MILLER: But they would count --

DR. KOCH: Yes, that's right. They would count as having the number of aphereses or 5 in that analysis in the numerator and they would not contribute to the denominator. So, this analysis is accounting for all aphereses done, as well as whatever penalties one would achieve with respect to those people who would stop because of adverse effect or something, and the denominator only counts the people who got to target.

DR. MILLER: Well, that wouldn't be a penalty. That would be a benefit because you're trying to have less phereses in a group. Correct?

DR. KOCH: Yes.

DR. MILLER: And if everybody has toxicity and only gets 1 phereses, you'll have less, but that didn't

happen.

DR. SIEGEL: Well, there were 10 people stopped short of the goal --

DR. VOSE: There were 10.

DR. MILLER: 10 overall and 5 --

DR. SIEGEL: -- on the stem cell arm because of toxicity.

DR. SHPALL: 3.

DR. LeMAISTRE: 3.

DR. GLASPY: 3.

DR. MILLER: No, no, but she said 10 on one and 5 on the other.

DR. SIEGEL: Oh, 3 for toxicity.

DR. VOSE: Dr. Follmann?

DR. FOLLMANN: I just wanted to have a comment on this statistic of number of aphereses, given that you met the target. If you're comparing the two groups in terms of that, it's not a randomized comparison anymore because not everyone meets target. In fact, it's differential in the two groups.

DR. KOCH: Oh, it is a randomized comparison because the numerator variable mean has a randomized comparison and the denominator variable mean has a randomized comparison. All you're doing is taking the ratio of two summary statistics. The numerator mean is the

same quantity that the FDA has analyzed when it looked at a difference of means, and the denominator quantity is essentially the difference in proportions meeting success which the sponsor has presented previously and is fully supported by a randomized comparison. It is a composite variable where you're taking the ratio of two means.

DR. FOLLMANN: Right, you're taking the ratio of two means. The numerator and denominator in that ratio are in my mind based on a mean for a nonrandomized set of people in each case.

DR. KOCH: No. The denominator of the means is the 100 patients in the intent-to-treat group. The one mean is 385 divided by 100. The other mean is 47 divided by 100. Basically you have two ratio means.

If you flip the ratio the other way around, the traditional incidence density which is widely used for many analyses in epidemiology and in a randomized study is fully valid. It is a composite variable, but it is fully supported by randomization. It is related to a variable that the sponsor analyzed when they were essentially doing a proportional hazards analysis, but that was not their primary analysis in their protocol. That was essentially the Wilcoxon analysis, but it does shed light on what both measures are doing.

DR. VOSE: I'm going to cut you off at this

point.

DR. SIEGEL: If you calculate the number of aphereses needed to determine an event that happens only to some people, like to save a life or something like that, then something like this may make more sense. But to calculate it compared to the number who reach target -- because the aphereses obviously didn't benefit the people who died anyhow, but to calculate versus the number who reached the target when there's significant benefit to the aphereses in all the patients and when, although there's been a lot of discussion here about whether more people will reach engraftable numbers, over 95 percent of the patients in both arms reached it. There were 4 on one arm and 3 on the other arm. They all engrafted. Not only that, but the ones that didn't reach the target, the ones who reached 3 million to 5 million engrafted as well as the ones who reached the target. At most, the ones who reached 1 million had a 1-day delay.

But notwithstanding, both variables are meaningful variables, the number who reached the target, the number who -- I don't think we need a --

DR. VOSE: The rest of us simplistic minds, people can't figure out what the heck they're talking about. So, let's move on.

(Laughter.)

DR. SIEGEL: I have some numbers, by the way. In the three trials compared to G-CSF, the numbers that failed to reach the target in this larger one were -- who failed to mobilize enough to undergo engraftment, were 4 versus 3 in this trial, 12 out of 54 versus 7 out of 48 in the 950123, the lymphoma trial where there was the highest numbers. So, these are the numbers we were talking about that don't achieve statistical significance. And 4 versus 2 in the 950124. So, we still have some very small numbers.

DR. AUCHINCLOSS: Very small numbers.

DR. SIEGEL: But all three are in the direction.

DR. AUCHINCLOSS: You know, clinically if it were me, I'm assuming I wouldn't use this drug in the vast majority of patients, because I would figure it wasn't necessary. I would figure that it's right for a subgroup of patients who were going to be a problem to get enough stem cells out there, whether it be 1 million or 5 million that I'm looking for. But of course, we don't have the data that tells us how to write an indication that way.

DR. VOSE: Let's move on to question number 2.

Are there any other benefits that anyone wants to talk about here that we haven't discussed?

(No response.)

DR. VOSE: Okay. Let's move on to question number 2 then which we've already discussed kind of in many ways.

In 1994, the Biologics Committee indicated that there were two acceptable measures of clinical benefit for a mobilizing agent: either an improvement in engraftment or fewer leukaphereses with equivalent engraftment. In comparing populations mobilized with SCF plus G-CSF to those mobilized with G-CSF alone the addition of SCF reduced the average number of leukaphereses by about a half, and the addition of SCF was associated with a minimal but statistically significant delay in neutrophil engraftment, which we have said is probably not clinically significant.

And also we have C, the study drug was associated with episodes of anaphylaxis, anaphylactoid reactions, or other allergic reactions and related toxicities.

Therefore, we need to discuss if the risk/benefit relationship has been demonstrated and is suitable for approval of this drug.

What I'd like to do is have some additional discussion on these, and then we're going to vote on this question.

Abbey, do you have other things to talk about?

MS. MEYERS: I believe -- I'm not sure, but Amgen also makes G-CSF. What I'm thinking is you did too good a job on that --

(Laughter.)

MS. MEYERS: -- because really it works. It has been working for years. We know its safety profile. And here you are adding this other thing to it, and you haven't proven that there's enough benefit to outweigh the additional risks that are clearly there when it comes to, no matter what you call it, anaphylaxis. So, if G-CSF was not good and you enhanced its whatever by 50 percent by adding this, then maybe there would be something, but I don't see any benefit.

DR. VOSE: Do you have further concerns about the risks as far as you want to talk about the risk/benefit relationship?

MS. MEYERS: I happen to have a sister who almost died of anaphylactic shock from two aspirin, and had taken aspirin, of course, all her life, but one morning got up with a headache, took aspirin, and ended up in the hospital for a week. So, I'm very sensitive to this, and whether this is a different type of anaphylaxis -- instead of it coming on quickly, as it did with my sister, it may come on over 5, 6, 7 hours. It's even more dangerous because my sister at least saw that something had happened

immediately and got to the hospital. These people might be at home and they might be sleeping, and their spouse might not even know and they wake up and find them dead in the morning.

So, I'm really, really worried about this. This is very serious. This is not a matter of you get a few pimples. This is not a small side effect. This is very serious.

DR. VOSE: Dr. Frieri?

DR. FRIERI: As Dr. Galli said, there's type I IgE mediated, which is clearly IgE, whereas this does not go through type I mechanisms. It doesn't cause that. So, the difference between anaphylaxis and anaphylactoid is pretty clearly defined in the allergy/immunology literature.

Most specialists know how to deal with this, but the patient doesn't know the difference between what is anaphylaxis and what is anaphylactoid. So, it is a difficult situation because aspirin is a different mechanism than IgE. It goes through pseudoleukotrienes and then we have mast cell degranulators that opiates can do and other things like thiamine. Patients could have a subvariant of mast cell diseases, such as idiopathic anaphylaxis which they take one tablet of something and have a reaction. So, it's difficult for the patient to

know if it's true anaphylaxis versus anaphylactoid.

However, we do have certain things that Dr. Galli mentioned such as tryptase which would tell whether it's truly IgE mediated, whether it's acute cardiac versus anaphylaxis. The tryptase is highly elevated and that's very clear.

But there are subvariants of patients that have an overlapped cross between "axis" and "oid" and it's difficult because an IV die contrast releases histamine in the urine and that is very severe, and yet it's histamine release. It's not IgE.

So, I think as an earlier comment that was made, that there has been very few true anaphylaxis reactions. The anaphylactoid events can occur, and I think until more patients are studied, it won't be known if some of them truly have type I IgE which is, although rare, a significant problem if it happens.

So, I think the allergy history is not enough here. The history can be taken just quickly in 10 or 15 minutes, but in order to tell if a patient truly has taken thiamine, has a subvariant of mast cell disease, is on hormones because hormones can give urticaria and hormones can trigger asthma -- so, it's very clear that more detailed history including maybe some other vital markers in some more at risk patients could be indicated.

DR. SIEGEL: I just want to clarify. We haven't seen anything, in terms of the mechanism of action, that would suggest that this induces IgE mediated reactions, although many drugs do that very rarely. It's possible that this will do that very rarely, but we're seeing what looks like direct effects on mast cells. There's every reason to believe that's the mechanism. Part of the terminology problems -- and I'm an immunologist -- is that I understand well the difference between anaphylactic reactions and anaphylactoid reactions. This is not an anaphylactic reaction, although I'm hearing different opinions as to whether anaphylaxis only refers to anaphylactic reactions or whether --

(Laughter.)

DR. SIEGEL: No seriously. Or whether anaphylactoid reactions might also be considered anaphylaxis. So, to the extent that this says anaphylaxis, it's not meant to imply that it's anaphylactic. We recognize that these are not anaphylactic reactions. These appear to be histamine release reactions. They're not IgE mediated.

I'm sure that clarified the issue entirely.

(Laughter.)

DR. SHEA: Dr. Vose, could I mention one thing just to clarify?

It's important to realize that we're very concerned about these reactions can occur 4 or 5 hours later. However, it's equally consoling to us as physicians that when they do occur, they don't occur immediately. People don't suddenly become short of breath or suddenly develop urticaria. In every case that we've identified as a serious reaction, these reactions have evolved over several hours. So, there is time for people to contact whoever they need to contact. We have not seen the kind of immediate hypotension, the kind of shocky syndromes that would appropriately scare everybody. So, it's not to say that with another thousand people that are treated that it won't occur. I think we all realize that that may appear, but that's nothing like what we have seen so far. Even in the serious reactions, people have had more than adequate time to contact people. They have not been found on the floor of their bathroom in the shocky state.

DR. VOSE: Thank you.

Dr. Leitman?

DR. LEITMAN: In terms of the risk/benefit ratio, it seems clear that for selected patients who are unlikely to achieve a minimal transplantable dose with any number of phereses, the risk not of anaphylactic shock but of increased discomfort, increased inconvenience is there because they'll come to transplantation. You can probably

start defining those heavily pretreated lymphoma patients, heavily alkylating agent treated myeloma patients, breast cancer patients with greater than 6 to 12 previous cycles. You can define those and I don't know whether that would go into a product insert as the indication to increase the likelihood of getting a transplantable dose.

On the other hand, for those patients not fitting into that category, increasing the yield from 4 million to 5 million or 3 million to 5 million per kilo in my mind may not be worth the increased risk. So, for selected patients, yes. For all comers, no.

DR. VOSE: Dr. Miller?

DR. MILLER: The question is, are we bound, when we're voting, by these two definitions of acceptable measures of clinical benefit? I think we've heard a lot of discussion around here whether these were the two things we can consider when we make a decision on the risks and benefits, that they have showed improved engraftment or fewer leukaphereses with equivalent engraftment.

From my standpoint, I think that again I agree with the last statement, that I think there's clinical benefit to this in subpopulations of patients, but I don't feel that I could say yes, that fewer leukaphereses was clearly statistically documented.

So, I want to know whether I'm bound by these

things to vote risk/benefit, or can I use my own clinical decision making of what the risk/benefit is? We can discuss the labeling. I don't know, but the flavor is that having decreased leukaphereses in the label is not to me clinically important.

DR. VOSE: Well, it might be clinically important if many leukaphereses were decreased, but it's not. It's .4 or .6.

DR. MILLER: Right.

DR. SIEGEL: The simplistic answer is that the committee is not bound to do anything. You can propose other questions, vote on other questions. You can vote on this question as you like.

From the point of view of trying to get maximally useful advice, I would ask, however, that you make sure we understand what you're voting on because if the benefits that you want to vote on are other than the benefit of reduced leukaphereses or improved engraftment, then in order to, A, determine whether those are benefits that are consistent with our policies in terms of acceptable benefits and, B, to write an appropriate label. If the benefit is the number who reach an engraftable and the trial showed 4 patients versus 3 patients, then we have to write that those are the data that support the primary label.

So, you need to let us know what benefit you think is demonstrated so we can determine if it's an appropriate indication, and if so, how to write the label for that indication. But if you believe that there are benefits other than better engraftment or fewer leukaphereses that we should consider, I certainly want to know that and would not want you to feel restrained by this question from determining that.

DR. VOSE: Dr. Miller, what would you say is the benefit?

DR. MILLER: Let me think for a minute.

DR. VOSE: Okay. Dr. Broudy.

DR. BROUDY: Did you call on me?

DR. VOSE: Yes, I did.

DR. BROUDY: I would not vote to approve this to decrease the number of phereses because in my own mind there are some statistical question there, probably .4 to .6 pheresis per patient on the average, and I don't think the risk/benefit, given the 4 percent that will have anaphylactoid reactions -- I think that outweighs the benefit of the slight reduction in number of phereses. So, I would vote against approving it for reduced number of phereses because of the risk benefit analysis we've just discussed.

On the other hand, I would vote to approve it,

as is the third sentence in the sponsor's proposed indication, to increase the proportion of patients reaching a peripheral blood progenitor cell target, and I would like to approve it for that purpose. That would be my vote.

DR. VOSE: Dr. Siegel, is something like that acceptable when it's a surrogate and there is no --

DR. SIEGEL: The advice certainly is acceptable.

(Laughter.)

DR. BROUDY: Thank you. I can go on.

(Laughter.)

DR. SIEGEL: No, no. What I'm saying is it's certainly acceptable for you to advise us to do that, and I think we would need to then look at whether the data that suggest that that would be an appropriate thing to do and that we should act on that with the product approval.

Maybe the best way to do it is to ask the question based on these measurable, clinically relevant outcomes of adverse events, engraftment and leukaphereses, the things that actually happen to patients. If we vote on that question the way it's asked, and then if there's a separate vote on whether in fact benefits have been shown because we believe that the higher number of CD34 cells is a real measure of preventing people from not getting engrafted, or however you all decide to frame it, we could

take that advice under advisement separately. I'm not sure.

So, I'm saying don't feel restrained not to give the advice, but I'm not sure I can give a definitive answer without looking at what it is you're going to suggest and what the data are and going back with the company and looking at more data to determine what to do with it.

DR. VOSE: I think that's a good suggestion actually to ask two separate questions. Do you have any comments?

DR. BERMAN: Yes, I had a question. One is if we approve it for the use of having more patients reach their target, should we phrase it or ask the sponsors -- we shouldn't ask the sponsor, but phrase it for everybody or is it for a selected group of people who have had more than six rounds of chemotherapy who had radiation? By approving it, do we give a broad entitlement for everybody or do we ask the company to look at the data and give us the data in terms of the pretreatment to a better degree than what we've seen this morning?

DR. SIEGEL: Certainly if you want to advise that, as a number of people suggested, that the indication be to some subset of people at higher risk of not mobilizing --

DR. MORSTYN: Could I just help maybe --

DR. SIEGEL: -- we could focus more on those data or perhaps come back to the committee or not, as you recommend.

DR. VOSE: I think that's a good suggestion. The problem with that is that the number of patients in those categories, in doing the predictability there is going to be difficult.

DR. MORSTYN: Could I suggest that it might also help if you do it by disease category? Because I think the lymphoma study, which I think I heard a lot of support for and it's the biggest benefit, I don't think there are the statistical disputes over the lymphoma study. It was prospectively defined based on an analysis of our phase I/II study. It seems to be the most clear-cut. Then there's the myeloma chemotherapy mobilization study. Then there's the breast cancer study. So, one way of asking the questions might also be by tumor type because I think that would give us something to work with.

DR. MILLER: We've tried to limit that, to limit tumor type discussions, because it then gets in trouble with insurance and leaving the clinician some leeway.

DR. VOSE: I think it would be better to try and, if possible, look at what were the predictors of the

poor engrafters and leave the tumor type a little bit out of it because you looked at it in both ways.

DR. MILLER: Which will just leave the clinician something -- not specific predictors but at high risk for non-engraftment, and that way we always cover Abbey's concern, which may not be a concern -- making sure that we don't leave people out in the cold who really could use it from an insurance and a labeling --

DR. VOSE: Because we all think we know who can engraft and not engraft, but that's not always true, unfortunately.

DR. MILLER: Right.

DR. FOLLMANN: I'd just like to say I'm a little uncomfortable with the tact the committee seems to be going in that these studies were designed to answer a specific question in a specific group of patients, and now we're at the point where we're looking at a subset of the patients defined perhaps just in the last hour or so maybe based on the number of cycles of chemotherapy or something. We're also looking at not the endpoints that were originally decided. So, I'm -- I don't know -- worried or troubled by that.

MR. PARKER: The only point I would make is that the lymphoma study did prospectively select patients at risk for poor mobilization based on prespecified

criteria, and that shows statistically significant differences in proportion of patients reaching the target as well as number of aphereses. Those endpoints were prespecified in the protocol, although those were secondary endpoints.

DR. SIEGEL: Right. The differences in the proportion reaching aphereses, but in terms of the proportion reaching enough to engraft, that's what was 12 of 54 versus 7 of 48, which looks to me to be about 22 percent versus maybe 15 percent. Not significantly different.

DR. SHEA: But you have to remember none of these are going to be powered to show the tightening of the tail on the curve. They all focus on the median, which I think as I showed in my initial presentation, looking at the literature, I think we've come to realize the median is not a very good marker for where we need to be. If we're going to be able to tighten the tail on the curve, we don't want to transplant people with 1. We want to try to transplant people with 3 or 4 or 5 at a minimum. That's where I think this agent is useful. It gets us up higher.

DR. SIEGEL: Right. I would just say, though, that we need to know that in fact we change that tail, which is to say, the drug may impact the median. It may increase the number of CD34 cells in the average and may

not in those who are at the highest risk. It may be that they're beyond help by stem cell factor.

I'm simply saying we have some trends, but we don't yet have proof even that we can achieve a different numerical target. We do for the 5 million target, that more of them will hit 5 million, as you said, but not that more of them will hit an engraftable number. If that's the proposed indication, that's what we'll have to look at.

DR. MORSTYN: Just one other issue. Somebody mentioned fairness. Since we had a prespecified pathway four years ago, the magnitude -- we're happy in the labeling to describe what the magnitude of pheresis reduction was or describe it in several ways so it has some meaning to clinicians.

I think what we're really asking for is that the agent be available for patients who are fully informed and physicians who are fully informed to be able to offer it, and for people at that level to make a decision based on complete information, including a description of magnitude in whatever is the appropriate way.

DR. SIEGEL: No. I understand. I say in the interest of fairness too what Dr. Follmann just said, that you prespecified what you were going to show and you were going to show equivalent engraftment and fewer leukaphereses. You showed a half fewer leukapheresis,

engraftment that was not improved and minimally different, and a toxicity profile. That's the question as worded in question 2, and in fairness we should answer that question. Then whether we look at different subsets and different endpoints is another question.

DR. VOSE: I would like to propose that we do two questions. One is the question that you have here and the second question is what Dr. Broudy said regarding voting on the ability to achieve a target, if that's an appropriate risk/benefit ratio. Would that be acceptable?

DR. BROUDY: No, I agree with that. I just didn't want to have the company advertise it as being able to reduce the number of phereses since I at least have some statistical question as to whether it really did. I don't want the many physicians out there to be giving people SCF just because every other patient will get a half a fewer pheresis, because in my own mind the risk/benefit really doesn't justify that. That's why I didn't want that advertised, and that's why I didn't want it to creep into the package insert.

DR. VOSE: Okay. Is there any other discussion?

(No response.)

DR. VOSE: I would like to go ahead and vote then on the question as stated. Given that we have

somewhat equivalent engraftment, perhaps slightly less neutrophil engraftment, and a .4 to .6 less leukapheresis, is the risk/benefit relationship with SCF demonstrated? Is it suitable for approval? Those that think it is suitable for approval, given those characteristics, please raise your hand.

DR. MILLER: Approval for the indication --

DR. VOSE: Approval for --

DR. MILLER: You're saying --

DR. VOSE: Saying this.

DR. MILLER: It met these two criteria.

DR. VOSE: Right, saying it has met those two criteria.

(A show of hands.)

DR. VOSE: One?

Those that think it's not approvable meeting those two criteria?

(A show of hands.)

DR. VOSE: Is that everyone? Are there any abstentions?

DR. LEITMAN: I have to abstain.

Were we going to add in selected patients or not?

DR. VOSE: That is going to be my second question, second new question I just made up.

So, you're going to abstain?

DR. LEITMAN: Yes.

DR. VOSE: Okay.

Then I'd like to vote on a second question and you can maybe help me, Dr. Broudy. Why don't you propose the question?

DR. BROUDY: Well, does the use of stem cell factor in addition to G-CSF increase the proportion of patients reaching a peripheral blood progenitor cell target? This is the exact phrase they have in their proposed indication.

DR. VOSE: Okay. Everyone that thinks it has appropriate risk/benefit ratio --

DR. SIEGEL: That's not the question we need advice on. We all agree that it increases the proportion. I think what you're asking is should the fact that it increases the proportion who reach a target be taken as an acceptable measure of clinical benefit. What I've heard is some of you think that might be the case specifically for the subpopulation who are at high risk of getting adequate numbers.

DR. VOSE: Right. I think we should take the question and add that it's only in a subpopulation of patients that have a difficult time reaching that number and also take into consideration the risk/benefit ratio

again in that second question.

DR. KEEGAN: Could you clarify what you mean by a target? I mean, it's awfully vague. What target you're thinking of as you frame this question.

DR. VOSE: You're referring to 5 times 10 to the 6th per kilo?

DR. BROUDY: Well, I don't think we really want to put in an actual number is the problem. It's a changing field.

DR. VOSE: No, because the problem is that the CD34 analysis is different in different places and if you put that in the label, it's a problem.

DR. KEEGAN: Yes. I guess what I'm trying to get a feel for is are you concerned about the patients who are unable to undergo engraftment because they have an inadequate cell yield, or are you looking at some other group?

DR. VOSE: We're looking at the patients -- at least I'm looking at the patients that would otherwise be unable to undergo transplantation and then could meet a specific target that they could undergo transplantation. That would be what I was talking about. Is that what you're talking about?

DR. BROUDY: Right.

DR. BERMAN: And you can trace it, meeting the

appropriate target, thereby leaving it open as to what that target will be, understood by the transplanters themselves and leaving it open for that to change.

DR. KEEGAN: But could you at least qualify the target as being an appropriate target necessary to allow patients to undergo transplantation?

DR. VOSE: Yes.

DR. AUCHINCLOSS: Can I take exception to that, just so you know that there is a range of opinion? Because I actually thought that the company made a pretty good case for 5 million being better than 1 million. So, if you have a subset of patients that you predict is going to come in at 1 or 2 and you could move them to 5, I think that that's another good thing to do. I'd like to see it studied and proven that it's a good thing, but I would take that --

DR. SIEGEL: Well, to date the studies suggest that they engraft as well at 1 and 2 without stem cell factor as they would with stem cell factor with larger numbers. That's the problem.

DR. AUCHINCLOSS: What about the slide number 1 or 2 of the initial presentation, that overall --

DR. SIEGEL: Right. In the randomized comparisons, there is little or no difference between people who received somewhat more than 1 million whether 1 to 3 or 1 to 5 on G-CSF, versus those who got 5 million on

the G plus stem cell factor. So, there is little or no data suggesting that, as you proposed, moving them from 2 to 5 would make a difference.

DR. AUCHINCLOSS: I understand.

DR. SIEGEL: These suggest that historically speaking -- and the data are very solid and generated by -- that people who get 1 or 2 do worse than people who get 5. That doesn't mean that moving them to 5 with any particular agent or even with more leukaphereses would improve their outcome.

DR. AUCHINCLOSS: I don't know that my assumption is correct, but I suspect it's true and therefore I'm separating myself from the others and saying this in my mind is a benefit not just in getting more people to transplantation, I suspect it will have benefit in more people on that far end of the tail having platelets that get all the way up.

DR. VOSE: But the data --

DR. AUCHINCLOSS: But I don't know that.

DR. VOSE: But the data doesn't support that.

DR. AUCHINCLOSS: I understand, but I'm not suggesting that we indicate the precise subset of patients. All I would suggest is, as Virginia has indicated, that it is reasonable to take this kind of thing into account, the achievement of a target, not specifying the target -- for

some people it's going to be 1 million; for some people it's going to be 5 million -- in selected groups of patients, again not necessarily identifying who the selected patients are because that will come out in the future studies.

DR. SIEGEL: It's reasonable to presume that the larger number of cells will translate into improved outcomes --

DR. AUCHINCLOSS: In some fashion.

DR. SIEGEL: -- despite --

DR. AUCHINCLOSS: But you're going to have to find that out somewhere along the way. Somebody is going to actually study that question.

DR. SIEGEL: Right, but the data to date suggest in all the trials that there were larger numbers of cells and worse outcomes, but --

DR. AUCHINCLOSS: I don't think that's fair.

DR. VOSE: No, it's not worse outcomes.

DR. SIEGEL: Well, in the 200-patient trial, they got a larger number of cells.

DR. AUCHINCLOSS: No, no. The only place --

DR. SIEGEL: There was no improvement in outcome.

DR. AUCHINCLOSS: -- for your platelet engraftment or failure of platelet engraftment in the 1 to

2 million CD34 --

DR. SIEGEL: I don't mean worse outcomes in terms of overall how patients did. I mean in the sense of engraftment time, we've yet to see in any of these studies improvements in either engraftment success or engraftment time attributable to the larger number of cells.

DR. AUCHINCLOSS: -- versus 14 or 10 versus 11. We've all been talking about that group out there at 3 months that still has not engrafted their platelets. That's the group that you're interested in. That should be studied.

DR. SIEGEL: Normally I would say that we want to see studies and see --

DR. VOSE: We can suggest follow-up studies to try and look at those issues better.

Dr. Sheridan?

DR. SHERIDAN: Yes. Well, there is actual data from the large randomized study in breast cancer that does, in fact, suggest that the outcome is improved for low doses of CD34 cells, moderate doses of CD34 cells, and high doses of CD34 cells.

DR. VOSE: But it's not statistically significant. Right?

DR. SHERIDAN: No, but that wasn't the question posed. So, I think that the statement was made that

there's no data that suggests that there's an improved outcome. Well, there is.

DR. VOSE: But not statistically significant.

DR. SHERIDAN: Right, because that wasn't the design of the study.

DR. SIEGEL: Right, but you now advise not to approve on the basis of what the studies were designed to show, but on the basis of something else. That will require both accepting a surrogate and accepting data that are not statistically significant.

DR. AUCHINCLOSS: One statistically significant piece of data, in the lymphoma study, the 5 times 10 to the 6th, which is again based on an assumption on my part that 5 is better than 1. It's a surrogate endpoint, but there is statistically significant data to go along with this kind of indication.

DR. BROUDY: I think we should vote.

DR. VOSE: I think we should vote. Vote on what is the question. Do we want to say that it's to a target and not specify what the target is? Is that what your proposal is? We want to try to approve it that it has an appropriate risk/benefit ratio to try and increase the number of patients that can apherese to a certain target CD34 value and --

DR. BROUDY: That permits them to undergo

transplant.

DR. VOSE: That permits them to undergo transplantation.

DR. BROUDY: Right, and it should say in conjunction with G-CSF.

DR. VOSE: Right.

DR. BROUDY: It should say in autologous transplants.

DR. VOSE: G-CSF in autologous transplants.

Are we all straight on that? Okay, everyone that thinks it has an appropriate risk/benefit ratio with that question to be approved, please raise your hand.

(A show of hands.)

DR. VOSE: It's unanimous.

DR. SIEGEL: Can you state what the question was?

(Laughter.)

DR. VOSE: I asked you if you were straight on that.

DR. SIEGEL: I'm sorry. At the time you were asking, I was looking the FDA review page 52 which shows that platelet engraftment, the indicator of concern to you, that in this high risk population, the median and the 95 percent confidence intervals were identical on the two study arms. The range is such that on the G arm, the

longest time to engraftment was 34 days, whereas on the stem cell factor arm, 1 patient took -- the range was 9 to 65. So, I don't know. That 1 patient can set a range. I don't know, but I was looking at whether we're going to find in that support of more rapid platelet engraftment or where. That aside, we'll have to look at that.

But what exactly was the vote?

DR. VOSE: The vote was it had appropriate risk/benefit ratio for approval to increase the -- to a target CD34 level that was adequate for engraftment with G-CSF and in an autologous transplant setting.

DR. SIEGEL: So, to reach a target that's adequate for engraftment.

DR. VOSE: Reach a target that is -- I'm sorry -- adequate for transplantation.

DR. SIEGEL: And is that constrained by a high risk patient population?

DR. BROUDY: Increased proportion of patients that achieve that. Then I think a paragraph should say something about -- as Dr. Leitman had brought up, that this would be most appropriate to be used in high risk patients.

DR. SIEGEL: I'm seeing heads going both ways. Maybe we should get some clarification as to whether the committee's recommendation is -- I heard Carole say you think it shouldn't be limited to a disease type, but ought

to be limited to people at high risk to fail to mobilize.

DR. VOSE: But the problem is it's not totally predictable who is at high risk to mobilize and who isn't based on their information.

DR. KEEGAN: So, everybody who wants to undergo autologous transplantation should have the opportunity to be exposed to this drug with no qualifications. I mean, that is what the committee is voting to do.

DR. VOSE: I understand.

DR. KEEGAN: Is that their intent?

DR. BERMAN: You can qualify it by saying that the data support the use of it in people who have been heavily treated.

DR. KEEGAN: We don't know that the data show yet.

DR. BERMAN: Well, but you see it in the lymphoma where patients by definition were chosen who were heavily treated, and there the data are more clear.

DR. SIEGEL: Well now, 12 versus 7 and a wider range of platelet engraftment.

We also understand -- perhaps you can correct me if I'm wrong -- that there's a lymphoma trial going on I think in Europe, is it, in which the interim analysis suggested a trend in the other direction?

DR. MORSTYN: Yes. We did another interim

analysis and we mentioned that the trend had now reversed on CD34 number. And we have that slide, if they could put it up?

DR. SIEGEL: Those are the data you said we haven't seen yet.

DR. VOSE: So, that was on data that hasn't been submitted yet.

DR. SIEGEL: It's a study that hasn't been completed yet, but we have seen earlier that there was trend in the wrong direction in that population.

Okay, well, I know what you voted on.

DR. VOSE: We've given our advice. Use it as you may.

DR. SIEGEL: Well, we will definitely take a very serious look at the data in support of that approach. It's possible we may not be done seeking advice.

DR. MORSTYN: It would really help us if you could just state the question of what was voted on just for the --

(Laughter.)

DR. SIEGEL: Maybe you ought to make a statement and actually write down a statement and then retake that vote to make sure that we all know exactly what was voted on. I think that would be helpful.

DR. AUCHINCLOSS: In a certain sense, I think

what we voted on was probably not quite the right question because you sort of stipulated that you already agree that this drug increases the number of CD34 positive cells in general. Right? And what I think the committee is saying to you is we think it's appropriate for you to take that into account as a good thing in some patients for some purposes. Is that a fair way to phrase that?

(Laughter.)

DR. SIEGEL: Another question I do need to have answered is, since we do have other drugs under development for this same indication, is whether we are in fact to indicate to sponsors that if they show that their drug increases CD34 cells, that's an indication. That's what they have to show. We could have saved a lot of clinical trials here if we had given that advice.

DR. BROUDY: You have to show that it increases CD34 cells but also that those cells are capable of prompt and sustained engraftment, and both of those criteria were well met by these series of studies. They were very convincing.

DR. SIEGEL: Right.

DR. BROUDY: So, not just a number of CD34's. They actually --

DR. SIEGEL: Right, but we also know in these studies that if patients got a third of the target, they

would have engrafted as well. So, we know that drugs that do increase --

DR. BROUDY: What I'm saying is I think the CD34 cells should have to perform in vivo. A number of CD34 cells is not enough. They did show their CD34 cells performed in vivo.

DR. LEITMAN: This maybe sounds like it would also recommend that sponsors perform studies powered to detect a statistically significant increase in a minimal number of cells available for transplant, as well as an optimal number.

DR. VOSE: Okay. Let's try this one more time. We're going to vote that there is an appropriate risk/benefit ratio for approvability of this drug to increase --

DR. BROUDY: How about in conjunction with G-CSF?

DR. VOSE: Wait, wait. I'm getting there.

(Laughter.)

DR. VOSE: In the setting of autologous transplants and with G-CSF, SCF has an appropriate risk/benefit ratio and is approvable to increase the proportion of patients able to hit a target CD34 count that permits transplantation. How's that? Is that acceptable?

DR. SIEGEL: What was the last few words?

DR. VOSE: That permits transplantation in the autologous setting. Is that acceptable to everyone?

DR. AUGUST: Read it once more.

DR. VOSE: In the setting of autologous transplantation and in conjunction with G-CSF, SCF has the ability to have an appropriate risk/benefit ratio for approval to increase the proportion of patients that are able to obtain a target CD34 count that permits transplantation.

DR. FOLLMANN: You know, I'd just like to say that we haven't really seen much data on that.

DR. SIEGEL: Yes. We certainly have the option, once we look at it, to bring it back here or to consider.

DR. FOLLMANN: That wasn't an endpoint that was identified in many, if any, of these studies.

DR. VOSE: I agree and we voted previously that they did not meet approvability based on their primary endpoints. This is taking our prerogative to vote on something different. They may or may not take this advice.

DR. SIEGEL: When you say reach a target that permits transplantation, you don't mean the target of 1 million that they used to permit transplantation because there were very little data on differences in that. You're talking about the target of 5 million which is a target

that --

DR. VOSE: I don't want to specify that in here because it is so different at different places that I don't think that's appropriate to specify a number.

DR. SIEGEL: Yes, but if you give 5 million and many don't work as well, it doesn't matter. We know that because you're still getting 1 million or 2 million that work. But if you get 1 million --

DR. VOSE: But as an example, at my center the CD34 assay is much different, and a 1.2 million or 1.5 million number is great. So, you cannot use a number. That's the problem.

DR. MILLER: The other way we can explain it, that we feel comfortable that this shows that an increase in number of CD34 cells in phereses products. The clinical significance of that is unknown and needs further investigation. That's another way of stating it. We feel there's an appropriate risk/benefit that -- if you feel that you need more CD34's, that we feel that this drug can be used. However, the clinical implications are still -- I mean, that's another way of stating it.

MS. MEYERS: Because clearly it has to say that the clinical significance has not been proven and maybe the company should do the studies --

DR. SIEGEL: Unless you believe quite strongly

that there is clinical significance to that, though, I would ask not that you give advice that we approve that with notification that clinical significance is unknown because that flies in the face of the law which says that drugs have to be effective and our policies which define efficacy in terms of clinical benefit or validated surrogates or in some cases surrogates reasonably likely to predict benefit. But we can't simply say it does this thing that may be of benefit. That is advice we can't take. We have to draw some sort of presumption that there's some benefit from it.

DR. MILLER: Well, we can tell you that we think that increasing CD34 in leukapheresis products is of clinical benefit and then you need to go back and get the sponsor to present the data in that way to actually look at, in all the studies, the magnitude of the increase in CD34's compared to the G-CSF.

DR. SIEGEL: Oh, those data we've seen. They're there.

DR. MILLER: Right, and so we're trying to say that, given the risk/benefit, that is an adequate marker --

DR. VOSE: That they have shown that, that that's an adequate marker, and given the risk/benefit ratio, but that the primary endpoints, as originally talked about and as the first question said, was not met.

DR. SIEGEL: And it's an adequate marker --

DR. VOSE: Yes.

DR. SIEGEL: -- surrogate for getting improved engraftability.

DR. MILLER: Right, or an improved stem cell product.

DR. VOSE: Do we need to revote on that question? Okay, everyone is okay on that?

DR. SIEGEL: Was that a unanimous vote or were there abstentions?

DR. VOSE: Abbey was out of the room.

MS. MEYERS: The patient would still have to get this as a drug, right? It wouldn't be used in the laboratory in a petri dish, right?

DR. VOSE: No. The patient would get it as a drug, and it's used in a petri dish too quite often.

Abbey, did you want to vote for that second question?

MS. MEYERS: I'm still worried about the safety, and I really would not vote -- I can't bring myself to vote for this drug getting on the market until the safety questions are --

DR. VOSE: Okay. So, you would have a no vote as far as the risk/benefit ratio on the second question that we asked.

MS. MEYERS: Right.

DR. VOSE: So, the vote was 10 to 1.

The last question concerning the side effects again in mast cell degranulation. A 4 percent incidence of, I guess, anaphylactoid type reactions was observed with a median time to development either 3 to 5.5 hours, depending on who we talk to, despite premedication. If approved, please discuss the period of time post injection that patients should be observed by health care workers for anaphylaxis or anaphylactoid reactions, and please discuss any additional precautions which should be recommended in the package insert.

Yes.

DR. FRIERI: In terms of mast cell degranulation, again I agree that you're calling it anaphylactoid, and the fact that steroids worked and only 1 patient got epinephrine, again that's against anaphylaxis. So, the steroids did lower reactions. We know mast cells, when they degranulate, also release cytokines and some of those cytokines, like IL-5, can also bring in the eosinophils. Now, cetirizine was chosen as one of the newer antihistamines, H1 blocker, which in a skin chamber model decreases eosinophil influx. So, that choice of an anti-inflammatory H1 is useful for these reactions which seemed to prevent the progression.

The question is the other additional precautions. If these were anaphylaxis and not "oid" -- of course, we agree it's o-i-d -- then you would need to put in the package insert patients on beta blockers because that can aggravate treatment of anaphylaxis, and other things. But in this case if we're talking about anaphylactoid, possibly patients that need IV die contrast for procedures that are not in their course of treatment where they're premedicated might be considered in there. If they're getting an IV contrast, they can release histamine and that can exacerbate their reactions.

DR. VOSE: So, you're recommending that those patients be in the insert as not being able to receive this medication?

DR. FRIERI: No. If they need a contrast procedure and they're not being premedicated at the time for their SCF, that they should be premedicated as if they were getting SCF.

DR. VOSE: Okay.

DR. FRIERI: Because that could release histamine.

And then other things as far as -- I don't know if the beta blocker issue is important here because if there is a patient that has full-blown anaphylaxis, being on a beta blocker is a problem.

DR. VOSE: And how about the time issue? Would you like to comment on that?

DR. FRIERI: The time issue, as you have here at 5.5 hours, again if it's anaphylaxis, if it's a biphasic anaphylaxis, it could extend even more, farther than 5 hours out. But in this case I believe earlier someone said 1 hour observation. Is that right?

DR. VOSE: That was what was in the study. It was a 1-hour observation.

DR. FRIERI: 1 hour, but contact by phone by the nurse coordinator I think is reasonable just in case someone does have a late reaction, not a late phase, but a later reaction.

DR. VOSE: I'm not sure you can really put that in a label or not.

DR. SIEGEL: Well, we can write labels cautioning how it should be used, in what setting it should be used, and also their patient information inserts.

But let me get a clarification. Are you saying that this should not be used in patients on beta blockers, or you're saying since it's anaphylactoid reaction, you don't have a problem with using it?

DR. FRIERI: Well, we're back to the definition again. We're not talking about IgE mediated anaphylaxis, type I. We're talking about anaphylactoid. But how can we

know that there may not be down the road a couple of these more type I patients?

DR. SIEGEL: Well, let me ask you this.

DR. FRIERI: We don't know that.

DR. SIEGEL: Even if it is anaphylactoid reaction, or even if it's histamine mediated, would not beta blockers exacerbate the problem and exacerbate your ability to treat it? I see that the incidence went down a lot with premedication, and one of the premedications that was used was ephedrine which I believe stimulates the release of sympathomimetic substances, and the reason they do that is so you get beta agonists. So, if beta agonists are preventing the side effect, you might not want to give it to people on beta blockers.

DR. FRIERI: Yes. Well, the beta blocker issue is primarily for IgE mediated because you can't reverse it. If a person needs epinephrine and they're on a beta blocker, you can't reverse it. But in this case I don't think that's an issue.

But what you mentioned about the ephedrine, I think ephedrine was removed. I think it's not just H1 and H2 without ephedrine. Isn't that --

DR. VOSE: Yes, toward the later study the ephedrine was stopped. That's correct.

DR. FRIERI: Yes, so no longer ephedrine. It's

just H1 and H2. The choice of the H2 blocker is a good one because it does affect eosinophils.

DR. VOSE: Dr. Arm, did you have an additional comment?

DR. ARM: There are a couple of cautions. One is that one would obviously have to put in the label the caution that there may be later reactions that don't necessarily occur within the hour.

DR. VOSE: Certainly.

DR. ARM: I think one would caution against concurrent administration of other mast cell secretagogues which would not only include opiates but also, for example, vancomycin comes to mind.

DR. VOSE: Vancomycin?

DR. ARM: Yes. That certainly act as a mast cell secretagogue in some individuals and we don't know whether it would be synergistic.

DR. VOSE: I imagine there were probably some patients that were on vancomycin because they had catheters. I don't know if you guys want to comment on anything about that.

DR. MORSTYN: I think we have to go back and look at the data.

DR. VOSE: Okay.

DR. ARM: The only other thing I just wanted to

mention, I'm not sure that the mechanism necessarily has a lot to do with whether or not patients should be on beta blockers because if a patient has a sufficient reaction to drop their blood pressure and require epinephrine or to have bronchospasm requiring the administration of beta 2 agonists, then you really want beta blockers on board. So, I don't think the mechanism necessarily is important there. So, I'd be a little more cautious about beta blockers.

DR. VOSE: Cautious about beta blockers.

DR. ARM: Yes.

DR. VOSE: Got that, Jay?

DR. SIEGEL: Yes.

DR. MILLER: I guess the question would be should we recommend that it be given by a qualified medical professional in that they raise concerns about being given subcutaneously and hitting the vein and going intravenously. I guess that's an issue that we need to sort of wrestle with, and I would like the sponsors and the clinicians who took care of these patients to see whether you felt that this could be given by the patients at home or whether you would recommend it be given in the clinic.

I think it would probably be recommended being given in the clinic.

MR. PARKER: As Dr. Steffen pointed out in the phase I trials, patients were allowed to self-administer

the drug. In the phase I/II and subsequent trials, we have not allowed self-administration outside of medical observation. In the lymphoma trial, which Dr. Stiff mentioned, we did allow patients, who wanted to, to self-administer under medical observation, and my understanding is that some of the patients did go home on the weekends and have a home health care nurse there while they were having the drug administered.

Actually there's a slide up. In aplastic anemia, we've treated over 40 patients with aplastic anemia and had some interesting responses. Several of those patients have been on the study for more than 2 years. Over 1,500 injections of stem cell factor have been self-administered by those patients at home, and aplastic anemia patients do have mast cells both in the skin and the bone marrow, so it's not that they don't have the effector cells.

DR. MILLER: But that's after prolonged giving or do you allow them to start at home?

MR. PARKER: We don't allow them to start at home. It's after some period of time and obviously patient education and demonstration of their ability to give an appropriate self-injection as well.

DR. MILLER: Because these people will only be given it for 5 to 9 days.

MR. PARKER: Right. it's a much shorter-term administration.

DR. VOSE: Since many of the reactions were much later, as long as the patients demonstrated their ability to give it without causing problems with intravenous injection, I think it would be adequate after the first dose.

DR. BROUDY: I guess I'd come down on the other side of that. Given the number of patients, even in the clinical trial, highly motivated patients who inadvertently gave themselves 50 micrograms or higher doses and a clear dose response, I guess I'd want to see it administered by a health care professional or else at least have the health care professional watch the patient self-administer. They can check the dose. Because that would be just disastrous to have a few patients anaphylax at home.

DR. MORSTYN: I'd just say that I think post-approval we plan to further fine tune the premed medication and study some of those issues.

DR. VOSE: Additional comments?

DR. SIEGEL: Those are all useful comments. I would like specific advice on the specific aspect of the question, although all of those comments would be quite useful, which is based on the incidence and nature of these toxicities that relate to anaphylaxis, or at least look

like them, wheezing, stridor, hives, urticaria, and so forth, and based on the incidence and the time course and the outcomes and the fact we have, what, 15 I guess so far serious, all reversible though, none fatal, some requiring overnight hospitalization and I guess relatively gradual onset, we're specifically asking about the time patients should be observed. Should the labeling reflect concerns that it isn't well enough known as to whether it's safe to allow patients to go home while at high risk for this, or should we simply suggest that it caution patients that this might happen and to seek attention?

DR. GLASPY: You asked for the clinician perspective. I think it doesn't make sense to require that it be given under physician observation because the time between the dose and when the symptoms have occurred has varied and has been long enough that it wouldn't be feasible to do that.

Secondly, we have found it to be safe self-administered.

Thirdly, there are experiences out there with other drugs that would be dangerous given intravenously and are not dangerous given subcutaneously. Insulin comes to mind. I think what that tells us is that it's very hard to intravenously inject something with subcutaneous needle. The one patient that was alluded to earlier -- it's not

clear at all. The reason people wondered whether it went intravenous was because the person had a side effect at a relatively low dose where the incidences of side effects are low and they had noticed blood in the syringe. But you all know from subcutaneous injections, that it's not easy to hit a vein.

For all those reasons, I think it's much more important that we focus on education for patients and doctors than on observation. It also doesn't happen on the first dose necessarily. You can't require that people be observed 24 hours a day for 7 days.

DR. SIEGEL: Well, whether you should require it depends less on the feasibility than on the safety issue.

DR. GLASPY: I agree. It's obviously --

DR. SIEGEL: And I'm not saying that it --

DR. GLASPY: It's not feasible. So, I'll emphasize what I said earlier, which is we have found it to be safe, and other subcutaneous medications that would be dangerous intravenously have been found to be safe.

DR. VOSE: It seems to me that the onset that they described is fairly gradual and I think that properly educated patients would be able to seek appropriate attention at the later time point. I would feel safe personally with the medical supervision of 1 hour. Is that

what you're going to suggest?

DR. BROUDY: I think that's how they did it in the majority of the clinical trials. I would think if a trained nurse or whoever gives the objection observes for an hour and the patient goes home and has got the education card that the company proposed, I think that would be fine.

What I'm concerned about is the patient giving themselves four times the dose at home, and that's why I think I'd like to recommend initially at least the nurses do it.

DR. VOSE: So, you recommend that each dose needs to be given under nursing supervision, observation for 1 hour.

Yes?

DR. FRIERI: I think in some cases it may be good if the patient is alone or there's not another person in the family if it's a solo person that there should be some type of contact with either the nurse or the health care provider and also a list of mast cell degranulating agents like vanco, thiamine, opiates, a list. I don't know if that's able to be put in there, but some people may not realize that the thiamine in vitamins can degranulate mast cells.

DR. VOSE: I'm sure that could be added to the labeling.

Dr. Siegel, does that answer all your questions?

DR. SIEGEL: Yes. We may check back for help with the list.

DR. VOSE: Okay. We'll break for lunch then if there are no further questions, and we're going to restart at 2:45.

(Whereupon, at 2:04 p.m., the committee was recessed, to reconvene at 2:45 p.m., this same day.)

AFTERNOON SESSION

(2:50 p.m.)

MS. DAPOLITO: Would the committee take their seats please so we can get started?

I'd like to welcome everyone to this afternoon's session. The committee was introduced this morning, but I would like to introduce the addition of Dr. Marian Michaels, Children's Hospital, Pittsburgh, and Dr. Dan Salomon, Scripps Institute. They'll be joining us for the xenotransplantation discussion today.

At this time we would like to open the floor for public comment. We have had no prior requests for public comment. At this time if there's anyone in the audience who would like to address the committee on this afternoon's issue, would you please raise your hand?

(No response.)

MS. DAPOLITO: Dr. Vose, I see no one. I turn it over to you.

DR. VOSE: We'll go ahead with topic number 2, Xenotransplantation Subcommittee report and Dr. Auchincloss will present that.

DR. AUCHINCLOSS: Did you want to make an introductory comment at all, either Jay or Amy, about the nature of this subcommittee?

DR. SIEGEL: Yes, I guess. You didn't

specifically prepare it.

DR. AUCHINCLOSS: I can do it if you want me to.

DR. SIEGEL: As a reminder to this committee, several of you were on this committee going back to -- was it 1995 when we initially had some discussions about xenotransplantation policy? A number of you alerted us to the fact that you did not consider yourselves xenotransplantation experts --

DR. VOSE: Like all of us?

(Laughter.)

DR. SIEGEL: -- and expressed some level of discomfort.

For those who are not aware of where we are on that question now obviously, as you recognized, this is a critical issue of importance to the agency, to the public health in general. What we have done in the interim is established a separate committee, the Xenotransplantation Advisory Committee, which exists as a subcommittee of this committee, which if you want an explanation as to why it's set up that way, you probably ought to ask Gail because I don't understand all the rules involving advisory committees.

But it is a committee peopled by two representatives from this committee, Dr. Auchincloss and

Abbey Meyers, and Dan Salomon, you're on that committee I think -- Dan will soon be joining this committee actually -- and a number of other experts in the field.

That committee has met last December, and as per procedure, the results of that committee will be at this time reported to this committee for its overview.

DR. AUCHINCLOSS: Gail asked me when I got down here if I had slides for this afternoon's presentation, and I do not. I didn't picture it quite in that vein. I pictured it more in the vein of presentation of laboratory reviews, et cetera.

Assuming that you have the document, the next-to-the-last tab, tab 4, of this book includes my report that I wrote up and basically what I was going to do is walk through that briefly with you.

As Jay has indicated, I think we think of this as, in a certain sense, a formality for the committee because the FDA wanted expertise and we're not it. That includes I think Abbey and myself. So, we're reporting to you only because we're your committee members who happen to be over there, but the only real expertise is sitting over there to my left where Marian Michaels can speak for all the virologists who were present at the committee meeting.

If you look on the second page, those in attendance, members of the committee and guests, just to

highlight some of the people such as Jonathan Allan, John Coffin, and Marty Hirsch, Marian Michaels, David Onions, and Robin Weiss, who are the real retrovirology who were present, those are the people the FDA wanted to hear from, frankly, not from us.

So, we'll tell you what they said and you can give us any feedback, if you like.

So, the issue that led to the convening of this subcommittee was that there were several reports that appeared in the literature in rapid succession indicating that replication-competent endogenous retroviruses exist in pig cells and that they could, in fact, in co-culture infect human cells. And on the basis of that finding, the FDA sent a letter in October of 1997 to all of the potential sponsors of clinical xenotransplant trials putting them on hold until this information could be further assessed.

The purpose of the subcommittee meeting in December was, in effect, to give the opportunity to the FDA to hear from some experts about how they should respond to this new information and, in particular, what assays should be required of sponsors and what should the FDA do with information that was gathered.

A special feature, as I point out on this page, of this question was that the focus of the subcommittee

report was narrowly defined. It was the public health issue associated with xenotransplantation. There are obviously, from the point of view of the individual recipient, many, many issues of safety of the tissue that is going in and the procedure involved, but this was a question really of public health safety, the public health risks associated with the porcine endogenous retrovirus and could it become a human pathogen or even potentially an unknown, never previously identified human pathogen that could present a risk to the population at large.

Now, as we always do in these committee meetings or subcommittee meetings, much of the meeting actually involved presentation of data partly from the FDA and partly from a number of the sponsors or potential sponsors. We learned a lot about the so-called PERVs, porcine endogenous retroviruses, that there appear to be at least four of these type C retroviruses in pigs, and at least two of them have shown the capacity to infect human cells under a variety of in vitro conditions.

I think it's a general summary of the wisdom of our retrovirology experts that these viruses, while they can get into human cells, do not look like they are highly infectious agents and, in the estimation of the experts, not very likely to be pathogenic via horizontal transmission.

Some technical features about the recent introduction of these viruses into the pig genome raised the possibility that you could potentially breed these out, but I think that the information about the PERVs is at this point insufficient and certainly that would take many, many years to eliminate them from pigs entirely.

A lot of talk about the various assays that were in use.

And then quite a lot of information about patients who have in fact already received pig tissue. It turns out that there may be as many as 200 patients who in one way or another have received pig tissue from various forms of xenotransplantation, skin grafts, eyelid transplants, and a variety of others. So, a number of different companies have been following these patients trying to determine whether there was any evidence of infection in any of them in previously performed trials, and there was also roughly an equivalent number identified of non-human primates who have received porcine tissue.

My estimate, as I listened to the day's presentations, was that maybe as many as 20 percent of the recipients of pig tissue amongst the primates had been tested for evidence of PERV infection and at this point the conclusion was there was no evidence of infection in any of those recipients.

We then heard, in addition, information from various potential sponsors about their potential products, and at this point all of them reported that they had been unable to identify the virus in their particular tissue. Now, having said that, I think our experts basically were suggesting to us that the porcine endogenous retroviruses really are present in all pig tissues, and it's only a question of trying to develop the assays that would reveal them. So, it may be false comfort to say, well, the products that we currently know about or are considering don't seem to have the virus. That's probably not true.

Now, the subcommittee was asked for comment on basically three areas. One was what tissue assays should be in place prior to a sponsor's proceeding ahead with trials. Here the committee affirmed what perhaps was its most important statement to the FDA, which was that it was the unanimous feeling that we thought it was quite appropriate for the FDA to require companies to demonstrate that they have assays in place to test their tissues before lifting the clinical hold on trials. The sponsor would be required at least for in vitro co-culture of both human cells and a more sensitive indicator line along with their prospective tissue, and the suggestion was that there should be at least five passages that would be assayed.

What was less clear is what the FDA should do

with information should any of those assays some day turn out to be positive. As I say, they haven't yet, but the experts basically believe that sooner or later you're going to find that the porcine tissue has PERVs within it because the notion is that it's everywhere.

The recommendation was clearly that, well, if you find it, go ahead quantitate, sequence, and test for the tropism of the virus from that particular tissue. I think that the general sense was that I think we kind of hedged for the FDA. When you get that finding, what are you supposed to do? I think the first company that comes up with a positive assay for porcine endogenous retrovirus may find itself on hold, at least for a while, was the impression I got in our back and forth with the FDA, as they consider what to do.

Then there were recommendations for further tests that were not necessarily required for proceeding with clinical trials, but more in the area of research: other inducing agents in the co-culture in order to get expression of the porcine endogenous retroviruses, a suggestion for testing a high dose PERV infection in newborn animals to assess infectivity in primates and pathogenicity, and recommendations to work further on the porcine endogenous retroviral genetics.

The second question had to do with what kind of

patient monitoring should be in place or available prior to initiating clinical trials. Once again the committee reaffirmed the feeling that it was appropriate for the FDA to require companies to demonstrate that they had assays in place, to test new and previously treated patients before lifting the clinical hold on the trials. Then I've listed here some of the specifics: weekly samples for several months, every three to four months for several years, yearly samples thereafter. Should sickness develop that was unexplained, that would be an additional indication for monitoring. And it was interesting that the experts seemed to be reasonably clear that peripheral blood cells and plasma was an adequate site to be monitoring patients, that invasive biopsies, et cetera were probably not necessary, that yes, if you had tissue available either from biopsies performed for other reasons or from autopsies, that that too should be assayed.

Now, here I think the committee was clear on its recommendation that if a human recipient of porcine tissue turned out to have evidence for infection in the human cells by the porcine endogenous retrovirus, that would in fact be an indication, the committee felt, to stop clinical trials at that point pending further evaluation. Again, with the workup of the virus as it was identified at that time, it would certainly be the trigger to screen more

intensively contacts of the recipient.

And there was then some discussion about what should be done for that particular individual recipient. Should he or she be treated? And the conclusion, as I heard it, was no, don't treat at this point without evidence of either efficacy of the agents for treatment or evidence of pathogenicity because, once again, I think underlying this conversation was the sense that if you really do porcine-to-human transplantation long enough, it's probably pretty likely that sooner or later you're going to find a human being with porcine endogenous retrovirus in the cells. That does not mean that it will be pathogenic and that does not mean that it will be transmissible. Those questions will then need to be asked and addressed but one shouldn't presume disease on the basis of that finding.

Again, research items that the patients who are out there who have already received porcine tissue should continue to be monitored but with not the sense from the subcommittee to the FDA that all such patients needed to be checked out prior to initiating clinical trials. Work could continue side by side and with particular emphasis on developing, which I believe would be said already has been developed, an assay for detecting antibody. Is that fair to say at this point, Amy?

Then there was some additional points that were touched on, many of them actually questions that were raised by the FDA for the subcommittee to address, a question of whether there was any preference for particular kinds of trials. Were there some that were safer from a public health point of view than others? I think the subcommittee's feeling was, yes, there are. There are those trials involving older recipients, for example, would probably put the public less at risk for reasons having to do both with longevity and sexual contacts, et cetera. And perhaps tissues that can be sampled well prior to transplantation might give rise to better trials.

The recommendation of the committee was that selection of patients does, in fact, warrant special consideration regarding their reliability for long-term follow-up.

It was pointed out and discussed that close contacts of a recipient of a xenotransplant in the future should be involved in the informed consent process and should be excluded from blood donation in the future.

Specifically we were asked whether there would be any situation in which we could imagine compassionate use of xenotransplantation for a patient basically because they were on the brink of death, and again I think the feeling was that because of the public health nature of the

risks involved, that compassionate use of xenotransplantation would not be appropriate essentially under any circumstances.

Now, that all makes it sound as if we are all in happy agreement and the day was over by about 9:30, but I don't want to suggest that to you. It was a very interesting day, but there was plenty of undercurrent and not just undercurrent, but explicit disagreement within the committee. So, this next page in your document tries to point out to you that we were not always consistent in what we were saying.

I think that there was a fairly substantial voice, particularly from the expert retrovirologists who said you really can reasonably assume that all pig cells have potentially infectious porcine endogenous retroviruses within them and therefore, in effect, the implication was there's no need to test the tissues prior to transplantation because if you don't see it, it just means your assay isn't good enough.

On the other hand, the actual recommendation to the FDA by the subcommittee was in fact to go ahead and test all pig tissues prior to any proposed procedure on the notion that some pig tissues are safer than others.

Secondly, a feeling expressed that it was neither practical nor reasonable to test every transplant

tissue or organ and therefore don't bother to test the individual tissues prior to transplantation. And then on the other hand from some of the experts, that it is not in fact reasonable to assume that one pig represents all pigs or all tissues are exactly the same even within a herd and, therefore, again that all tissues should be tested.

In the ethical areas, it's very difficult to be absolutely consistent. So, for example, the committee was very strong in its feeling that informed consent should involve a detailed, informed consent process, much more so than in "ordinary" clinical trials and that it should include the close contacts. Yet, having said that, the committee was explicit in stating that comatose patients should not be excluded from xenotransplantation, nor those whose close contacts refuse to participate. So, make sense out of that one. Of course, there's no easy way to make any sense out of all of these kinds of questions.

Then the last one, perhaps the most contentious of all or most difficult to come to grips with, on the one hand the feeling expressed that you should never transplant tissue with infectious porcine endogenous retroviruses into humans at this time because we don't have enough information to assess its safety. Then on the other hand, the statement as I've suggested to you already, that it's reasonable to assume that all pig tissue has potentially

infectious porcine endogenous retroviruses. I think the general consensus of the committee that in fact it was appropriate, with the safeguards that the FDA was putting in place, to proceed with xenotransplantation at this time cautiously with careful, careful monitoring as the FDA was mandating.

Now, it's hard to draw firm conclusions from a committee that covered as much territory and had as many different people in there. I'm summarizing what I took to be the consensus, but it's sort of a chairman's prerogative kind of conclusion. We didn't vote. There was no expression of unified endpoint on this.

I think that the general sense certainly that I emerged with from listening to the experts was that the public health risk involved in xenotransplantation really should be understood to be in the category of remote, the risk involved. Now, that did not apply when talking potentially about the use of non-human primates as donors, but the assessment of the risk was very, very low.

I think another point that emerged over the course of the day was that in point of fact you're never really going to know what that risk is or be able to evaluate the safety issues associated with xenotransplantation until you, in fact, do pig-to-human xenotransplantation, that there's no animal model that will

accurately predict the outcome in the pig-to-human situation.

There was a strong sentiment expressed many times throughout the course of the day that xenotransplantation has the potential of enormous benefits to both individual people and to society as a whole on that basis, and therefore this final conclusion that, yes, it was appropriate for the FDA to approve further clinical trials in xenotransplantation with all of the kinds of safeguards that they were putting in place so that detection of any infectious agent both in tissue and in the recipients could take place as quickly as possible and we would then be able to determine what to do with the information if in fact that event comes about.

So, let me stop there and maybe we can have Jay and Amy and Phil give us a little of their sense of did I capture this correctly. And Abbey and Marian Michaels and Dan were there also. So, all of you can chime in.

DR. SIEGEL: I think that was an excellent summary, and I think it might help this committee to know that most of our issues -- and most of our committees face very complicated issues with mixed opinions and sometimes conflicting advice. But I think that was an excellent summary of the proceedings.

Abbey, you were there and probably ought also

to speak because I know you expressed some perspectives there that may not have been emphasized.

MS. MEYERS: You know, the funny thing was I came out of the room with the conclusion that everybody agreed that these experiments should not go forward until appropriate assays were developed and in place.

DR. AUCHINCLOSS: That I think was clear.

MS. MEYERS: So the tissue should be tested and there would be a testing of the human beings to find out if they had antibodies.

Then I opened up the newspaper about two weeks later and it said, FDA approves xenotransplantation and experiments are underway. So, you tell me what happened.

(Laughter.)

DR. PATTERSON: That's a correct observation, Ms. Meyers, but the reason for it is that during the months preceding the advisory subcommittee meeting, several sponsors were actively engaged in designing assays based on the viral sequence that had been published earlier for the porcine endogenous retrovirus and developing co-cultivation assays that could assess whether these viruses, using the new techniques available today, were indeed capable of infecting human cells. And they were also busy developing the antibodies that the committee discussed. So, what you were seeing was the application of the assays that had been

in development since March of that year.

What we did in December was to take to advisory committee our remaining questions and qualms about, okay, we know that these assays are being developed. What do we do with the data when it comes in? Because as the experts at the table said, given enough time, in a sense enough assay, they expected that virtually all porcine xenografts would test positive for this virus which leaves you with the question, should the graft be used.

So, what we had in December, by the time we went to advisory committee meeting, were a number of sponsors who actually had been developing the assays, had been testing patients, and had been developing antibody assays.

MS. MEYERS: So, a few months later you agreed to lift the hold?

DR. PATTERSON: The hold was lifted on a case-by-case basis based on what assays each sponsor had developed and based on the data they had obtained in testing their xenograft products and also testing the patients, if they had patients, already treated on that protocol. We felt it was, although the committee report said that you may or may not test the product, it may be of questionable value because most products will test positive inevitably. The agency has taken the position that that

information on what variant of the virus is present in a given porcine xenograft is actually quite valuable because that gives you the information to accurately screen your patients for that particular variant of PERV.

MS. MEYERS: And the tissue.

DR. PATTERSON: And the tissue, right, exactly.

MS. MEYERS: Have you done that?

DR. PATTERSON: Yes.

MS. MEYERS: What are the results in the last few months?

DR. PATTERSON: I think what we're going to do is have sponsors come forward again to the subcommittee and present those results, but in sum, the sponsors who have been allowed to come off hold have been testing their product. Those have come out negative and they have -- with appropriately sensitive and specific assays.

MS. MEYERS: So, you found that there was no PERV in their products?

DR. PATTERSON: Right. There's PERV if you amplify the pig's genome. The virus sequence is present in the pig chromosome. What we're testing for in the product is whether that virus is able to infect human cells in an in vitro setting using a co-cultivation assay. Those have been negative with appropriate controls so far.

Likewise, the patients who have been screened

so far with the state-of-the-art assays that are available to date have been negative. We are asking sponsors to continue screening their product and screening patients because we expect that the assays will evolve.

MS. MEYERS: When you say negative, you haven't found any antibodies to the PERV in the patients.

DR. PATTERSON: We haven't so far. We haven't found any patients with evidence of PERV infection. That's correct.

DR. BERMAN: What are the products that the companies have been looking at?

MS. MEYERS: Well, one is a liver machine, isn't it?

DR. PATTERSON: Right. One is a liver assist device which has isolated porcine hepatocytes in a cartridge and it's used for ex vivo --

DR. BERMAN: Is that extracorporeal or is that --

DR. PATTERSON: It's extracorporeal.

Then other products include porcine neurografts that are implanted into the patient. So, you have grafts that are both in direct contact with patients and also grafts which have a membrane, a semi-permeable membrane, separating them from direct contact with patients.

DR. BERMAN: Are we talking about numbers of 10

or 20 patients or larger numbers? 5 patients?

DR. PATTERSON: In aggregate we are talking close to 80 patients right now that have been screened.

DR. SIEGEL: It should be clear that number doesn't represent the number subsequent to the hold. Virtually all of those patients had been treated when PERV was first discovered.

Just to clarify, we did in fact follow, it's hard to say exactly, the advice of the committee but the consensus as described by Dr. Auchincloss and by Ms. Meyers. The studies all remained on hold until such time as they had provided adequate evidence of testing of patient and tissues. It's not the case, as may have been implied in the story you read, that two weeks later everybody came off hold. The first sponsor who had, in the period from March when the virus was discovered through December, done a great deal of work and came off hold then. Some still remain on hold. Is that not the case? So, it has been a continuing process, but we're ensuring that they have the adequate testing. I think the numbers of patients that have been treated since that time probably you could count on the fingers of your hand or something like that.

MS. MEYERS: So, the 80 were before the hold went on.

DR. SIEGEL: That's right.

DR. NOGUCHI: We even went to the extent that some of the companies have different INDs and each specific IND, each different application, they had to pass all the requirements that we were talking about. That included the development of the assay, screening of the patients. Informed consent is something we didn't discuss too much here, but that actually was a very extensive process that Dr. Patterson oversaw personally. That part often took in itself up to six months to accomplish. So, even companies coming off hold didn't mean that -- it was each individual project, case by case.

MS. MEYERS: There was also something we discussed at the meeting, a mandatory patient registry for all of these patients so that if the virus is found, we could go back and contact all of these people. Who is going to be responsible? Is somebody going to do it?

DR. PATTERSON: Yes. There is indeed not only a plan or a concept, but actual implementation of a national xenotransplantation registry or database. It's a computerized database. FDA at present is the lead agency on that. It's a joint effort between FDA, CDC, and NIH, and it will prospectively track all xenotransplant recipients for their lifetime for adverse events that may represent an infectious disease outcome from a xenotransplant. It will also track health events in the

animal facilities that are providing grafts to give an early signal if there's a problem in the animal facility even before it appears in the patients. So, it's a double-pronged approach. But you are exactly right.

Right now we have a pilot program. We're working with three transplant programs, three sponsors who have multiple INDs to test the pilot. That's going on right now. The ultimate plan is that every xenotransplant program in the U.S. will participate in this.

MS. MEYERS: So, you're getting some of these patients who may have had a transplant a year or two ago.

DR. PATTERSON: Right.

MS. MEYERS: You're going back.

Are there any complaints about privacy from any of these people?

DR. PATTERSON: It will have to be part of the patient informed consent, and that is being done. We are addressing patient confidentiality. Data would not be disclosed to the public by personal identifier or names. We do intend the information from the registry or information derived from the registry will be publicly discussed so that the public will be aware of what are in aggregate the adverse events or if there are clusters of infectious disease outcomes, that that can be discussed and appropriately dealt with.

MS. MEYERS: Have the sponsors been asked for all future subjects who go through this type of experiment, that the informed consent document should say, in the event of your death, we will ask your family for an autopsy, provision for an autopsy?

DR. PATTERSON: Yes. As I think you may remember from the days of gene therapy, that's sometimes often difficult to get. Actually the process that we're advocating that sponsors use is to engage the patient in that discussion with their families and the investigator early on so that the family is cognizant of the patient's wishes and not confronted with that request for consent for autopsy at a time of grief and mourning, but rather they know a priori that this is a condition for signing up for the protocol and this is the patient's wish.

DR. VOSE: In the early days of the stem cell transplantation, there was something similar that was put into the informed consent. So, I think there's a precedent for that.

DR. PATTERSON: Right.

MS. MEYERS: It has been precedent in gene therapy, but a lot of the investigators just don't put the sentence in the informed consent.

DR. VOSE: It sounds like they have it covered.

Dr. Salomon?

DR. SALOMON: I had just a couple comments. I think you also did an excellent job, but just to make a couple points.

As you said, we don't agree on everything. One point was -- I don't want to get into an argument about what's an expert. There have been many different definitions of expertise given.

But I think the way you gave it initially implied that the major current issue in xenotransplantation is this infectious issue, and I would like to, just for the sense of perspective, take a little issue with that and say that it is an extremely important issue, but there are other issues and I think we've already begun touching on them: patient selection, the influence of immunosuppression, how these patients are going to be followed, how information is going to move from experts in infectious disease to experts in transplantation. So, I'd like to just leave the group with a slight dissent, that there are a lot of different experts that are going to need to come to the table.

Certainly I think the expertise in stem cell and bone marrow transplantation that sits around the BRMAC is actually -- you're not as far off of this area as you think because as we begin to think about trafficking of infected cells, many of these endogenous retroviruses --

such as feline leukemia virus, for example, is an exogenous virus in the same family as the porcine endogenous retrovirus -- actually track back to the bone marrow, and the bone marrow is a rich reservoir for them. So, I don't think you're going to find this -- we're going to be on your home territory soon.

A couple other quick comments here. Pig to primate. Yes, there have been a whole lot of pig to primate studies, but one of the things to emphasize here -- and it gets to a final point about clinical trials -- is the current data suggests that it's not a good model because transmission of porcine endogenous retrovirus to primate tissues has not occurred, whereas the same setup has allowed transmission to readily occur to human cell lines. So, even though at one time the committee was very happy about this great abundance of pig-to-primate transplant material that we could settle these issues in, that blew away in the wind when that came to our attention.

So, I think that one of the issues that Dr. Auchincloss made and I really strongly support is that some of the questions of xenotransplantation are not going to be answerable except in well-designed clinical trials. Abbey, that's an issue that also relates back to I think the willingness of the FDA under very controlled circumstances to let some of this go forward. I think many of us agree

with that.

MS. MEYERS: Well, one of the issues from my perspective is that the trials going forward go forward in the commercial sector and all the information is going to be a trade secret and the public won't have access to it.

DR. SALOMON: Right.

MS. MEYERS: And that's where I have a problem.

DR. SALOMON: I think the important thing to emphasize -- and I think you alluded to it, but to say it specifically -- is these studies are all under IND. So, I think that the point here is that they're subject to very well-developed, tried and true, tested means of keeping track of risks within clinical trials, even though they are occurring in the private sector. I think the evolution of the Xenotransplantation Advisory Committee at a more national level -- I think, Amy, Phil, you'll have to address those developments. I mean, that's an issue. I don't know. The IND issue I think is very comforting, though.

DR. NOGUCHI: In addition to the IND mechanism, we did say in January at our Public Health Service workshop that in fact one of the goals and one of the fast track items we have will be regulations that will state that for xenotransplantation and for gene therapy, the information that has been available, which so far has all been publicly

available except for certain proprietary manufacturing secrets, will continue to be available and the agency is committed to that.

MS. MEYERS: So, if there is an accident and a virus is infectious and three people get sick, the public will know. Is that correct?

DR. NOGUCHI: Everyone will know. That's correct. We are taking the position that in these areas adverse events are not proprietary by any means.

DR. SALOMON: I wanted to just finish my comments, though, by bringing up the point there is still a significant need for further research. I think the issues that you bring up highlight those. The idea is do all tissues have equal risk, which is what Dr. Auchincloss mentioned, and I don't believe all tissues will have equal risk. I think that transcriptional activation of infectious virus from the genome is not going to occur with equal propensity in equal tissues, and I think that's one issue.

The second issue is if you take, for example, a sponsor who wants to do a pig hepatocyte extracorporeal circulation and I take normal pig hepatocytes, clean, wonderful -- I just isolated them -- co-culture them in fresh media with a little bovine fetal calf serum for 7 days and tell you that, aha, there was no transmission to,

what, U293 embryonic kidney cell or something like that, so therefore I can go ahead with my study, my response to you is I'm not sure about that. In other words, transplantation, activation of cells, cytokine release, apoptosis, necrosis, stress, all the different things that that implies also implies significant changes in cellular transcriptional events that all could affect the propagation of the virus.

There's one last thing that I wanted to end on is one unsettled issue here -- and I am very frustrated with it -- is a lack of definition about whether we're dealing with non-human primate donors for xenotransplantation or pig donors as xenotransplantation donors. You alluded to them, but I'm very frustrated that in the guidelines and in the official discussions of all these groups we have not yet had the guts to deal with the fact that in my opinion non-human primates should not at this point be considered for these trials, period, because of their incredibly higher infectious risk potential.

DR. MICHAELS: You made a number of points which I do agree with except for perhaps that last one. While I think that I really feel that the PHS comments that came out in the last PHS meeting in January actually were really quite reasonable in terms of rather than putting a definition to which species could and could not be used

because you don't know tomorrow which animal might be brought up as a potential source animal, that it was more important to make sure that the structure was present for what kinds of testing needed to be done in order to proceed with any animal source. And I still hold by that.

DR. AUCHINCLOSS: I was just about to say before we wrap this up, maybe Amy wants to offer perhaps a few comments on the national committee, what's going on internationally, and what's going on with the revised guidelines.

DR. VOSE: Quickly.

(Laughter.)

DR. PATTERSON: On the first topic, as was presented at the January Public Health Service workshop on xenotransplantation, we discussed the proposal that the Department of Health and Human Services has put forward to establish the National Advisory Committee on Xenotransplantation, and those plans are becoming a reality. There's a commitment to establish a national committee. We're in the process of writing a charter and discussing how indeed that might be implemented to serve as a resource to the public so that they can hear in a public forum about the adverse events and other types of outcomes from these trials, serve as a resource to each of the agencies that is charged with grappling with the public

health issues, serve as a resource to FDA making the regulatory decision, at what point does this research go from bench to bedside, to CDC as they address some of the epidemiologic and infectious disease concerns, and to NIH in terms of funding the research that can address in a very fundamental way some of the questions that have been raised here today. So, there will be a national advisory committee. Stay tuned on that one.

In terms of the draft guidelines, it has been revised by the agency. It's entering now legal review at each of the agencies and upper management review for clearance. I'm probably being optimistic but also realistic when I say end of 1998 for the final guidelines.

DR. AUCHINCLOSS: International efforts.

DR. PATTERSON: International efforts.

DR. AUCHINCLOSS: You are talking to other to countries.

DR. PATTERSON: Right. Since viruses do not carry passports, or indeed no microbes carry a passport, we think it's very important that our efforts here and the standards established in the U.S. be discussed and vetted with the standards being set forth in other countries.

Canada has prepared draft guidelines that actually mirror ours and are due out any time now.

The World Health Organization has issued their

final guidelines on the ethics in infectious disease issues which again closely mirror ours but also stress the importance of informed consent, autopsy, the recognition that individual rights of being able to withdraw from a trial may be overcome if there's a need for quarantine. So, this has been addressed.

The UK has established an interim regulatory authority to entertain protocols much in the way that FDA does here.

So, there's quite a bit of activity and we're doing our best to join forces and work out a system that is reasonable.

DR. AUCHINCLOSS: Thank you.

DR. VOSE: Thank you. We need to vote.

Did you have something to say, Jay?

DR. SIEGEL: Yes, I want to make a quick plug I guess.

Dr. Salomon pointed out the fact that not all tissues are the same. There are different activating signals. I just want to use that as an opportunity to note that, as I think was apparent to all who were there in December, but perhaps not to the remainder of the BRMAC, which also oversees our research work, that some of the seminal findings, for example, regarding the fact that lymphocyte activating signals can induce production of this

virus, of infectious virus, come from Center for Biologics labs of Dr. Carlin Wilson and co-worker who is, I am proud to say, in my office and in the division that Phil and Amy are in and that those laboratories have additionally made important strides in looking at areas ranging from PCR testing to co-cultivation testing to ensure that not only that the tests that are used are state-of-the-art, but that the state of the art moves along as rapidly as possible to the best possible testing. So, we both recognize those concerns and are addressing them not just from a pure review and regulatory perspective, but from a research perspective as well.

DR. VOSE: We need to vote on the report. Everyone who feels that we should vote on the report without modifications, please raise your hand.

(A show of hands.)

DR. VOSE: Unanimous.

It's time to take a break. We're not going to do that. We're going to move immediately on to the next topic. Next is topic 3, update on research programs in the Laboratory of Immunology. First Dr. Amy Rosenberg will talk about an update on the Laboratory of Immunology.

DR. ROSENBERG: I'd like to take this opportunity to thank very much all who were involved in our site visit and in evaluating our research programs,

particularly Dr. Berman, the chair.

In the interest of time, I'm going to skip over some slides. To summarize the products that are regulated by the Laboratory of Immunology, this is in the Division of Hematologic Products. We evaluate products that range from products of known efficacy for major killers, such as the thrombolytic and anti-thrombotic agents, to highly experimental agents that are being used now for treatment of immunologic disorders that have been notoriously refractory to therapy. So, we have agents for induction of immunologic tolerance, as you see, hematopoietic growth factors and inhibitors of stem cells, and of course, a major portion of our regulatory aegis is our cell separation devices for hematopoietic stem cell transplantation which you guys have been inundated with.

Our staff takes a very active role in participating in policy issues regarding tissue regulation, pediatric labeling, gender issues in clinical trials, and safety testing for immunologic therapies.

It's rather costly and slow to try and import expertise as new issues arise. It certainly makes more sense for centers to have expertise that can evaluate novel therapeutic agents, and as such we feel our laboratory certainly has the capacity to evaluate exciting novel therapies such as the anti-angiogenic factors, transgenic

animals which will be used as sources for biotech products, treatment of autoimmune disease in populations that have been excluded from treatment because of childbearing potential, effects of concurrent therapies on tolerance inductions, and on models of autoimmune disease and xenotransplantation. In addition, antioxidants as therapeutic agents we believe we have the capacity to evaluate.

In terms of our operating budgets, we've had a major cut in our operating budgets which have forced people to try and get grant money elsewhere, and some of us have been very successful at that.

Just to give you an update, since the site visit, which was in early May, the most pertinent fact is that Dr. Vacchio is leaving CBER and this is a critical loss for us for a number of reasons. Dr. Vacchio had a lot of expertise in evaluation of immunologic products and particularly had an interest in autoimmune diseases. So, that is a severe loss for us.

In addition, all of the regulatory burden that she was carrying is now put to others. Increasing workloads with a shortage of resources to handle both laboratory and regulatory load are not good for morale. I fear that even greater losses in the center will cause a further downward spiral in our ability to perform excellent

science as well as excellent regulation.

Just in terms of the more trivial updates, some of us who have had manuscripts submitted at the time of the site visit have had those accepted.

To point out what happens with regulatory loads of people leaving, since Dr. Vacchio is leaving, for instance, Dr. Shores is receiving 10 new INDs from Dr. Vacchio. I've received five new ones, and others in our division have also received new INDs to evaluate. So, the regulatory workload is increasing dramatically.

I'm going to leave it at that and turn it over to Dr. Epstein.

DR. VOSE: Thank you.

Next we will have a report of the Laboratory of Molecular Immunology from Suzanne Epstein.

DR. EPSTEIN: I'm going to use my opportunity slightly differently.

The work I presented to the May 1st site visit focused on mechanisms of protective immunity to influenza virus infection. We study responses to both viral and plasmid vectors. So, the work is relevant to two different areas of CBER responsibility, both protective responses that are induced by vaccines and then in gene therapy, immune responses that are induced by either viral or plasmid vectors and these can be inadvertent and can

interfere with therapy, or in the case of some cancer therapies, they can in fact be helpful. But the responses we're studying pertain to both these kinds of products.

Now, in the May site visit, I discussed three overall project areas. First of all, broad cross protection against influenza strains in mice that is challenged with a strain differing from the vaccinating strain. Then I discussed DNA vaccination against influenza, including an analysis of the mechanisms responsible for protection during challenge. And thirdly, studies in immunoglobulin knock-out mice testing potential for protection by T cells acting alone.

And to explain this a bit more, this third project tests potential for T cells acting alone because vaccines have been proposed that would require T cell immunity to provide effective protection, but without evidence that it does. The issue calls for reexamination for new approaches because past views and assumptions do not satisfactorily account for all the recent data. A doctor's transfer of T cells asks a somewhat different question because cell trafficking may not be physiological and the results do not always agree with results for active T cell immunizations.

So, using a somewhat different experimental system than the labs of Doherty, Braciale, and Gerhard, we

have aimed to achieve several things. We want to isolate the role of active T cell immunity, first of all, in protection by viral vaccination; secondly, in immunopathology; and thirdly, in protection by DNA vaccines. So far in the work that was presented to the site visit, we've shown protection against homologous virus. An example of future plans mentioned in the briefing package is a study of H1/H3 cross protection in the antibody knock-out mice? Is immune protection against flu of a different subtype than the immunizing strain induced in the absence of all antibody? And is this the case for the viral immunization? Is this the case for DNA immunization? That's currently unknown.

Another topic that led to a lot of discussion at the May 1st site visit was the possibility that NK cells play some role in what we're terming cross protection. This is in fact ruled out by some data in the literature which there was not time to discuss on May 1st. This is work from Walter Gerhard's lab. And here's cross protection. If you give a flu A virus of one subtype challenged with a different subtype, there's protection. Flu B is too distantly related. So, there is no cross protection.

What Gerhard's lab did was an immunization with a flu A virus, then a mixed challenge with another subtype,

plus flu B, the distantly related virus. The outcome is that in challenge only the flu A subtype virus is controlled; flu B replicates uncontrolled. The conclusion was that even locally in the same lung, cross protective immunity is mediated by antigen-specific effectors. I think NK cells and cytokines can't explain this result, and that's why our studies have focused on immunoglobulins and T cells. I spent a lot of time May 1st discussing subpopulations of T cells.

Then to give a brief progress update since the May 1st site visit, we have further analyzed the effects of anti-CD4 treatment in our mice, looking at phenotypic and functional depletion. In collaboration with Howard Mostowski, we've done two color flow cytometry using stains for CD4 and also CD3, and what we found is that any residual CD4 cells do not have a T cell receptor. There were no doubly positive cells detected. So, our depletion does remove all specific T cells of the CD4 type.

Secondly, functional depletion. If we CD4 deplete and then give virus, there is no help for an IgG antibody response. The response in control mice is in the thousands. There is no response at all in the CD4 depleted mice.

So, this information about both phenotypic and functional depletion by anti-CD4 has been added to our

manuscript that's nearly finished on DNA vaccination.

Then just some other professional updates. I've been invited to chair a workshop, Mechanisms and Uses of DNA Immunization, at a 1999 Keystone symposium. Then the post-doctoral fellow has been recruited to start September 1st, supported by my National Vaccine Program grant. That grant was awarded for studies of cross protective mechanisms, including studies in the antibody knock-out mice and also IgA selective knock-out mice and for studies of DNA vaccination, including challenge with Hong Kong H5 and 1 virus in collaboration with CDC.

Finally, an update on ongoing regulatory activities. The most active of the INDs I'm working on recently involved immune reconstitution by transduced stem cells and also plasmid DNA products for direct in vivo use in the patient. There have been pre-IND reviews and meetings in the area of plasmid DNA products.

In the policy area, I've been involved recently in discussions about potency assays for plasmid vectors. There's an interesting issue whether one must show simply expression of the gene or whether one must show activity, and it will depend on the product.

Then I've been involved in discussions about testing for vector localization to the gonads in gene therapy.

Then oversight of IND and license application reviews of the other members of the lab staff continues.

I want to thank you very much for this opportunity and thank the people who participated in the site visit.

DR. VOSE: Thank you.

We're going to go ahead and move to close the session unless someone has any questions for the investigators or laboratories.

Okay. We're going to move to close the session then. Everyone who is not supposed to be here leave.

(Laughter.)

(Whereupon, at 3:45 p.m., the committee recessed, to reconvene in closed session.)