

# TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICAL EVALUATION AND RESEARCH

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BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

NINETEENTH MEETING

Pages 1 thru 329

Bethesda, Maryland  
July 24, 1997

MILLER REPORTING COMPANY, INC.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICAL EVALUATION AND RESEARCH

6174 '97 AUG -8

BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE  
NINETEENTH MEETING

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Thursday, July 24, 1997

8:05 a.m.

Holiday Inn Bethesda  
8120 Wisconsin Avenue  
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546-6666

## PARTICIPANTS

Julie M. Vose, M.D., Chairperson  
William Freas, Ph.D., Executive Secretary

## MEMBERS

Hugh Auchincloss, Jr., M.D.  
W. French Anderson, M.D.  
Charles S. August, M.D.  
Ellin R. Berman, M.D.  
Virginia C. Broudy, M.D.  
Janice Dutcher, M.D.  
Richard A. Goldsby, Ph.D.  
Pamela Hartigan, Ph.D.  
Richard Hong, M.D.  
Eugenie S. Kleinerman, M.D.  
Paul R. McCurdy, M.D.  
Susan F. Leitman, M.D.  
William M. O'Fallon, Ph.D.  
Sandra M. Swain, M.D.

## CONSUMER REPRESENTATIVE

Abbey S. Meyers

## PATIENT REPRESENTATIVE

Venus Gines (Topic I)  
Wilma J. Carroll (Topic II)

## INDUSTRY REPRESENTATIVE

Alton Floyd, Ph.D. (Topic II)

## FDA

Patricia Keegan, M.D. (Topic II)  
Richard O. Steffen, M.D. (Topic I)  
Jay P. Seigel, M.D.  
Karen Weiss, M.D.

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## P R O C E E D I N G S

## Opening and Administrative Remarks

1  
2  
3 DR. FREAS: Good morning. We have a very full  
4 agenda today and so I would like to go ahead and get  
5 started. I am Bill Freas and I am the Executive Secretary  
6 for this morning's meeting. This is the Nineteenth Meeting  
7 of the Biological Response Modifiers Advisory Committee.  
8 Both today's session and tomorrow's session are welcome to  
9 the public; you are welcome to participate in all the  
10 sessions of this Committee.

11 I am the designated federal official for this  
12 Committee, so should anyone in the audience need to talk to  
13 either the Chair or any of the Committee members, please see  
14 me during the break. I will be more than glad to relay your  
15 message either to the Chair or the Committee members. We  
16 ask that you do not directly approach the Committee members  
17 themselves, especially during the breaks. They will be  
18 busy, trying to get caught up and ready for the next  
19 session.

20 At this time, I would like to go around and  
21 introduce the members seated at the head table. I will be  
22 starting on the right-hand side of the room, the audience's  
23 right-hand side of the room. We have Dr. French Anderson,  
24 Director, Gene Therapy Laboratory, University of Southern  
25 California School of Medicine. Next is an empty seat that

1 will be occupied by Dr. Hugh Auchincloss, Associate  
2 Professor of Surgery, Harvard Medical School. Next is Dr.  
3 Ellin Berman, Associate Professor, Memorial Sloan-Kettering  
4 Cancer Center. Next is Dr. Richard Hong, Professor, Vermont  
5 Cancer Center, University of Vermont. Next is Dr. Eugenie  
6 Kleinerman, Professor, University of Texas M.D. Anderson  
7 Cancer Center. Next is a new Committee member that I would  
8 like to welcome to the table, Dr. William O'Fallon, Chair,  
9 Department of Health Sciences Research at Mayo Clinic. Next  
10 is Dr. Carole Miller, Assistant Professor in Oncology, The  
11 Johns Hopkins University. One of the empty seats will be  
12 filled shortly by Dr. Pamela Hartigan, Statistician, West  
13 Haven V.A. Medical Center.

14           Coming around the corner of the table we have  
15 another new member to the Committee. I would welcome Dr.  
16 Richard Goldsby, Professor, Amherst College. Next is Dr.  
17 Virginia Broudy, Associate Professor of Medicine, University  
18 of Washington School of Medicine. Next is the Chair of this  
19 Committee, Dr. Julie Vose, Associate Professor, University  
20 of Nebraska Medical Center. Next is patient representative,  
21 Miss Venus Gines. The seat next to that will be for our  
22 consumer representative, Abbey Meyers, President and  
23 Executive Director, National Organizations for Rare  
24 Disorders, New Fairfield, Connecticut.

25           Around the table is Dr. Charles August, Division

1 of Hematology and Oncology, Miami Children's Hospital. Next  
2 is Dr. Paul McCurdy, Director, Blood Resources Program,  
3 Division of Blood Diseases and Resources. When the other  
4 people come to the table, I will make the announcement that  
5 they are at the table.

6           Sitting at the table as well is a member of FDA,  
7 Dr. Karen Weiss, Director of the Division of Clinical Trial  
8 Design and Analysis, and she will be assisting in the  
9 discussions today and the presentations. I welcome  
10 everybody here this morning.

11           At this time, I need to read into the official  
12 public record the conflict of interest statement. The  
13 following announcement addresses the issue of conflict of  
14 interest with regard to this meeting, and is made part of  
15 the record to preclude even the appearance of a conflict of  
16 interest.

17           Pursuant to the authority granted under the  
18 committee charter, the lead deputy commissioner of the Food  
19 and Drug Administration has appointed the following  
20 participants as temporary voting members for topics I and  
21 II: Dr. Janice Dutcher, and Dr. Sandra Swain. In addition,  
22 the lead deputy commissioner of the FDA has appointed Dr.  
23 Alton Floyd as a temporary non-voting representative for  
24 topic II.

25           The Director of the Center of Biologics Evaluation

1 and Research has appointed the following participants as  
2 temporary voting members: Dr. Charles August, for all  
3 topics; Miss Helaine Baruch, for topic IV; Dr. David Larr,  
4 topic III; Dr. Susan Leitman, topics I and II; Dr. Paul  
5 McCurdy, all topics; Miss Venus Gines, topic I; and Miss  
6 Wilma Carroll, topic II.

7           Based on the agenda made available, it has been  
8 determined that all financial interests in firms regulated  
9 by the Center for Biologics Evaluation and Research, which  
10 have been reported by the participating members and  
11 consultants as of this date, present no potential for an  
12 appearance of a conflict of interest at this meeting, with  
13 the following notations:

14           Dr. Hugh Auchincloss, the Agency approved a  
15 limited waiver to permit his participation in discussions  
16 and deliberations on topic III. Dr. Auchincloss will not  
17 vote on this topic. There are no restrictions on his  
18 participation in topics I, II and IV.

19           Dr. Virginia Broudy, the Agency approved a waiver  
20 on November 8th, 1995 regarding her financial holdings. The  
21 holdings remain unchanged.

22           Dr. Janice Dutcher reported that she has an  
23 unrelated contract from the firm associated with topic I.  
24 Dr. Susan Leitman reported that as part of her official  
25 government duties she was associated with a firm involved in

1 topic II. Miss Abbey Meyers reported that her employer  
2 received charitable donations in 1996 and 1997 from firms  
3 that could be affected by discussions for today and  
4 tomorrow.

5 Dr. Carole Miller, a waiver was approved by the  
6 Agency permitting her full participation in Committee  
7 discussions and deliberations for topics I and IV. There  
8 are no restrictions on her participation in topic III.  
9 Also, Dr. Miller disclosed that she attended a meeting in  
10 May, 1996 with the sponsor of topic I. She received a fee  
11 for her attendance. She also reported receiving a grant and  
12 fees for consulting with a competing firm on unrelated  
13 activities for topic III. In addition, Dr. Miller has  
14 excused herself from participating in topic II.

15 Dr. Julie Vose, a waiver was approved by the  
16 Agency to permit her full participation in discussions,  
17 deliberations and vote on topic I. There are no  
18 restrictions on Dr. Vose's participation on topics II and  
19 IV. In addition, Dr. Vose reported that she consulted on  
20 unrelated issues and had unrelated paid speaking engagements  
21 with a firm associated with topic IV. Dr. Vose is excluded  
22 from participating in topic III and will step down as Chair  
23 for that topic. Dr. Virginia Broudy has been appointed to  
24 serve as Acting Chair for topic III.

25 Miss Helaine Baruch, a patient representative,

1 disclosed that her employer, the Leukemia Society, received  
2 an unrelated grant from a firm associated with topic IV.

3           The following temporary voting members, industry  
4 representatives and patient representatives had no interests  
5 to report: Drs. French Anderson, Charles August, Alton  
6 Floyd, Richard Goldsby, Pamela Hartigan, Richard Hong,  
7 Eugenie Kleinerman, Paul McCurdy, William O'Fallon, Sandra  
8 Swain, David Larr, Miss Wilma Carroll, Miss Venus Gines and  
9 Christina Heineman.

10           In the event that the discussions involve other  
11 products or firms not already on the agenda for which FDA  
12 participants have a financial interest, the participants are  
13 aware of the need to excuse themselves from such involvement  
14 and their exclusions will be noted for the public record. A  
15 copy of the waivers is available by request under the  
16 Freedom of Information Act.

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

21           So ends the reading of the conflict of interest  
22 statement. Dr. Vose, I would like to turn the microphone  
23 over to you.

24           DR. VOSE: Thank you, Dr. Freas. The first item  
25 on the agenda is the open public hearing. Dr. Freas, do we

1 have any announcements regarding the open public hearing  
2 speakers?

3 DR: FREAS: At this time, Dr. Vose, I have only  
4 received one request to speak in the open public hearing and  
5 we have been asked to hold that until after lunch. Is there  
6 anybody in the audience this morning who would like to speak  
7 during the open public hearing and address the Committee at  
8 this time?

9 Should anybody like to address the Committee  
10 during the open public hearings, there will be one after  
11 lunch and two tomorrow, please come and see me during the  
12 break. I will make sure that your name is recorded and that  
13 you have the opportunity to address the Committee during one  
14 of our open public hearings. Again, FDA welcomes the public  
15 and encourages participation during these open public  
16 hearings because, believe it or not, that is what these  
17 meetings are here for, the public. So see me during the  
18 break if you would like to speak. Dr. Vose, I turn the  
19 microphone over to you. Thank you.

20 DR. VOSE: Thank you, Dr. Freas. We will go ahead  
21 and proceed with item one on the agenda, which is topic I,  
22 the application for Neumega by Genetics Institute. We will  
23 proceed with the first presentation.

24 **Introduction, John C. Petricciani, M.D.**

25 DR. PETRICCIANI: Thank you, Dr. Vose.

1 (Slide)

2 Members of the Committee, we appreciate the  
3 opportunity to meet with you this morning to discuss  
4 Neumega, which is recombinant interleukin-11 which I will  
5 refer to also as IL-11.

6 (Slide)

7 Neumega is a megakaryocyte growth factor that can  
8 prevent thrombocytopenia due to cancer chemotherapy. As an  
9 introduction, I would like to set out some of the background  
10 against which this product was developed, and highlight the  
11 major points we will be making during this presentation.

12 (Slide)

13 Human IL-11 was cloned and isolated at Genetics  
14 Institute in 1990. After we completed our preclinical  
15 studies an IND was filed in October, 1992, and human  
16 clinical trials were initiated that year.

17 In developing our clinical program, we benefited  
18 considerably from periodic discussions with FDA and our  
19 clinical investigators. This was an especially important  
20 point for the IL-11 program since there are no FDA, European  
21 or international guidelines for clinical studies of  
22 thrombopoietic growth factor. The two most important  
23 meetings we had CBER were in August of 1995 at the end of  
24 Phase II studies and in August of 1996 before we developed  
25 our license application.

1           The outcome of the 1996 meeting was agreement  
2 that, in fact, it was reasonable to proceed with a license  
3 application for Neumega, which we submitted in December of  
4 1996. At this point I would like to thank the FDA staff who  
5 worked with us throughout the development and the review of  
6 this product.

7           (Slide)

8           I would now like to highlight the most important  
9 biological features of IL-11. It is a naturally occurring  
10 protein whose major hematopoietic effect is to stimulate the  
11 expansion of all phases of megakaryocyte development. In  
12 vitro IL-11's effects are generally observed in conjunction  
13 with signals from other early acting cytokines and other  
14 megakaryocyte growth factors, such as thrombopoietin or TPO.  
15 However, IL-11 can stimulate thrombopoiesis independently of  
16 TPO, as shown in a TPO knockout mouse system.

17           When given to animals Neumega consistently causes  
18 increases in platelets both in untreated animals, as well as  
19 animals that received myelosuppressive treatments. In  
20 addition, platelets produced in IL-11-treated animals are  
21 structurally and functionally normal.

22           These preclinical observations on the basic  
23 biology of IL-11 led us to examine Neumega for its potential  
24 in treating chemotherapy-induced thrombocytopenia, as you  
25 will hear shortly from Dr. Kaye.

1 (Slide)

2 The molecule chosen for clinical development is  
3 19kD non-glycosylated protein with a 177 amino acid sequence  
4 identical to the natural molecule, except that the amino  
5 terminal proline is absent. The protein is produced in E.  
6 coli as an IL-11 thioredoxin fusion protein, from which the  
7 IL-11 is subsequently cleaved and then IL-11 is purified  
8 from the cleavage mixture.

9 (Slide)

10 The specific indication that we are seeking for  
11 Neumega is for the prevention of chemotherapy-induced  
12 thrombocytopenia and the reduction of the need for platelet  
13 transfusions in patients with nonmyeloid malignancies.

14 Within that framework, we believe we have  
15 identified populations of patients with characteristics most  
16 likely to benefit from Neumega therapy.

17 (Slide)

18 These are patients who have undergone enough  
19 cycles of standard or dose-intense chemotherapy to already  
20 have experienced thrombocytopenia and, second, those who are  
21 at risk for developing thrombocytopenia because they are  
22 being given higher than standard doses of chemotherapy. For  
23 example, patients who are going to receive several cycles of  
24 dose-intense chemotherapy prior to entering a program of  
25 high-dose chemotherapy with stem cell support. Taken

1 together, this is still a limited population, as evidence by  
2 the fact that the FDA has designated Neumega as an orphan  
3 drug for this use.

4 (Slide)

5 With that brief background and overview, I would  
6 like now to review the rest of the agenda for today.

7 (Slide)

8 Dr. Linda Elting is the director of clinical  
9 epidemiology and informatics at M.D. Anderson Cancer Center.  
10 Dr. Elting will report on data which showed that  
11 thrombocytopenia is a clinically significant event,  
12 occurring in up to one-quarter of patients with solid tumors  
13 and lymphoma who receive chemotherapy. Dr. Elting's data  
14 also support the premise that the risk of bleeding increases  
15 as platelets decrease, and that maintaining platelet counts  
16 above 1000 minimizes serious clinical outcomes.

17 Dr. Kenneth Anderson is a practicing oncologist  
18 and is head of the blood bank of the Dana Farber Cancer  
19 Center. In addition, he is the former chairman of the  
20 Transfusion Practice Committee of the American Association  
21 of Blood Banks. Dr. Anderson will remind us that even  
22 though the nation's blood supply is certainly safer than it  
23 has been, there is still a measurable risk associated with  
24 giving the transfusions. Certainly, from a patient's  
25 perspective, the risk is not insignificant and should not be

1 ignored.

2 Dr. James Kaye is the medical director responsible  
3 for IL-11 platelet program at Genetics Institute. Dr. Kaye  
4 will review the results of our clinical studies with Neumega  
5 and, in particular, two different but complementary studies  
6 which demonstrate that Neumega is effective in reducing the  
7 need for platelet transfusions and is safe in the  
8 populations studied. Other studies which Dr. Kaye will  
9 mention will support the dose and schedule selected and give  
10 additional perspective on Neumega's clinical utility.

11 Lastly, Dr. Michael Gordon is associate professor  
12 of medicine and practicing oncologist at the Indiana  
13 University Medical Center. He is also an IL-11 clinical  
14 investigator. Dr. Gordon will provide his perspective on  
15 the need for a thrombopoietic agent. Dr. Gordon concludes  
16 that Neumega has an acceptable benefit-risk profile, and  
17 should be made available to patients as an alternative to  
18 platelet transfusions.

19 (Slide)

20 In addition, we have invited several other  
21 individuals, with expertise in various areas, you may call  
22 upon during the discussion period to assist in clarifying  
23 certain points if needed.

24 They are Dr. John Smith, one of our clinical  
25 investigators from Portland, Oregon; Dr. Archie Bleyer,

1 chairman of pediatrics at the M.D. Anderson Cancer Center.  
2 He also chairs the Children's Cancers Group. Dr. L.J. Wei,  
3 professor of advanced statistics at Harvard University; Dr.  
4 Craig Pratt, professor of medicine at Baylor College of  
5 Medicine and former chairman of the FDA Cardiorenal Advisory  
6 Committee; and Dr. Philip Podrid, professor of medicine,  
7 Boston University.

8 Overall, we believe that our studies were rigorous  
9 tests which provide sufficient data to conclude that Neumega  
10 is safe, effective and well tolerated. The presentations  
11 that follow will support those conclusions. Now I would  
12 like to introduce Dr. Linda Elting.

13 **Thrombocytopenia and Bleeding in Patients with Solid Tumors**  
14 **and Lymphoma Receiving Chemotherapy, Linda Elting, Dr.P.H.**

15 (Slide)

16 DR. ELTING: Ladies and gentlemen, today I will  
17 discuss the problem of chemotherapy-induced  
18 thrombocytopenia, focusing on the results of studies that  
19 were conducted at M.D. Anderson Cancer Center and their  
20 relationship to previous research. These findings have been  
21 previously published in abstract form in the 1997 ASCO  
22 proceedings, and in 1996 in Volume IV of Supportive Care and  
23 Cancer.

24 I will address the incidence, the risk and the  
25 outcomes of chemotherapy-induced thrombocytopenia, with

1 particular emphasis on major and minor bleeding and,  
2 although this is not an endpoint in the studies to be  
3 presented today by Genetics Institute, on the delay of more  
4 than 7 days in a subsequent cycle with chemotherapy. The  
5 serious clinical outcomes will also be examined with respect  
6 to the depth of thrombocytopenia and to the effectiveness of  
7 platelet transfusion prophylaxis.

8 (Slide)

9 Our studies examined chemotherapy-induced  
10 thrombocytopenia which was defined as a platelet count less  
11 than 50,000 in adult patients with solid tumors or lymphoma,  
12 who managed at M.D. Anderson Cancer Center. The studies  
13 were limited to Houston area residents whose entire care was  
14 provided at M.D. Anderson.

15 The incidence of chemotherapy-induced  
16 thrombocytopenia was estimated from cycles of chemotherapy  
17 administered to these Houston area residents in the  
18 outpatient clinic during 1992 and 1993. The risk and  
19 outcomes data were derived from a random sample of Houston  
20 area residents receiving both in- and outpatient cycles  
21 during 1994 and 1995.

22 (Slide)

23 M.D. Anderson is a comprehensive cancer center and  
24 routinely accepts patients with disseminated disease who are  
25 referred for investigational treatments. However, the

1 Houston area residents treated at the center are somewhat  
2 more typical of those treated in community centers in that  
3 they frequently have only local disease or a single  
4 metastatic site, and they receive standard chemotherapy  
5 regimens in conventional doses. For example, among the  
6 patients with breast cancer in this study, 70 percent were  
7 receiving FAC in conventional doses, 17 percent in the  
8 adjuvant setting where the patient had no evidence of  
9 disease. Limiting the studies to Houston area residents has  
10 the advantage of producing results that are more easily  
11 generalized to community oncology practice.

12 (Slide)

13 We characterized superficial bleeding of the skin  
14 or the mucosa as minor, as in the examples listed here, and  
15 frank, bright red bleeding or major organ hemorrhage as  
16 major bleeding, characterized here. Patients who  
17 experienced both minor and major bleeding, or major bleeding  
18 plus a delay in chemotherapy are characterized in our  
19 analysis as major bleeding.

20 (Slide)

21 Almost one-quarter of all the tumor patients who  
22 received chemotherapy developed thrombocytopenia, and 10-25  
23 percent additionally of all patients experienced platelet  
24 counts below 20,000. Despite changes in the antineoplastic  
25 agents, the combinations and dosages used, this estimate has

1 been consistent across at least these two centers for the  
2 last 15 years. Although the effects are relatively small in  
3 absolute number of individuals annually, thrombocytopenia is  
4 important because it results in serious clinical events,  
5 such as bleeding and chemotherapy delay. These events lead  
6 to increased morbidity and occasional mortality.

7 (Slide)

8 Given the severity of these events, it is  
9 important to identify factors that may predispose to their  
10 development. Among the most important is the platelet count  
11 nadir.

12 As demonstrated in our studies, the risk of  
13 bleeding or chemotherapy delay increases as the nadir of  
14 platelets decreases. Only 9 percent of cycles, demonstrated  
15 here, with a nadir between 40,000 and 50,000 were  
16 complicated by either chemotherapy delay or bleeding. That  
17 is the sum of 4 percent with major bleeding, 4 percent with  
18 chemotherapy delay and 1 percent with minor bleeding,  
19 compared to 32 percent total, right here, during cycles with  
20 a nadir less than 5000, obtained by summing a 15 percent  
21 incidence of minor bleeding, here, 10 percent of major  
22 bleeding and 7 percent incidence of chemotherapy delay.

23 (Slide)

24 This finding is not unique to the patients at M.D.  
25 Anderson. A similar pattern was observed in a study of

1 solid tumor and lymphoma patients from the Kansas City V.A.  
2 Hospital, conducted in 1978. Bleeding was significantly  
3 more common in cycles during which the platelet count fell  
4 below 10,000. Although the overall rate of bleeding in our  
5 patients was a bit lower than in the Kansas City V.A. study,  
6 the same general pattern was observed. The risk was lower  
7 in patients with a nadir greater than 20,000, illustrated  
8 here; significantly higher in those with a nadir less than  
9 10,000, in the bottom line; and was intermediate in those  
10 whose nadir fell between 10,000 to 20,000, illustrated here.

11

12 (Slide)

13 Since the introduction and widespread use of  
14 granulocyte growth factors thrombocytopenia is among the  
15 most common causes of a delay in subsequent cycle of  
16 chemotherapy. In our study, 87 percent of these delays,  
17 those illustrated here, were related at least in part to  
18 profound thrombocytopenia although there were other  
19 contributing factors, such as infection, illustrated here,  
20 and granulocytopenia in this group.

21 (Slide)

22 The threshold for prophylaxis of bleeding related  
23 to chemotherapy-induced thrombocytopenia has been the  
24 subject of some controversy in recent years. In contrast to  
25 the 20,000 platelet threshold that is often used in oncology

1 practice, some authors now suggest that a threshold of  
2 10,000 or even 5000 may be more appropriate. Despite this  
3 controversy, a threshold of 15,000 to 20,000 or more  
4 continues to be employed at M.D. Anderson in over 90 percent  
5 of cases, illustrated here, and those patients that receive  
6 platelet transfusions.

7 (Slide)

8 Development of bleeding is a multifactorial  
9 phenomenon. So it is necessary to account for the influence  
10 of these factors when measuring effectiveness of bleeding  
11 prophylaxis. We used logistic regression to develop a model  
12 of the risk of bleeding during thrombocytopenia. This model  
13 suggests a highly protective effect of maintaining higher  
14 platelet counts, illustrated here by a highly significant  
15 odds ratio of 0.15 for platelet transfusion prophylaxis.

16 This protective effect probably also reduces the  
17 incidence of bleeding and chemotherapy delay below that  
18 which would be observed if prophylaxis were not used.

19 (Slide)

20 In summary, thrombocytopenia is a clinically  
21 significant problem in that it occurs 20-25 percent of  
22 chemotherapy cycles in adult solid tumor patients. It  
23 results in bleeding in 10-15 percent of cycles. It causes a  
24 delay in a subsequent chemotherapy cycle in additional 6  
25 percent of cycles. Decreasing platelet counts are

1 associated with an increased risk of these events, and  
2 prophylactic platelet transfusions have been used, usually  
3 at a threshold of 20,000 platelets to avoid serious clinical  
4 outcomes by avoiding low platelet count nadirs.

5 Our observational data suggest that the practice  
6 of using transfusion to avoid low platelet counts is  
7 widespread, and generally successful since it results in a  
8 statistically significant protective effect.

9 Our results correspond closely with those reported  
10 previously, and the consistency of the results underscores  
11 the broad generality of our findings, and provides strong  
12 evidence that interventions that reduced the depth of  
13 thrombocytopenia will also reduce the risk of serious  
14 clinical outcomes.

15 (Slide)

16 Dr. Ken Anderson will now discuss the risks  
17 associated with platelet transfusion.

18 **Risks Associated with Platelet Transfusion,**

19 **Kenneth Anderson, M.D.**

20 (Slide)

21 DR. ANDERSON: Thank you very much. As was  
22 mentioned, for the next few minutes I am going to provide a  
23 framework for you in your evaluation of interleukin-11 in  
24 terms of the risks that are attendant to current platelet  
25 transfusion against which one can compare alternative

1 strategies, such as interleukin-11, which you are going to  
2 be evaluating shortly.

3 (Slide)

4 On this slide I will remind you, as Dr. Kaye has  
5 already said, that the risk of hemorrhage is related to  
6 platelet count, and we have known this for over 40 years.

7 This classic study from Dr. Freinrich reminds us  
8 that when one starts with 50,000 platelets/mcL and moves  
9 towards the origin and zero platelet count, the risk of  
10 clinical hemorrhage increases. It was shown also nearly 40  
11 years ago that when one transfuses homologous platelets from  
12 the untreated line to the transfused line on this slide, one  
13 can in so doing increase the attendant risk of hemorrhage.

14 Now, over the ensuing forty years there have been  
15 multiple studies of the use of prophylactic versus  
16 therapeutic platelets and, in particular, the threshold at  
17 which it would be most appropriate to transfuse platelets  
18 prophylactically. The early studies were confounded because  
19 the patients were on aspirin, and subsequent studies have  
20 been heterogeneous.

21 (Slide)

22 So on this slide is part of the Transfusion  
23 Practice Committee of the American Association of Blood  
24 Banks. We had the chance recently to survey institutional  
25 members of that organization as to current transfusion

1 practice.

2           On this slide we see the results of what was  
3 determined when we asked institutional members of the AABB  
4 whether they transfused to pediatric recipients or adult  
5 recipients either prophylactic transfusions, defined as  
6 transfusions to prevent bleeding, or therapeutic  
7 transfusions, defined as transfusion only after bleeding had  
8 developed. You can see on this slide that approximately 60-  
9 70 percent of institutions in the United States provide  
10 prophylactic transfusions.

11           (Slide)

12           This slide goes further. If you, in fact, did  
13 provide prophylactic transfusions, what was the trigger or  
14 threshold that was utilized for transfusion?

15           The first point here, both in children and adult  
16 recipients, is that there is marked heterogeneity, but the  
17 most common trigger or threshold utilized was 20,000  
18 platelets/mcL, used here 55-60 percent of the time. I point  
19 that out because that is the threshold that was utilized for  
20 transfusion in the studies of IL-11, about which you will  
21 hear shortly.

22           (Slide)

23           This slide is also from that Transfusion Practice  
24 survey. It, in fact, makes the point that when one  
25 transfuses pooled random donor concentrates, one transfusion

1 exposes your recipient patient to multiple homologous donors  
2 per transfusion episode. As part of the survey, this  
3 depicts the fact that at academic institutions it is common  
4 to pool 6 different donors' platelets for a single  
5 transfusion, whereas, out in the community it is more common  
6 to use more donors' platelets transfused in a single  
7 episode.

8 I think we need to emphasize this because one of  
9 the major advantages of using an alternative to platelet  
10 transfusion would be to minimize homologous donor exposure  
11 and the immunologic attendant infectious risks of which I  
12 will speak shortly.

13 (Slide)

14 On this slide, another alternative for avoiding  
15 homologous donor exposure and the immunologic and infectious  
16 risks would be to limit the number of donor exposures per  
17 transfusion episode. I wanted to include this one slide to  
18 just mention and provide for you a framework that says that  
19 in the United States the number of platelet transfusions  
20 have been increased, and this is data that has now been  
21 published and it is old but the trend continues.

22 Importantly, of the platelets that are transfused, the  
23 relative fraction of platelets that are not pooled random  
24 donor exposures, that is, that do not expose the recipient  
25 to multiple donor antigens and infectious risk per episode

1 of transfusion but the number of platelets that are  
2 transfused from single donors, and are called single-donor  
3 apheresis platelets, grew to nearly half the platelets  
4 transfused by 1992. Again, we think this is a reflection of  
5 trying to minimize the risks of donor exposures associated  
6 with transfusion.

7 (Slide)

8 On this slide I would like to review with you the  
9 two categories of risks of transfusion that are most common.  
10 The first is immunohematologic and the second is infectious.

11 (Slide)

12 This slide displays for us the immunohematologic  
13 complications of transfusions that I would like to mention  
14 briefly. The first is febrile transfusion reactions, and  
15 these are due to the contaminating white cells that are  
16 within transfused platelets. Traditionally it was thought  
17 that these were due to antibodies in the recipients directed  
18 to the contaminating leukocytes within platelets. But more  
19 recently there is data that cytokines, such as interleukin-  
20 1, IL-6, IL-8 or other cytokines released from the white  
21 cells with storage of the platelets mediate these reactions.

22

23 The second category of immunologic complications  
24 of platelet transfusion is alloimmunization, and that is the  
25 development in the recipient of antibodies to class 1 HLA

1 antibodies that are expressed on white cells and on the cell  
2 surface of platelets transfused. You will all remember that  
3 for a long time now we have known that the development of  
4 these antibodies is associated with refractoriness to  
5 transfusion and requires special therapy.

6           Infections can be transmitted, in this case I am  
7 particularly referring to the transmission of cytomegalo-  
8 virus or other viruses that might be cytopathic for the  
9 contaminating leukocytes that are attendant to platelet  
10 transfusion.

11           Graft versus host disease is a complication of  
12 platelet transfusion related again to the contaminating  
13 lymphocytes. It is a fatal complication of transfusion and  
14 requires the additional cost expense and logistical concerns  
15 of gamma irradiating the product before transfusing patients  
16 who are at risk for this complication.

17           Finally, there is a building literature that by  
18 transfusing homologous platelets one can, in so doing,  
19 immunosuppress recipients, and the clinical sequelae that  
20 have been reported to date are increased perioperative  
21 infection rate and increased cancer recurrence rate,  
22 although this remains controversial at the present time.

23           (Slide)

24           More importantly perhaps, on this slide is the  
25 point that there are multiple new reactions to platelets

1 that are being recognized each year. I have included this  
2 slide to remind you of one of them. Again, as part of the  
3 Transfusion Practice Committee last year we had the  
4 opportunity to study what appears to be a new kind of  
5 reaction to platelet transfusion, characterized by  
6 hypotension and respiratory distress. In this case, Heather  
7 Hume and colleagues noted that of these 17 reactions, most  
8 of them occurred quite rapidly upon the beginning of  
9 platelet transfusion. They were characterized, as I  
10 mentioned, by respiratory distress. They dissolved rapidly  
11 with stopping the transfusion and, importantly, they seemed  
12 to be associated with filtration over a negative filter.  
13 There is a literature building now that cytokines may be  
14 released in this setting, such as bradykinin which may be  
15 implicated in such hypotensive reactions.

16           The point here is that we need to be on the  
17 lookout, and there are new reactions to homologous platelet  
18 transfusions being recognized each year.

19           (Slide)

20           On this slide then are the infectious  
21 complications that I just want to close with. You all know  
22 this very well. It has been a concern of the FDA and the  
23 AABB and other agencies, and joint strategies have been  
24 quite effective at limiting the infectious risks of  
25 transfusion.

1           You know that the viral risks are mainly HIV type  
2 1 and 2, hepatitis B and C, HTLV-1 and cytomegalovirus.

3           For today's discussion, in terms of bacterial  
4 contamination of platelets, it is a major concern and  
5 remains so. The reason we think this is particularly unique  
6 to platelets is that they are harvested and stored for five  
7 days at room temperature in plasma on a rotator, which are  
8 ideal conditions for the growth of both gram-positive and  
9 gram-negative organisms.

10           Other infections agents you know well, like the  
11 Creutzfeldt-Jacob disease, parasites, etc. There is a  
12 program that has been developed for donor screening as well  
13 as serologic testing for a variety of these agents which is  
14 quite effective at decreasing the risk of homologous  
15 transfusion. But with these strategies the approximate  
16 risks of homologous transfusion are displayed on the next  
17 slide.

18           (Slide)

19           They are as follows: In fact, the risk of HIV-1  
20 when we were screening just utilizing antibodies to HIV-1  
21 was something on the order of 1 in 400,000 to 1 in 6000,000  
22 per unit risk. The risk of hepatitis B was on the order of  
23 1 in 200,000. Hepatitis C was on the order of 1 in 2000 to  
24 1 in 6000, perhaps a little less at the present time. But,  
25 again to emphasize, bacteria, particularly in platelets, is

1 on the order of 1 in 2000 to 1 in 12,000 per unit risk  
2 exposure, which is still quite high.

3 (Slide)

4 The final slide I have illustrates the concern  
5 with which we, as a society and FDA in particular, have in  
6 terms of infectious risks of transfusion. The FDA and other  
7 agencies have mandated that we, in the blood banking  
8 community, not only screen donors with questionnaire with  
9 serologic testing for antibodies, but now with HIV p24  
10 antigen testing each and every donor, each and every time.

11 The rationale behind this was obvious, that the  
12 antigen positivity precedes the development of serologic  
13 response in an infected individual, and the strategy or the  
14 rationale was to allow for identifying 5 to 10 HIV-infected  
15 donors who would have been antigen positive but antibody  
16 negative and be in the window period there for 5 to 10 such  
17 donors out of 15 million donors annually in the United  
18 States. This maneuver is estimated to cost ten million  
19 dollars for each HIV transmission that is prevented. I  
20 wanted to include this just to highlight the extent to which  
21 we, as a society, are willing to go to avoid any infectious  
22 risk of transfusion.

23 So in closing, what I have attempted to do is  
24 provide a framework for the 20,000/mcL platelet threshold  
25 that was used in the studies of interleukin-11, and also a

1 framework for when you evaluate the efficacy of this product  
2 and also the risks of this product, they need to be compared  
3 with the infectious and the immunohematologic risks of  
4 homologous platelet transfusion.

5 (Slide)

6 It is now my pleasure to introduce Dr. James Kaye,  
7 who is the director of clinical research at Genetics  
8 Institute. He will tell you of the clinical studies of  
9 interleukin-11.

10 **Review of Neumega Effectiveness and Safety Data,**

11 **James Kaye, M.D.**

12 DR. KAYE: Thank you, Dr. Anderson. Dr. Vose and  
13 members of the Committee, it is my privilege this morning to  
14 summarize the clinical data that support the licensure of  
15 Neumega for treating chemotherapy-induced thrombocytopenia.

16 (Slide)

17 First I will present an overview of the clinical  
18 program. Then I will highlight key pharmacokinetics and  
19 Phase I study results. Next I will discuss the efficacy  
20 results from two randomized, placebo-controlled trials in  
21 patients receiving chemotherapy, study 9308, in which  
22 patients had previously experienced thrombocytopenia, and  
23 study 9416, a primary prophylaxis study in women with breast  
24 cancer. Then I will review the safety data, focusing on the  
25 two pivotal studies. After that I will mention an ongoing

1 pediatric study and our dosing recommendation for children.  
2 Finally, I will conclude with the main points regarding the  
3 efficacy and safety of Neumega and the proposed indication.

4 (Slide)

5 Ten studies of Neumega were submitted to FDA in  
6 our application. These include a Phase I study in women  
7 with breast cancer; the 2 randomized chemotherapy studies; 1  
8 ongoing study in children undergoing chemotherapy; 2 studies  
9 in patients receiving high-dose chemotherapy with stem cell  
10 support; and 4 studies of pharmacokinetics and  
11 pharmacodynamics in normal volunteers.

12 In the clinical program 393 subjects were studied  
13 submitted in supported of the application. Data on 102  
14 additional patients participating in an ongoing randomized  
15 chemotherapy study were also recently submitted in a routine  
16 safety update, bringing the total number of subjects to  
17 nearly 500.

18 This clinical program has given us enough  
19 experience to have a well-developed understanding of both  
20 Neumega's efficacy and its safety profile.

21 (Slide)

22 In the normal volunteer study the bioavailability  
23 of Neumega after subcutaneous injection was more than 80  
24 percent compared with IV dosing. This enables the use of  
25 subcutaneous dosing clinically.

1           The pharmacokinetics of Neumega are absorption  
2 rate limited. The mean residence time after subcutaneous  
3 injection is approximately 10 hours. Because the kinetics  
4 are absorption limited, this is a better measure of the  
5 drug's time course in the body than half-life. Finally, the  
6 pharmacokinetics of Neumega after subcutaneous dosing are  
7 similar in men and women.

8           (Slide)

9           Now I will summarize the Phase I study. This was  
10 an open-label dose escalation study in women with breast  
11 cancer. Patients were entered in groups of 3, treated  
12 initially with Neumega in escalating doses from 10-100  
13 mcg/kg subcutaneously once daily for 14 days before  
14 receiving any chemotherapy. There was then a 14-day period  
15 without treatment.

16           This was followed by up to 4 therapy cycles in  
17 which patients received cyclophosphamide and doxorubicin, at  
18 the doses shown, followed by Neumega for 12 days on each  
19 cycle at the same dose each patient received in the pre-  
20 chemotherapy cycle.

21           (Slide)

22           In this study Neumega increased platelet  
23 production in all patients treated at doses of 10-75 mcg/kg.  
24 The increases were dose related, with the patients in the  
25 highest dose group having a peak platelet count that was on

1 average approximately 3 times their baseline platelet count.

2

3 Platelet nadirs in the first 2 therapy cycles were  
4 higher among patients treated with doses of 25 mcg/kg or  
5 more compared with the 10 mcg/kg cohort and historical  
6 control patients. Treatment was well tolerated at doses up  
7 to 50 mcg/kg.

8 (Slide)

9 The most common adverse events were anemia and  
10 mild edema. I will come back to these in the discussion on  
11 safety.

12 Our conclusion from this study was that Neumega  
13 doses of 25 and 50 mcg/kg should be tested further in  
14 placebo-controlled studies.

15 (Slide)

16 I will turn now to a description of the two  
17 randomized chemotherapy studies and their results. Listed  
18 here are several important features common to both of the  
19 randomized chemotherapy studies. All enrolled patients were  
20 at high risk for developing severe chemotherapy-induced  
21 thrombocytopenia, defined in these trials as a platelet  
22 count nadir of 20,000 cells/mcL or lower.

23 The primary endpoint in each study was whether or  
24 not patients avoided platelet transfusions during their  
25 required randomized cycle or cycles. The number of platelet

1 transfusions in each group was an important secondary  
2 endpoint.

3 Another key element of both studies is that the  
4 protocol did not allow investigators to reduce chemotherapy  
5 doses, as is often done in subsequent cycles after a patient  
6 becomes thrombocytopenic.

7 In both studies platelet counts were checked 3  
8 times weekly and daily if the most recent count was less  
9 than 50,000. Finally, platelet transfusions were given in  
10 both studies for a platelet count of 20,000 cells/mcL or  
11 lower.

12 (Slide)

13 Study 9308 was a test of the efficacy and safety  
14 of Neumega in patients who had already experienced  
15 chemotherapy-induced thrombocytopenia.

16 (Slide)

17 The objectives of this study were to compare the  
18 efficacy of each of 2 doses of Neumega, 25 and 50 mcg/kg, to  
19 placebo, and prevent the chemotherapy-induced  
20 thrombocytopenia during the masked study cycle, and to  
21 assess its safety during up to 2 cycles of treatment.

22 (Slide)

23 This was a randomized, masked, placebo-controlled  
24 study with each patient assigned to 1 of the 3 treatment  
25 groups. There was 1 masked cycle of treatment. Patients

1 were already receiving chemotherapy, and in this study they  
2 had to continue the same doses and schedule of the  
3 chemotherapy they were on during the cycle just before study  
4 entry.

5           We stratified for the amount of prior treatment  
6 patients received, and also the number of days over which  
7 their particular chemotherapy regimen was administered.  
8 Patients were allowed to use G-CSF if they had used it in  
9 the previous cycle. Routine safety monitoring included  
10 chemistries, chest x-rays, EKGs and Holter monitoring which  
11 was added to the protocol near the end of the study. Holters  
12 were done on the first and tenth day of study drug. There  
13 was also one optional open-label cycle of treatment.

14           (Slide)

15           The patients in this study had solid tumors or  
16 lymphoma. They had all received at least one platelet  
17 transfusion for a count of 20,000 or lower in the cycle just  
18 before entry. They had to have adequate hematologic  
19 recovery before entering the study.

20           (Slide)

21           The treatment schedule is shown here. In this  
22 example, the patients received a chemotherapy regimen given  
23 over 3 days. Neumega or placebo was started after  
24 chemotherapy and continued for 14 days minimum. If the  
25 patient's platelet count had recovered to 100,000 by that

1 time, treatment was stopped. But if the platelet count was  
2 still below 100,000, treatment was continued for another 7  
3 days until the platelet count recovered to that level.

4 (Slide)

5 Ninety-three patients were accrued to this study  
6 at 20 investigational sites over a period of 14 months.

7 (Slide)

8 The patients' demographic characteristics are  
9 shown here. The average age was in the mid to late 40s but  
10 with quite a wide range. The study included men and women.  
11 About 4/5 of the patients were white and the rest were  
12 African American, Latino or from other minority groups.

13 (Slide)

14 Most of the patients in the study had relatively  
15 good performance status, ECOG 0 or 1. Cancer diagnoses in  
16 general were evenly distributed among the groups. The only  
17 notable imbalance is that there were more patients with non-  
18 Hodgkin's lymphoma in the 50 mcg/kg group than in the other  
19 groups. However, this imbalance did not affect the primary  
20 efficacy outcome. The "other" category at the bottom, here,  
21 includes patients with sarcomas, testicular cancer and a  
22 variety of other malignancies.

23 (Slide)

24 These patients were receiving 24 different  
25 chemotherapy regimens. The most common regimens were dose-

1 intense cyclophosphamide, etoposide and cisplatin;  
2 ifosfomide, carboplatin and etoposide; Cytosan and  
3 adriamycin; carboplatin as a single agent; the DHAB regimen,  
4 MAID and so on. The other regimens listed were each used in  
5 3 patients or fewer.

6 (Slide)

7 The results were analyzed both in an intent-to-  
8 treat population and in a prospectively defined evaluable  
9 subgroup. All patients randomized were included in the ITT  
10 analysis, and all patients who were treated and who complied  
11 with the rules of the protocol were included in the ESG.

12 (Slide)

13 A successful outcome was defined in this study as  
14 avoiding platelet transfusions during the masked cycle. Let  
15 me point out that this was an extremely challenging endpoint  
16 in this patient population, given that they had already  
17 required platelet transfusions in a previous cycle, and  
18 chemotherapy-induced thrombocytopenia tends only to get  
19 worse in subsequent cycles when chemotherapy doses are  
20 maintained. Any patient who was transfused was considered a  
21 failure in the efficacy analysis.

22 We were conservative in our analysis in that we  
23 did not make any assumptions about missing values. We  
24 assigned outcomes according to whether each patient was  
25 actually transfused or not because, although our endpoint

1 was closely tied to the nadir platelet count through the  
2 transfusion policy, we wanted to focus on a clinically  
3 meaningful event rather than a blood count per se.

4           The rules were established before the end of the  
5 study while treatment assignments were still masked. They  
6 were written in the rule book and were not changed after the  
7 randomization code was broken.

8           (Slide)

9           As you can see, there was a highly significant ITT  
10 result for the 50 mcg/kg dosage. Specifically, in the  
11 placebo group only 2/30 patients, or 7 percent, had a  
12 successful outcome, whereas, in the 50 mcg/kg group 12/32  
13 patients, or 38 percent, avoided platelet transfusions. The  
14 absolute difference in success rate between the 50 mcg/kg  
15 and placebo groups is 31 percent. This difference has a p  
16 value of 0.005.

17           The success rate in the 25 mcg/kg group was 6.31,  
18 or 19 percent. This rate is not significantly different  
19 from placebo but does contribute to a dose-response trend.

20           (Slide)

21           For the evaluable group analysis we excluded 11  
22 patients identified in the rule book before the study was  
23 unmasked. You can see that they were distributed across all  
24 3 treatment groups. Five patients withdrew consent to  
25 participate before started the masked study drug, and 6

1 patients had major protocol violations. Two of these had  
2 significant chemotherapy dose reductions, greater than 10  
3 percent; 3 had platelet transfusion violations; and 1  
4 patient was ineligible because of a chronically low platelet  
5 count.

6 (Slide)

7 Again, the ESG analysis showed a very significant  
8 result for the 50 mcg/kg dosage. Only 1/27 patients, or 4  
9 percent, in the placebo group had a successful outcome  
10 compared with 8/27 patients, or 30 percent, in the 50 mcg/kg  
11 group. The p value for this difference is 0.02. The  
12 outcome in the 25 mcg/kg group was again intermediate  
13 between placebo and 50 mcg/kg, showing a dose response.

14 (Slide)

15 This figure shows the platelet nadirs for the 14  
16 patients in ESG who avoided platelet transfusions. The 50  
17 mcg/kg patients, shown on the right, had nadirs ranging from  
18 26,000 up to nearly 80,000. The 1 patient in the placebo  
19 group who had a successful outcome was quite unusual in that  
20 this patient developed extreme thrombocytosis during the  
21 study, a platelet count more than 2 million. She developed  
22 bilateral bronchopneumonia and died of progressive  
23 metastatic lung cancer several weeks later.

24 Notice that 3/5 patients with a successful outcome  
25 in the 25 mcg/kg group had nadirs just above 20,000, again

1 suggesting a dose-response effect.

2 (Slide)

3 This table shows that the patients treated with  
4 Neumega received fewer platelet transfusions than those in  
5 the placebo group. This was an important additional  
6 endpoint. The analysis shown here was planned in the study  
7 protocol.

8 Please note that the term platelet transfusion  
9 here refers to platelet transfusion events, not units of  
10 platelets. As Dr. Anderson mentioned, the platelet  
11 transfusion event consists of either 1 bag of single donor  
12 apheresis platelets or usually 4-8 units of random donor  
13 platelets.

14 In the placebo group patients had an average of  
15 3.4 platelet transfusions, with a range up to 17, whereas,  
16 in the Neumega 50 mcg/kg group the average was 2.2 and the  
17 upper end of the range was 9. The difference between the  
18 placebo and 50 mcg/kg groups is nearly significant by the  
19 Wilcoxon rank sum test, with a p value of 0.07. Since the  
20 number of platelet transfusions was a secondary endpoint and  
21 the study was not deliberately powered to show a difference  
22 here, this is an impressive result.

23 (Slide)

24 This frequency histogram of platelet transfusion  
25 data illustrates that the benefit of Neumega treatment is

1 not limited to the patients who avoided transfusion. For  
2 clarity, only the placebo and 50 mcg/kg groups are shown.

3 Notice that there are more patients with no  
4 transfusions in the Neumega group than in the placebo group.  
5 This is the primary efficacy result. Also note that there  
6 are fewer patients with 3 or more transfusions in the  
7 Neumega group than the placebo group. So what you are  
8 really seeing is that the whole Neumega group distribution  
9 has shifted to the left with lower numbers of transfusions.

10 So in summary, we have shown a highly significant  
11 result in this study, indicating that Neumega 50 mcg/kg is  
12 effective in preventing the need for platelet transfusions  
13 in patients who have already experienced severe  
14 chemotherapy-induced thrombocytopenia, and that the benefit  
15 of reduced platelet transfusion requirements extended to  
16 patients throughout the Neumega group even if they did not  
17 avoid platelet transfusions completely.

18 (Slide)

19 Now I would like to turn to the efficacy data from  
20 the second pivotal trial. Study 9416 was a test of Neumega  
21 in patients with breast cancer during treatment with 2  
22 cycles of cyclophosphamide and doxorubicin.

23 (Slide)

24 The objectives of this study were to compare the  
25 efficacy of Neumega to placebo in preventing platelet

1 transfusions during 2 cycles of dose-intense chemotherapy,  
2 and to assess the safety during a total of 6 courses of  
3 treatment.

4 (Slide)

5 Study 9416 was also a randomized, masked, placebo-  
6 controlled study. The active treatment group received  
7 Neumega at a dose of 50 mcg/kg. Patients received 2 cycles  
8 of masked treatment, with no crossover between cycles.  
9 Chemotherapy was given at 21-28-day intervals.

10 Importantly, we stratified prospectively in the  
11 randomization by whether or not patients had received any  
12 prior chemotherapy and also by investigational site. All  
13 patients received G-CSF and prophylactic ciprofloxacin  
14 throughout the study. Routine safety monitoring was similar  
15 to that in study 9308. Holter monitoring was done on the  
16 first day of study drug and again on the tenth day in both  
17 cycles. In this study there were 4 optional open-label  
18 cycles.

19 (Slide)

20 Eligible patients had breast cancer that was Stage  
21 2 with 4 or more lymph nodes involved, or Stage 3 or 4.  
22 Other standard eligibility criteria are listed.

23 (Slide)

24 The dosing schedule is shown here. Chemotherapy  
25 was given on day 1 of each cycle. Cyclophosphamide was

1 given at a dose of 3200 mg/M<sup>2</sup> and doxorubicin at a dose of  
2 75 mg/M<sup>2</sup>. Neumega or placebo was started the next day and  
3 continued for 10 days. If the patient's platelet count had  
4 recovered to 50,000 or higher after 10 days of treatment,  
5 that is by day 11, treatment was stopped. However, if the  
6 platelet count was below 50,000 treatment was continued 1  
7 for one more week.

8 (Slide)

9 Seventy-seven patients were accrued to this study  
10 at 14 investigational sites over 1 year. Shown here are the  
11 demographic characteristics of the 77 women entered into the  
12 study. As in the first study, the mean age was in the mid-  
13 40s and again about 1/5 of the patients were minorities.  
14 Stage of disease was balanced between the treatment groups,  
15 except that there were about 40 percent more patients with  
16 Stage 4 disease in the Neumega group than the placebo group.

17

18 (Slide)

19 Most of the patients had excellent performance  
20 status, and about 1/3 patients in each group had received  
21 some prior chemotherapy.

22 (Slide)

23 The efficacy analysis for this study was also done  
24 on both an ITT population and on a prospectively defined  
25 evaluable subgroup. The ITT analysis included all patients

1 randomized. The ESG analysis was done on the patients who  
2 were treated in both of the required study cycles and who  
3 complied with the protocol. But also included in the ESG  
4 were patients transfused in cycle 1 who discontinued before  
5 cycle 2 and who obviously would have been failures for the 2  
6 cycles overall.

7 (Slide)

8 This was a 2-cycle study. So a successful outcome  
9 was prospectively defined as avoiding platelet transfusions  
10 in both cycles. As a footnote, I should mention that the  
11 original primary endpoint of the study was reduction in the  
12 number of platelet transfusions but early on we noticed that  
13 there were more patients than expected who were completing  
14 the study without transfusions. So the endpoint was  
15 modified to avoiding platelet transfusions altogether, which  
16 is even more clinically meaningful. I want to emphasize  
17 that this was based on a review of only masked data. We  
18 discussed the change with Dr. Steffen, our FDA medical  
19 reviewer, and formally amended the protocol. The original  
20 primary endpoint was retained as an important secondary  
21 endpoint.

22 Patients were considered to have failed if they  
23 had any platelet transfusions in either cycle or if they  
24 were not treated in both cycles for any reason, and 13  
25 patients fell into this category. They were considered to

1 have failed in the ITT analysis because they were not  
2 treated in cycle 2. One of these 13 patients died during  
3 cycle 1 and the other 12 discontinued before starting cycle  
4 2. That is, the 13 patients includes 5 who were transfused  
5 in cycle 1 and discontinued and 8 who were not transfused in  
6 cycle 1 and discontinued.

7           Let me comment briefly on the decision to classify  
8 all 13 of these patients who discontinued before cycle 2 as  
9 failures in the ITT analysis whether or not they had been  
10 transfused in cycle 1. We thought that this would be the  
11 most conservative and, therefore, the most reasonable way to  
12 handle the dropouts. We reasoned that if Neumega-treated  
13 patients were discontinuing preferentially because of  
14 adverse events, it would be impossible to defend calling the  
15 patients who dropped out successes. This decision, again,  
16 was made while the study was masked, and all the analysis  
17 rules were documented and submitted to the FDA with the  
18 final study report.

19           (Slide)

20           In the ITT analysis there was a statistically  
21 significant difference between treatment groups. Only  
22 15/37, or 41 percent, of the placebo group avoided  
23 transfusions compared to 27/40 patients, or 68 percent, in  
24 the Neumega group. The difference in success rate is 27  
25 percent. This difference is significant, with a p value of

1 0.02.

2 (Slide)

3 When the data for the ITT group are analyzed  
4 taking into account the prospective stratification factor of  
5 prior chemotherapy the results are even more significant.  
6 Among the patients with no prior chemotherapy, 52 percent in  
7 the placebo group avoided transfusions compared to 70  
8 percent in the Neumega group. Among patients with any prior  
9 chemotherapy the difference is even more pronounced, with  
10 only 10 percent of the placebo patients avoiding  
11 transfusions compared with 62 percent in the Neumega group.  
12 The p value for the influence of Neumega treatment across  
13 both strata by the Mantel-Haenzel test is 0.01. This  
14 analysis shows how the efficacy of Neumega was somewhat  
15 diluted in this study by inclusion of patients with  
16 relatively good prognosis, those with no prior chemotherapy  
17 who made up about two-thirds of the study population.

18 (Slide)

19 For the ESG analysis we excluded the patients  
20 whose outcomes were uncertain for any reason. There were 10  
21 such patients. As I mentioned, 8/10 discontinued before  
22 cycle 2 without having been transfused in cycle 1. the  
23 other 5/13 dropouts were transfused in cycle 1 and are  
24 included in both the ESG and the ITT analyses as failures.  
25 The other 2 patients had major protocol violations relating

1 to platelet count monitoring or the transfusion policy.

2 (Slide)

3 This shows the primary efficacy result in the ESG.

4 Only 14/30 patients, or 37 percent, avoided platelet

5 transfusions in the placebo group compared with 26/37

6 patients, or 70 percent, in the Neumega group. The p value

7 for this difference is 0.08.

8 So while the difference between the treatment

9 groups did not quite reach significance in the ESG, there is

10 a clear trend that supports the efficacy seen in the intent-

11 to-treat analysis.

12 (Slide)

13 Moreover, the stratified ESG analysis shows a

14 statistically significant result. Among the patients with

15 no prior therapy, 59 percent in the placebo group avoided

16 transfusions compared to 73 percent in the Neumega group.

17 Among those with any prior chemotherapy, only 12 percent

18 avoided transfusions in the placebo group compared with 64

19 percent in the Neumega group. As in the stratified ITT

20 analysis, the observed difference in success rate is greater

21 among the patients who had prior chemotherapy. The absolute

22 difference in success rate between the treatment groups in

23 this stratum is over 50 percent. The p value for the effect

24 of Neumega in the stratified ESG analysis is 0.04.

25 (Slide)

1           Later this morning Dr. Steffen is going to present  
2 several sensitivity analyses of the primary efficacy result  
3 in this study. We recently performed another analysis which  
4 was suggested by our FDA statistical reviewer, Dr. Terry  
5 Niemann, that shows Neumega was effective in this study.

6           The Kaplan-Meier method was used to estimate the  
7 proportion of patients who avoided platelet transfusion over  
8 2 cycles in each treatment group within each of the  
9 prospectively defined prior chemotherapy strata.

10           This method incorporates into the estimate the  
11 notion of time to first transfusion, cycle 1 or cycle 2. I  
12 should say that this table is not presented in either of  
13 your briefing books but our FDA reviewers and we have agreed  
14 that it is the most appropriate sensitivity analysis.

15           The 8 patients who discontinued without having  
16 been transfused are censored after cycle 1. They are  
17 considered at risk of being transfused in cycle 1 but not in  
18 cycle 2. The result of this analysis shows that when  
19 adjusted for the influence of prior chemotherapy the overall  
20 effect of Neumega on the proportion of patients who avoided  
21 transfusions over 2 cycles was significant, with a p value  
22 of 0.04.

23           Note that patients on Neumega did better than  
24 those on placebo in both strata but, again, the difference  
25 is more prominent among the patients who had prior

1 chemotherapy. So this study provides additional valuable  
2 information by suggesting that when patients have not  
3 already required platelet transfusions in a previous cycle,  
4 prior chemotherapy is a marker for which patients are most  
5 likely to benefit from Neumega treatment.

6           As for the other prospectively defined  
7 stratification factor, investigational site, we found that  
8 among the 10 centers that enrolled at least one patient in  
9 each treatment group the Neumega group did better than the  
10 placebo group in all but one center, and at that center the  
11 outcomes were the same. So there was no center in which the  
12 placebo group did better than the Neumega group. This  
13 further supports the main efficacy result in this study  
14 since these findings would have been very unlikely to occur  
15 by chance.

16           (Slide)

17           As I mentioned, the original primary endpoint for  
18 this study was the number of platelet transfusions in each  
19 group. Remember that these are platelet transfusion events.  
20 In the placebo group patients were given an average of 2.2  
21 transfusions, with a range up to 18. In the Neumega group  
22 patients required an average of only 0.8 transfusion with a  
23 smaller range, only up to 6. The difference between the  
24 groups in this important additional endpoint is significant  
25 by the Wilcoxon test, with a p value of 0.04.

1           This supports the conclusion that Neumega is  
2 effective not only in preventing platelet transfusions but  
3 also in reducing platelet transfusion requirements in  
4 general.

5           (Slide)

6           This conclusion is illustrated even more clearly  
7 on this slide which shows the cumulative percentage of  
8 patients receiving a given number of platelet transfusions  
9 or fewer. At zero, you can see that 70 percent of the  
10 Neumega patients had no transfusions compared with only 47  
11 percent of the placebo patients. Again, this graphically  
12 represents the primary efficacy endpoint.

13           As one follows the curves into the region where  
14 there are patients who required some transfusions, you can  
15 see that there are always more in the Neumega patients than  
16 placebo patients requiring a given number of transfusions or  
17 fewer.

18           For example, nearly 85 percent of the Neumega  
19 patients required only 0 or 1 transfusion as compared to  
20 about 65 percent of the placebo patients. This means that  
21 the remaining 15 percent of the Neumega group required more  
22 than 1 transfusion compared to 35 percent of the placebo  
23 group.

24           Looking at another point on each curve, you can  
25 see that nearly all of the Neumega patients are included in

1 the distribution by the time we get up to 4 or fewer  
2 transfusions compared to only about 80 percent in the  
3 placebo group. So the other 20 percent of the placebo group  
4 is represented in this long tail that extends out to the  
5 right all the way to 18 transfusions.

6 This reinforces the results seen in study 9308 and  
7 provides independent substantiation of the finding that  
8 Neumega benefits the whole group of patients treated, not  
9 just those who avoid transfusions completely.

10 (Slide)

11 Now I would like to turn to the safety data.  
12 First I will discuss adverse events. Then I will review  
13 important hematologic safety endpoints, discuss deaths and  
14 long-term follow up and finally summarize the experience in  
15 treating patients with Neumega over multiple cycles.

16 (Slide)

17 Two hundred and seventy-seven adult oncology  
18 patients have contributed to the safety data base that is  
19 most relevant to the proposed indication. A total of 105  
20 patients in the 5 oncology studies in our submission  
21 received 50 mcg/kg as their assigned treatment.

22 In study 9308 the 29 patients who received a dose  
23 of 25 mcg/kg had a very similar safety profile to those of  
24 the 50 mcg/kg group. So since 50 is the dose recommended  
25 for licensure, the integrated safety analysis I will present

1 focuses on 136 patients from our pivotal studies. These are  
2 the 69 patients randomized to 50 mcg/kg in the 2 studies and  
3 the 67 patients randomized to placebo.

4           Because patients undergoing chemotherapy  
5 experience many adverse events as a result of their disease  
6 or their treatment, we focused the safety analysis on these  
7 136 patients' adverse events. Comparing the placebo and  
8 Neumega groups in the randomized cycles of the two gives the  
9 clearest assessment of Neumega's safety profile in the  
10 proposed indication.

11           (Slide)

12           This slide shows the most common adverse events  
13 that occurred with comparable incidence in the placebo and  
14 Neumega groups among the 136 patients in the core safety  
15 analysis. These events are all commonly associated with  
16 chemotherapy or cancer itself in patients such as those we  
17 studied. Importantly, there was no difference in the  
18 placebo and the Neumega groups in the incidence of  
19 neutropenic fever.

20           (Slide)

21           Only a few adverse events occurred significantly  
22 more often in the Neumega group than in the placebo group.  
23 We used Fisher's Exact Test with a nominal p value of 0.05  
24 to define these events as associated with Neumega treatment.  
25 There were no grade 4 events among these.

1           Edema and dyspnea were the most common associated  
2 adverse events. If one subtracts out the incidences of  
3 these events among the placebo patients, they occurred in an  
4 excess of 44 percent and 26 percent of Neumega-treated  
5 patients respectively. Edema generally occurred during the  
6 second week of treatment, was usually mild and resolved  
7 spontaneously in most cases. Dyspnea was almost always only  
8 exertional, that is, grade 1 or 2 in the WHO toxicity scale  
9 used in these studies.

10           Conjunctival injection typically was not  
11 associated with other symptoms such as itching or burning,  
12 suggesting that it is simply vasodilation rather than  
13 inflammation. I will come back to atrial fibrillation in a  
14 moment.

15           Pleural effusions were usually reported as an  
16 increase in pleural fluid in patients who already had  
17 effusions at the time of study entry. All 7 patients with  
18 pleural effusions were in study 9416. All of them had Stage  
19 4 breast cancer and most had preexisting effusions that  
20 increased on study. So this probably means that patients  
21 who already have pleural effusions are at increased risk for  
22 having them worsen during the Neumega treatment.

23           (Slide)

24           We believe that edema and dyspnea associated with  
25 Neumega treatment were related to fluid retention. Recall

1 that in the Phase I study mild anemia occurred in all  
2 patients during the pre-chemotherapy cycle. We showed in  
3 normal volunteers that anemia induced by Neumega is  
4 dilutional and associated with an increase in plasma volume  
5 rather than a decrease in red cell counts. Neumega-  
6 associated fluid retention is clearly distinguishable from  
7 what has been called the capillary leak syndrome, such as  
8 occurs in patients receiving IL-2, for example.

9           Pulmonary interstitial infiltrates are not  
10 observed on chest x-rays. Hypotension requiring pressers  
11 has not been reported and patients did not develop renal  
12 insufficiency.

13           Finally, it is clear from normal volunteer studies  
14 that the increase in plasma volume caused by Neumega can be  
15 largely explained by renal sodium and water retention. This  
16 fluid retention generally results in mild to moderate  
17 symptoms, if any occur. It is reversible after completing  
18 or discontinuing Neumega dosing and usually does not require  
19 any treatment.

20           Weight gain was only rarely reported as an adverse  
21 event in the oncology studies, and in normal volunteers  
22 Neumega-induced fluid retention has resulted in a net weight  
23 increase of only about 1 kg.

24           (Slide)

25           The incidence of atrial fibrillation or flutter

1 was 10 percent higher in the Neumega group than the placebo  
2 group in our 2 studies. But it is important to recognize  
3 that among the 8 patients who had AF in the Neumega 50  
4 mcg/kg group only 3 had symptomatic clinical events as  
5 compared with 1 who was symptomatic with AF in the placebo  
6 group. Of these 3 patients, 1 had a well-documented history  
7 of AF during the chemotherapy cycle before study entry and 1  
8 had an AF complicating bout of congestive heart failure and  
9 was found to have critical aortic stenosis and subsequently  
10 underwent aortic valve replacement. The other 5 patients  
11 had events that were transient and detected only by Holter  
12 monitoring. These 5 patients with Holter only events did  
13 not require any medical intervention, and of the 7 patients  
14 in the 50 mcg/kg group in these studies who continued to  
15 receive Neumega for varying times after having a bout of AF,  
16 6 did not have any recurrence. None of these 8 patients had  
17 any medical complications.

18 (Slide)

19 Although Neumega causes hemodilution, the mean  
20 number of units of red blood cells transfused was similar  
21 between the two treatment groups in each randomized study.  
22 So the benefit of avoiding blood transfusions is not offset  
23 by any significant increase in red blood cell transfusion  
24 requirements.

25 (Slide)

1           The median duration of severe neutropenia, shown  
2 here for cycle 1 in each study, was nearly identical between  
3 the 2 treatment groups. So Neumega has no adverse effect on  
4 neutrophil recovery. All but 3 of the 136 patients in these  
5 studies were treated with G-CSF. So these results also show  
6 that Neumega does not impair the activity of G-CSF in  
7 accelerating neutrophil recovery.

8           (Slide)

9           This shows one other important hematologic outcome  
10 measure which was analyzed retrospectively, the incidence of  
11 bleeding, and 51 percent of the placebo group had bleeding  
12 events compared with only 28 percent in the Neumega group.  
13 This finding is consistent with the primary efficacy result,  
14 and also provides clinical evidence that platelets produced  
15 in Neumega-treated patients function normally, as predicted  
16 by in vitro observations and preclinical studies.

17           (Slide)

18           I would like to continue the safety presentation  
19 by discussing briefly the patients who died within a month  
20 after starting study drug in their first or second cycle.

21           Patients from all of the completed and ongoing  
22 randomized oncology studies are shown here including 9313,  
23 the study of patients undergoing high-dose chemotherapy with  
24 stem cell support and 9504, the ongoing masked chemotherapy  
25 study.

1           The patient who died in 9416 was a 51-year old  
2 woman with Stage 4 breast cancer. She had pleural effusion  
3 at the time of study entry that worsened on Neumega  
4 treatment in the setting of a staphylococcal catheter  
5 infection. She died on day 5 of treatment. Although the  
6 patient had enlarging pleural effusions, the investigator  
7 considered her death unrelated to study drug because she  
8 clearly also had progression of metastatic breast cancer by  
9 CT scan.

10           In 9504 2 sudden deaths were reported to us in  
11 patients with severe hypokalemia. This protocol originally  
12 included daily administration of a diuretic for patients in  
13 the Neumega group and a placebo form of the diuretic in  
14 those receiving placebo. The independent data monitoring  
15 board for this study, which includes a cardiologist who is  
16 an expert on arrhythmias and a former member of FDA's  
17 Cardioresenal Advisory Committee, reviewed these cases and the  
18 board concluded that the deaths were due to hypokalemia,  
19 which was likely exacerbated by diuretic treatment.  
20 Systematic use of a diuretic is no longer included in this  
21 or any other study protocols. We do not recommend routine  
22 use of a diuretic in patients receiving Neumega, however,  
23 diuretics are not contraindicated, if there is a reason to  
24 use them, as long as fluid status and electrolyte balance  
25 are monitored appropriately.

1           Two other patients in the ongoing study died of  
2 sepsis during a period of neutropenia. These patients'  
3 treatment assignments are still masked because these events  
4 were not considered unexpected in the population of these  
5 patients.

6           All of the deaths in the Neumega-treated patients  
7 in these masked or open-label cycles in all of these studies  
8 were due to cancer progression.

9           (Slide)

10          Tumor response and survival have been evaluated in  
11 all of our randomized studies. There have been no  
12 differences between treatment groups in the proportion of  
13 patients with cancer progression. Shown here, there is also  
14 no difference between the groups in progression-free  
15 survival in the pivotal chemotherapy trials. Overall  
16 survival has also been similar between the groups.

17          So these data confirm Neumega does not adversely  
18 affect the anti-cancer activity of the chemotherapy regimens  
19 these patients are receiving. Indeed, we did not expect to  
20 see any such effect based on preclinical studies.

21          (Slide)

22          Counting both the masked and open-label cycles,  
23 more than 60 patients received two or more cycles of Neumega  
24 in the pivotal studies. In these multiple cycles of  
25 treatment there was no increase in the incidence of adverse

1 events associated with Neumega, nor were there any  
2 significant new adverse events related to Neumega in these  
3 cycles.

4           Red blood cell transfusion requirements did not  
5 increase substantially, nor was there any progressive  
6 failure of neutrophil recovery. Although the data are  
7 anecdotal, more than half of the patients who had three or  
8 more cycles of Neumega in study 9416 avoided platelet  
9 transfusions throughout. So the ability of patients  
10 receiving Neumega to withstand therapy without requiring  
11 platelet transfusions is certainly not limited to one or two  
12 cycles.

13           (Slide)

14           Before concluding, I want to mention one other  
15 ongoing study of Neumega in pediatric patients. This is a  
16 Phase I study of patients receiving ICE chemotherapy of  
17 ifosfamide, carboplatin and etoposide. Twenty-eight  
18 patients have been enrolled. These patients have received  
19 Neumega doses up to 100 mcg/kg for up to 28 days during 2-8  
20 chemotherapy cycles. No serious unexpected adverse events  
21 related to Neumega treatment have been reported in this  
22 study. The safety profile has been similar or better than  
23 that observed in adults. In particular, edema and dyspnea  
24 have each been reported in 25 percent or fewer of patients,  
25 and no patient has had atrial arrhythmia.

1 (Slide)

2 Pharmacokinetic analysis of data from these  
3 patients has shown that the clearance of Neumega is  
4 inversely related to age within this range. The mean  
5 residence time in children is approximately 7 hours compared  
6 to about 10 hours in adults. The data suggest that  
7 pediatric patients receiving Neumega can be treated with  
8 approximately 1.5 to 2-fold higher doses per unit body  
9 weight dose.

10 (Slide)

11 In conclusion, efficacy of Neumega has been  
12 demonstrated in 2 randomized, placebo-controlled studies in  
13 patients with chemotherapy-induced thrombocytopenia. In  
14 study 9308 platelet transfusions were avoided by 38 percent  
15 of the Neumega-treated patients compared with only 7 percent  
16 of the placebo group, and in study 9416 about 68 percent of  
17 the Neumega-treated patients compared with only 41 percent  
18 in the placebo group. In addition, platelet transfusions  
19 were decreased overall in whole Neumega-treated group  
20 compared to the placebo in both studies. These benefits  
21 were obtained while chemotherapy was maintained at planned  
22 doses in these patients.

23 (Slide)

24 Adverse events associated with Neumega treatment  
25 are nearly always mild to moderate, reversible, and often

1 due to fluid retention. The most common are edema and  
2 dyspnea. Atrial arrhythmias were reported in excess of 10  
3 percent of patients treated with Neumega in the pivotal  
4 studies. However, most of these events were asymptomatic,  
5 detected only by Holter monitoring, and most did not require  
6 any treatment.

7 (Slide)

8 These studies have shown a benefit to several  
9 different groups of patients with chemotherapy-induced  
10 thrombocytopenia. Study 9308 enrolled patients who had been  
11 previously transfused with platelets for severe  
12 thrombocytopenia and who were almost certain to experience  
13 it again when their chemotherapy was given without dose  
14 reduction.

15 Study 9416 enrolled patients who had not  
16 experienced thrombocytopenia but who were receiving several  
17 cycles of dose-intense chemotherapy which was likely to  
18 produce it. In this study Neumega was especially helpful to  
19 patients who had any prior chemotherapy.

20 We believe that the benefits of Neumega treatment  
21 outweigh its side effects in patients such as those enrolled  
22 in these studies. Patients avoided platelet transfusions  
23 which carry a risk of alloimmunization and transmission of  
24 infectious diseases. Since reducing chemotherapy doses can  
25 only be detrimental in the treatment of cancer, many

1 oncologists would rather maintain chemotherapy doses and use  
2 a supportive therapy to ameliorate thrombocytopenia.

3           We believe the study results presented this  
4 morning show that Neumega is safe and effective for the  
5 prevention of chemotherapy-induced thrombocytopenia.  
6 Neumega represents a significant advance in the supportive  
7 care of patients with cancer, and it should be available as  
8 a useful alternative to reducing chemotherapy doses or  
9 relying on platelet thrombocytopenia in patients who can  
10 benefit from its ability to prevent thrombocytopenia.

11           (Slide)

12           Before I turn the podium over to Dr. Gordon to  
13 comment on the benefit-risk assessment, I will remind the  
14 Committee of the indication we have requested. We propose  
15 that Neumega be indicated to prevent chemotherapy-induced  
16 thrombocytopenia and to reduce the need for platelet  
17 transfusions in patients with nonmyeloid malignancies.

18           Thank you, and I will be happy to answer any  
19 questions you may have at the end of the presentations.

20           (Slide)

21           Now I would like to introduce Dr. Gordon, director  
22 of the clinical hematology and cytokine program from the  
23 Indiana University Cancer Center.

24           **Neumega Benefit-Risk Assessment, Michael Gordon, M.D.**

25           DR. GORDON: Thank you, Jim. Dr. Vose, members of

1 the Committee and colleagues, I am pleased to be here today  
2 to provide some perspective on the need for interleukin-11  
3 in the management of chemotherapy-induced thrombocytopenia  
4 and on the benefit-risk ratio of the data we have just seen.

5  
6 In my opinion, there is a clear need for a  
7 hematopoietic growth factor that can help us reduce the  
8 severity of chemotherapy thrombocytopenia. Dr. Elting has  
9 reviewed the data from the M.D. Anderson Cancer Center  
10 regarding the incidence of this event, as well as some of  
11 its implications for treating patients with cancer. It is  
12 clearly a clinically significant issue both for patients and  
13 physicians alike.

14 (Slide)

15 Our options for managing patients with severe  
16 chemotherapy-induced thrombocytopenia include dose reduction  
17 or delay with the inherent concern regarding decreased  
18 response and poorer outcome. We previously heard from Dr.  
19 Anderson as he discussed the risks associated with platelet  
20 thrombocytopenia including infectious risks, both viral and  
21 bacterial, transfusion reactions which are uncomfortable and  
22 can be associated with additional immunologic complications,  
23 as well as the risk for alloimmunization which can  
24 negatively impact upon patients who subsequently will  
25 require transfusion because of future planned therapy.

1           We must also, I believe, look at this from the  
2 patient's perspective. There are clearly social issues  
3 which are associated with severe thrombocytopenia, including  
4 time taken off from work for frequent blood checks, as well  
5 as for prophylactic platelet transfusions, as was previously  
6 noted. Thrombocytopenia and transfusions also impact upon a  
7 patient's quality of life and relate to their fears  
8 regarding the need for transfusions and/or their risks of  
9 bleeding.

10           (Slide)

11           This slide highlights a common phenomenon  
12 experienced in the course of discussions with patients  
13 regarding dose-intensive chemotherapy, whether for a solid  
14 tumor malignancy or lymphoma. I think it is fair to say  
15 that, given an option, patients would prefer to not receive  
16 a platelet transfusion if at all possible.

17           (Slide)

18           I believe that we in this room share the  
19 responsibility for making a clinically effective and safe  
20 thrombopoietic growth factor available. With the advent and  
21 increasing use of myeloid colony stimulating factors,  
22 neutropenia is no longer the absolute dose-limiting  
23 toxicity. This has led to progressive increase in  
24 chemotherapy dose intensity, as well as the investigation of  
25 new chemotherapeutic regimens and drugs. These events have

1 now redefined thrombocytopenia as a new dose-limiting  
2 toxicity for many such therapies.

3           Like myself, many of you on the panel have been  
4 involved in evaluating several different hematopoietic  
5 growth factors for their thrombopoietic activity. While  
6 many have shown exciting preclinical or Phase I data, none,  
7 including those shown on this slide, has been able to  
8 produce positive randomized, placebo-controlled Phase II or  
9 Phase III trials. Hence, the standard to which we have held  
10 thrombopoietic events is defined not by our successes but  
11 more by our failures. For this reason, I think that the  
12 availability of positive data in the controlled clinical  
13 trials with IL-11 is of major significance.

14           (Slide)

15           The data we have seen today is comprised  
16 principally of two randomized, placebo-controlled Phase II  
17 trials. The first, which was published last year in Blood,  
18 is what has been termed the secondary prophylaxis study.  
19 This trial design represents an exciting and novel approach  
20 in the study of hematopoietic growth factors. For the first  
21 time we are able to identify a high risk patient population  
22 and attempt to abrogate the need for platelet transfusions.

23  
24           Among these patients studied, with nearly 100  
25 percent of the placebo patients requiring a platelet

1 transfusion, the data very clearly and convincingly showed  
2 that patients with IL-11 at 50 mcg/kg experienced a  
3 significant reduction in the need for platelet transfusions.

4 (Slide)

5 The second trial was a primary prophylaxis study  
6 in women with breast cancer. It used a dose-intensive  
7 regimen which is similar to that used in previous trials by  
8 the CALGB and the NSABP. This, I believe, underscores my  
9 earlier comment regarding the increasing use of dose-  
10 intensive regimens given the availability of myeloid colony  
11 stimulating factors.

12 In this trial there was also a significant  
13 decrease in the development of severe thrombocytopenia and  
14 the need for platelet transfusions in the IL-11-treated  
15 patients. Overall, this improvement represents a similar  
16 percentage difference as seen with the myeloid colony  
17 stimulating growth factor effect on the prevention of  
18 febrile neutropenia seen in published randomized, placebo-  
19 controlled trials.

20 Both studies demonstrated a reduction in the  
21 number of transfusion events for patients receiving IL-11  
22 compared with the placebo. Thus, even for patients who  
23 continue to need platelet transfusions IL-11 has the ability  
24 to reduce the overall number of transfusions required.

25 (Slide)

1           The efficacy data is exciting and clearly  
2 demonstrates that IL-11 is the first agent where randomized,  
3 controlled clinical trials have demonstrated the ability to  
4 reduce the absolute need for transfusions as well as the  
5 number of transfusions.

6           (Slide)

7           It is clear that IL-11 is associated with a  
8 variety of side effects including dyspnea, peripheral edema,  
9 tachycardia and conjunctival injection. It has been  
10 hypothesized that these events are related to the plasma  
11 volume expansion which is seen with IL-11.

12           Review of the safety data demonstrates that the  
13 majority of adverse events experienced were mild, rapidly  
14 reversible and easily managed, and tended not to limit the  
15 ability to administer the study drug in the vast majority of  
16 patients.

17           There were several cases of atrial arrhythmias,  
18 the majority of which were asymptomatic and spontaneously  
19 reversed without intervention. Other side effects, such as  
20 tachycardia or palpitations were also noted but, again, were  
21 not clinically significant.

22           I think it is important to recognize that there  
23 did not appear to be any increased risk of thrombosis or  
24 thrombotic events in the studies, nor was there any  
25 incidence of excessive thrombocytosis during the recovery

1 period subjecting patients to risks of such events. Hence,  
2 while there are side effects seen with IL-11, I believe the  
3 safety profile, as demonstrated in the clinical trials and  
4 in the cumulative data to date, is favorable.

5 (Slide)

6 In conclusion, I think we can all agree that there  
7 is a need for an active thrombopoietic growth factor. Many  
8 of us have been searching for such a factor for several  
9 years, and it is not just we who seek this agent but also  
10 our patients who face the risks and fears associated with  
11 transfusion therapy.

12 I believe that IL-11 meets any reasonable standard  
13 for efficacy as an active thrombopoietic agent. No other  
14 agent previously studied has been able to meet these  
15 criteria in randomized, controlled clinical trials.

16 The safety profile of IL-11 is favorable. The  
17 adverse effects are generally manageable and primarily of  
18 low grade. I think we would all agree that the benefits of  
19 IL-11 as demonstrated in these two pivotal studies outweigh  
20 its risks. There is a need for those of us who treat cancer  
21 patients, as well as for the patients themselves, to have  
22 the option of IL-11 to reduce the need for and the risks  
23 associated with platelet transfusions, and to possibly avoid  
24 having their chemotherapy doses reduced.

25 In my opinion, the approval of this agent has the

1 potential to overcome a significant hurdle in the treatment  
2 of patients and may facilitate the development of new  
3 options for our patients with cancer.

4 Thank you very much for the opportunity to be here  
5 for what I regard as an important event in the treatment and  
6 management of chemotherapy-induced thrombocytopenia.

7 (Slide)

8 I would like to now reintroduce Dr. Petricciani  
9 who will summarize the presentation.

10 Summary, John C. Petricciani, M.D.

11 DR. PETRICCIANI: Actually, I will not try to  
12 summarize all of the data.

13 (Slide)

14 I do have a few points, however, that I would like  
15 to make. First of all, we have defined the Neumega safety  
16 and efficacy profile in rigorous randomized, placebo-  
17 controlled trials, and have shown, as Dr. Gordon just  
18 mentioned, that its benefits outweigh its risks.

19 (Slide)

20 Second, if we look at our overall data, it  
21 suggests that there is a range of responses to Neumega based  
22 on patient population characteristics and treatments. At  
23 one extreme there are patients with a normal marrow reserve  
24 and no prior therapy who will be treated with conventional  
25 dose chemotherapy. Such patients probably would benefit

1 least from Neumega.

2 At the other end are patients with extensive prior  
3 chemotherapy whose marrow reserve is largely depleted and  
4 the number of remaining progenitors is likely to be too low  
5 for Neumega or any thrombopoietic growth factor to have a  
6 reasonable chance of preventing the need for platelet  
7 transfusions. For that reason, Neumega should be used  
8 before patients enter into this late stage of chemotherapy.

9 But there is a middle group between those two  
10 extremes, and it is this group where the benefits of Neumega  
11 are maximized. Those are cancer patients who have had some  
12 prior chemotherapy, who have reasonable marrow reserves, and  
13 who have already experienced thrombocytopenia or who are at  
14 significant risk for thrombocytopenia because of dose-  
15 intense chemotherapy. It is this middle group that we are  
16 seeking approval for. It is relatively small compared to  
17 the entire chemotherapy patient population which, in part,  
18 is why FDA has designated Neumega as an orphan drug.

19 (Slide)

20 Finally, as has already been stated several times,  
21 this product represents a major step forward by providing  
22 clinicians and patients the opportunity to continue  
23 chemotherapy treatments without dose reductions while also  
24 freeing them from any of the risks associated with platelet  
25 transfusions.

1           That concludes our formal presentation but we  
2 would certainly be happy to respond to any questions that  
3 the Committee may have either now or later in this session.

4           DR. VOSE: Thank you very much for the  
5 presentations this morning. Next we will take some time now  
6 to have questions from the Committee for any of the  
7 presenters this morning. Dr. Berman?

8           DR. BERMAN: I have a question for you about the  
9 patient who died who was hypokalemic. Were these patients  
10 receiving potassium supplementation at the time where the  
11 potassium was less than 2?

12           DR. KAYE: The question has to do with the  
13 potassium supplementation of the patients with hypokalemia.  
14 One of those two patients was in the hospital and did  
15 receive potassium supplements but had a fall in potassium  
16 from a normal value to under 3 within one day of dying. So  
17 I think it was apparent that the supplementation was not  
18 adequate.

19           The other patient was seen in the clinic and had a  
20 potassium level of 2.1 found but not until after the patient  
21 had returned home, and the patient was told to take an oral  
22 potassium supplement but, unfortunately, died that night.  
23 So I think potassium supplementation was probably not  
24 adequate in either patient.

25           DR. BERMAN: The second question relates to the

1 issue of calcium flux, which was mentioned in our handout  
2 but not today. Evidently some patients developed  
3 hypocalcemia as well. Was this thought to be at all related  
4 to the incidence of atrial fibrillation, and can you comment  
5 on the mechanism perhaps of the atrial fibrillation?

6 DR. KAYE: The question has to do with calcium and  
7 mechanism of atrial arrhythmias. I would like to divide  
8 that question into two parts, if I could, and talk about  
9 calcium serum concentration first. I would like to begin  
10 doing that by going back to what we know about the effect of  
11 Neumega on plasma volume.

12 (Slide)

13 I would like to mention in a little more detail  
14 the results of a study that we did in normal volunteer  
15 subjects who received a dose of Neumega for seven days and  
16 were confined to a standard salt intake. In these patients  
17 we directly measured plasma volume using iodine-labeled  
18 albumin, and we directly measured red cell mass using  
19 chromium-labeled red blood cells. This was a placebo-  
20 controlled study and it was masked.

21 From baseline to day 8, what you can see in the  
22 plasma volume on this side, is that the Neumega patients  
23 started off lower. But if you compare the baseline to day 8  
24 you can see that there was little change in the placebo  
25 group but an increase in the Neumega group, whereas, in the

1 red blood cell mass there was a decrease in both groups from  
2 baseline to day 8. It was really due to the blood drawing  
3 that was being done daily in these subjects.

4 (Slide)

5 This slide shows the percent changes from baseline  
6 in these two parameters, plasma volume and red blood cell  
7 mass, that were observed in this study. What you can see is  
8 that the plasma volume increase that I showed you amounts to  
9 about a 25 percent increase in plasma volume. So this is  
10 what accounts for the dilutional anemia.

11 In association with that, we have seen that plasma  
12 proteins also decrease in concentration, and about the same  
13 decrease in concentration is observed in total globulins and  
14 also in serum albumin, which we believe is dilutional  
15 predominantly. Along with the decrease in albumin  
16 concentration, which amounts to about 0.5 g/dL, there is  
17 also concomitant decrease in serum calcium concentration  
18 because we were measuring total calcium in the serum in  
19 these studies. As you know, it is ionized calcium which is  
20 the tightly regulated component of the blood, and when one  
21 makes adjustment for the decrease in albumin serum calcium  
22 concentrations really don't change appreciably in patients  
23 receiving Neumega.

24 The second part of the question has to do with  
25 mechanism of atrial arrhythmias. In our preclinical

1 toxicology studies we have never observed that Neumega has  
2 any direct cardiotoxic or arrhythmogenic effect. We have  
3 done a series of animal studies for this and I would like  
4 just you mention a few of them.

5 (Slide)

6 We have studied animals, actually isolated rat  
7 heart in what is called the Langendorff preparation, in  
8 which IL-11 is infused directly into the coronary arteries  
9 at concentrations up to 500 ng/mL, which is more than an  
10 order of magnitude higher than the concentrations we obtain  
11 clinically, and we have seen no effect on heart rate,  
12 coronary flow or the incidence of arrhythmias in these  
13 hearts.

14 In whole animals, guinea pigs, we have used the  
15 model that has been developed to detect the arrhythmogenic  
16 potential of different drugs. In guinea pigs, first of all,  
17 directly treated with doses up to 20 mg/kg IV we have seen  
18 no effect again on blood pressure or incidence of  
19 arrhythmias.

20 Then in the model that is designed to detect  
21 arrhythmias we have seen no effect of Neumega. The model  
22 involves giving the test drug, in this case Neumega, and  
23 then infusing ouabain at increasing concentrations and  
24 measuring what the ouabain dose threshold for production of  
25 arrhythmias is. Neumega has had no effect on this

1 threshold. So, again, there is no evidence that it is in  
2 any way directly arrhythmogenic.

3 This study has also recently been done in which  
4 the Neumega was given over the course of a week of treatment  
5 to try to simulate the plasma volume effect which is also  
6 seen in these animals and, again, there was no effect on the  
7 induction of arrhythmias.

8 So I think our preclinical data strongly support  
9 the contention that Neumega is not cardiotoxic or directly  
10 arrhythmogenic. We have discussed this with a number of  
11 consultants, cardiology experts, and our hypothesis is that  
12 in some patients at least the plasma volume effect is likely  
13 playing a role.

14 Let me just show you what we have done to look  
15 into our clinical data to see what risk factors there are  
16 for atrial arrhythmias.

17 (Slide)

18 We have taken all 277 patients, who are summarized  
19 on this slide down here, from all 5 adult oncology studies  
20 and studied potential risk factors for atrial arrhythmias in  
21 these patients.

22 (Slide)

23 What we have identified in a logistic regression  
24 analysis is that there were in all these studies a total of  
25 7 patients with atrial arrhythmias in either the Neumega or

1 the placebo group. And in the older age, use of cardiac  
2 medications or, in fact, some influence of a history of  
3 doxorubicin exposure are risk factors.

4 This is a retrospective exploratory analysis. But  
5 there are no surprises here because these are factors that  
6 can be associated with arrhythmias in general, and  
7 particularly older age is strongly associated with atrial  
8 arrhythmias in the general population. Neumega treatment  
9 obviously fell out of this as an associated risk factor, but  
10 the point is that there are patient characteristics that  
11 place individuals at higher risk for experiencing these  
12 complications.

13 (Slide)

14 Since Neumega is not arrhythmogenic in animal  
15 models, and also I should mention in neither animal models  
16 nor in our clinical studies, it has no effect on cardiac  
17 conduction intervals. We believe the ability of Neumega to  
18 precipitate atrial arrhythmias in susceptible patients may  
19 be related to the increase in plasma volume, at least in  
20 some patients, because we know that atrial arrhythmias occur  
21 in conditions where there is atrial distention, such as in  
22 congestive heart failure or mitral stenosis. We have seen  
23 this complication commonly in the bone marrow transplant  
24 population who are receiving high-dose chemotherapy in  
25 potentially cardiotoxic doses of cyclophosphamide in

1 chemotherapy studies and the other risk factors are as I  
2 have mentioned.

3 DR. BERMAN: Are you going to recommend that  
4 patients who have any history of heart disease or, in fact,  
5 have received any prior adriamycin be not recommended, that  
6 this drug is not recommended for their use?

7 DR. KAYE: The answer is that the risk factors  
8 that I showed in that exploratory retrospective analysis are  
9 relatively weak risk factors, except for age. Doxorubicin  
10 exposure and history of heart disease confer relative risk  
11 only in the 2- to 3-fold magnitude, which is fairly small  
12 for this type analysis.

13 (Slide)

14 We do believe that Neumega should be used with  
15 caution in patients who have severe or uncompensated  
16 congestive heart failure because of the ability it has to  
17 increase plasma volume. We recommend that the benefit-risk  
18 be considered seriously in patients who have a history of  
19 atrial arrhythmia or other cardiovascular disease.

20 But I should point out, as I mentioned in the  
21 presentation, that among the patients who have experienced a  
22 brief episode of atrial arrhythmia while receiving Neumega,  
23 the majority have continued to receive the product without  
24 having a recurrence. There have been some recurrences but  
25 the majority have not had a recurrence during the remainder

1 of their treatment which included up to another additional  
2 cycle. So we don't feel that there should be any absolute  
3 contraindication. It is a matter of individual medical  
4 judgment.

5 DR. BROUDY: I would like to ask a quick question.  
6 You showed convincing evidence that Neumega treatment  
7 expands the plasma volume and that that may explain, in good  
8 part, a drop in the hematocrit. Have you looked at the  
9 effect on retic. counts? Because I would expect in those  
10 normal patients who are extensively phlebotomized that they  
11 would have stimulated reticulocytosis. Was that  
12 reticulocytosis blunted in the Neumega-treated population?

13 DR. KAYE: I don't believe we observed any  
14 significant change in the reticulocyte counts over the seven  
15 days of our experiment.

16 DR. BROUDY: But they were monitored and there was  
17 no decrease in the ability of the patients to mount a  
18 reticulocyte response?

19 DR. KAYE: I don't believe we observed any changes  
20 in the reticulocyte counts. I think the question you are  
21 getting at, if I am interpreting your question correctly,  
22 probably is what might the effect be on red cell production  
23 in patients undergoing chemotherapy. Of course, patients  
24 who are undergoing chemotherapy have marrow suppression from  
25 the chemotherapy.

1 I think the most important observations we have  
2 made relating to that are that the red blood cell  
3 transfusion requirements are not significantly increased in  
4 the patients on Neumega. There appears to be some  
5 compensation over the course of one or two weeks of  
6 treatment for the plasma volume effect. So I think things  
7 tend to even out after several weeks.

8 DR. MILLER: Can you expand on the bleeding  
9 complications in the studies?

10 DR. KAYE: Yes. The question relates to the  
11 bleeding complications that occurred in the studies.

12 (Slide)

13 As I said, this was a retrospective analysis or  
14 spontaneously reported adverse events. Frankly, going into  
15 this we didn't believe that patients who were being managed  
16 with the transfusion policy of 20,000 or lower that we would  
17 see much bleeding at all. At least, that is what the recent  
18 literature has suggested. But, indeed, we did count up all  
19 the events that could be considered as any sort of bleeding,  
20 and totaled them between the two groups, and the results are  
21 what I showed in the presentation. About half of the  
22 placebo patients had some bleeding event and only about a  
23 quarter of the Neumega-treated patients. But most of these  
24 were not serious bleeding, as you would expect in patients  
25 being prophylactically transfused at 20,000 and who were

1 being watched very closely in a clinical trial setting.  
2 There were only 3 grade 3 events reported among all of  
3 these. It so happened that all 3 of those were in the  
4 placebo group, but the numbers are small.

5 DR. VOSE: Additional questions?

6 DR. AUGUST: At the outset it was stated that one  
7 of the methods of this was going to be that there was going  
8 to be fewer dose reductions and delays in therapy so that  
9 dose intensity could be maintained. The slides that you  
10 showed us for the overall outcomes didn't show any  
11 difference between the treated patients and their controls.  
12 I am wondering whether, in fact, the goal of achieving the  
13 intended dose intensity was in fact reached in a group of  
14 patients, or whether there were delays and so forth  
15 engendered by other irrelevant or unrelated phenomena, for  
16 example neutropenia and infection?

17 DR. KAYE: Right. The question I think is really  
18 have we shown anything about therapy dose or schedule in  
19 these studies. The studies were designed, remember, with  
20 the provision that chemotherapy doses not be decreased.  
21 This is in contrast to what is recommended in the labeling  
22 for most chemotherapeutic agents. In fact, we have a slide  
23 that shows a summary of the chemotherapy dose reductions  
24 that are recommended for various chemotherapeutic agents. I  
25 will show it in a second.

1 To summarize what it will show, about two-thirds  
2 of the chemotherapy doses that are used in the United States  
3 have some recommendation in their labeling that chemotherapy  
4 doses should be reduced either during the cycle in which a  
5 patient has thrombocytopenia or during a subsequent cycle.

6 (Slide)

7 These are the ones, and 64 percent recommend that  
8 in the current cycle and 58 percent recommend it in the  
9 subsequent cycle. In about two-thirds of the cases there is  
10 this recommendation one way or the other. The brighter red  
11 is in reference to specific platelet thresholds and the  
12 purplish color is without reference to a specific platelet  
13 threshold.

14 So the recommendation in labeling that  
15 chemotherapy dose be reduced for thrombocytopenia was not  
16 followed in our studies. We took patients in 9308 who had  
17 already had a platelet count nadir below 20,000 and been  
18 transfused, and we said let's maintain the chemotherapy  
19 doses in all these patients, in the Neumega-treated patients  
20 and in the placebo group. So we couldn't see any difference  
21 by the design of the study what the outcome of maintaining  
22 chemotherapy doses was but that was the design of the study.  
23 Except for a very small number of patients, as I pointed  
24 out, whom we excluded from the evaluable subgroup, those  
25 chemotherapy doses were maintained.

1           In 9416, again from the first cycle to the second  
2 cycle the rule was to keep the cyclophosphamide and  
3 doxorubicin doses as specified in the protocol, and that was  
4 adhered to.

5           So we didn't design the studies to look at the  
6 effect of chemotherapy dose reduction or maintenance versus  
7 not. We also didn't design the studies to look at the  
8 potential effect of chemotherapy delays on subsequent  
9 outcomes. But we did have the potential of making some  
10 observations about the possible timing of the next cycle of  
11 chemotherapy because we looked at time to platelet recovery.

12           (Slide)

13           For the 9803 study, I am going to show you the  
14 result of an analysis which is not the way one typically  
15 analyzes a randomized trial. This is a retrospective  
16 subgroup analysis. What we have done here is to look at  
17 time to platelet recovery. This is sort of an upside down  
18 Kaplan-Meier curve. This is for patients who had a  
19 successful outcome on the study. Most of these were on  
20 Neumega treatment, obviously, compared to those who had  
21 transfusions during the course of the study, Neumega or  
22 placebo.

23           What this shows is that all of the patients who  
24 had a nadir above 20,000 and avoided transfusion were back  
25 to a platelet count of 100,000 by day 21, whereas, even out

1 5 weeks later we are still picking up the tail end of the  
2 curve for the patients that failed.

3 This is not meant to be a comparison of Neumega  
4 versus placebo. It isn't. All it is meant to show is that  
5 there is a correlation between avoiding platelet  
6 transfusions, as we have measured it in our studies, and  
7 having more rapid platelet recovery. Of course, it would  
8 take much larger trials than we had to show a potential  
9 benefit of that on the chemotherapy effects on cancer  
10 outcomes. But we think it is a possibility and it should be  
11 further evaluated in larger studies in the future

12 DR. VOSE: Thank you, Dr. Kaye.

13 DR. SWAIN: In the 9308 study, the secondary  
14 prophylaxis study, more patients on the 25 mcg arm, which  
15 really wasn't discussed, received carboplatin. There was  
16 about 42 percent. On the placebo arm there was about 37  
17 percent. Only about 16 percent on the 50 mcg arm received  
18 carboplatin. Is there any way that could explain some of  
19 the difference or the benefit that you saw?

20 DR. KAYE: Well, the numbers are small and it is  
21 hard to rule out that possibility I think, but I will show  
22 you a list of the regimens that the patients who had the  
23 successful outcome were receiving.

24 (Slide)

25 These are their diagnoses and these are the agents

1 they were receiving. This patient was on a carboplatin  
2 regimen. This patient was on cisplatin. There is another  
3 carboplatin patient here. So about half the patients were  
4 on platinum-containing regimens. There were several in the  
5 carboplatin group. The study, obviously, was not  
6 prospectively planned to evaluate efficacy in specific  
7 chemotherapy regimens because patients were entered into the  
8 study receiving whatever chemotherapy they were receiving  
9 and we couldn't prospectively stratify for that, but we  
10 certainly are interested in additional studies that will  
11 hone in on specific chemotherapy regimens and the utility of  
12 IL-11.

13 DR. SWAIN: It seems like there is such a major  
14 imbalance in the three different arms.

15 I just have a quick other minor question. Getting  
16 back to the atrial arrhythmia, I think that I read in there  
17 somewhere that with increased dose you saw more atrial  
18 arrhythmias in one of the studies at the higher doses?

19 DR. KAYE: In our Phase I bone marrow transplant  
20 study, 5/14 patients treated with 50 mcg/kg or 75 mcg/kg had  
21 atrial arrhythmias while they were in the hospital and going  
22 through their transplant procedures. It is very difficult  
23 to sort out whether it was a dose relation or whether it has  
24 to do with that particular setting. In the transplant  
25 setting we have noticed a slightly higher incidence of

1 atrial arrhythmias than we did in the ambulatory  
2 chemotherapy studies that I have described this morning.  
3 There is also a higher tendency to recur, probably because  
4 the fluid and electrolyte management of patients undergoing  
5 transplantation is even more complex than in the ambulatory  
6 outpatient population.

7 DR. SWAIN: Is there any evidence that it is  
8 thrombogenic and those patients may be throwing small  
9 pulmonary emboli? I think I also read that at higher doses  
10 fibrinogen is increased.

11 DR. KAYE: The question is about thromboses and  
12 fibrinogen. We do know that Neumega stimulates increases in  
13 fibrinogen. The serum concentrations were about two-fold in  
14 the dose range that we were using clinically. This has not  
15 been associated with thrombotic events in the clinical  
16 studies nor in our clinical trials. I will show you the  
17 slide on thrombotic events that were reported in the two  
18 chemotherapy studies.

19 (Slide)

20 There were very few events. Those that were  
21 reported were really rather minor. There was catheter  
22 thrombosis reported in one patient in each of the treatment  
23 groups. There was only a single report of what was called  
24 phlebitis in the upper arm, superficial process in the upper  
25 arm in one patient on placebo. There were no deep vein

1 thromboses or pulmonary emboli reported to us in either  
2 study. Since we haven't seen it in preclinical studies and  
3 have not had adverse event reports, we do not think that  
4 Neumega predisposes to thrombotic events. We have also  
5 looked at platelet function in the context of both our Phase  
6 I study and normal volunteers and have not seen any increase  
7 in platelet activate ability. So we believe that that is  
8 not a risk associated with Neumega.

9 DR. SWAIN: One final question, do you have to  
10 reduce this with renal impairment?

11 DR. KAYE: Reduce the dosing with renal  
12 impairment? A recently completed pharmacokinetic study in  
13 patients with renal failure, patients who are on dialysis,  
14 shows that the area under the concentration time curve for  
15 patients who are functionally anephric is about twice what  
16 it is in normal adults. So the renal route of excretion is  
17 not the only route of excretion. These subjects do excrete  
18 Neumega, or at least clear it from the serum. We are going  
19 to have some further discussion with FDA about specifics of  
20 labeling in that regard. But those data are available.

21 MS. GINES: As a Hispanic breast cancer survivor  
22 and a person who has had a history of thrombocytopenia, I am  
23 curious about study 9416. Of the two patients that were in  
24 the study not receiving Neumega, was there a reason for  
25 that? Also, what was the racial component of those who

1 died?

2 DR. KAYE: I think the first question is why were  
3 there two patients in the placebo group?

4 MS. GINES: There were only two Hispanics in the  
5 study and none received Neumega. So I was just curious as  
6 to why. Also I wanted to know the racial component of the  
7 patients who died.

8 DR. KAYE: The small number of patients of any  
9 particular subgroup doesn't ensure that there is going to be  
10 equal randomization between the groups. So where there are  
11 only two patients identified, they could have easily fallen  
12 in one or the other by chance. The randomization  
13 assignments were in a masked fashion. So there was no way  
14 to control the stratification for racial background or  
15 ethnic group. So that just happened by chance.

16 I can't answer the question about the patients who  
17 died, but we have the data in our database and we can look  
18 that up and find the answer for you. I can't answer it  
19 offhand.

20 DR. SIEGEL: You noted a difference in the  
21 reporting of oral moniliasis, one case versus ten. I wonder  
22 what information you might have about the reasons for that.  
23 Are there immunological studies, animal studies? Is there  
24 other evidence of other types of infectious risks and,  
25 specifically, do you know the type of sepsis in the sepsis

1 patients?

2 DR. KAYE: The question is about oral moniliasis  
3 and potential other infections and associations. In the two  
4 studies combined there was a higher incidence of oral  
5 moniliasis in patients receiving Neumega. This was a  
6 surprise because there was no increased incidence of fungal  
7 infection at other sites, nor was there any reported  
8 incidence of fungal sepsis in either group, nor was there  
9 any difference in use of antifungal agents between the two  
10 groups.

11 I have to say that these adverse events were not  
12 typically confirmed with stains. These were clinical  
13 adverse events that were reported to us and collected in the  
14 usual fashion. So we are not sure they all were oral  
15 moniliasis.

16 To answer your second question, assuming there is  
17 a difference, in vitro studies have shown no effect of  
18 Neumega on neutrophil function, which is generally thought  
19 to be the primary defense against superficial fungal  
20 infections. There is a slight effect of Neumega on  
21 macrophage function in that some of the inflammatory  
22 mediators, such as TNF, can be suppressed. Whether that is  
23 at all related to this observation I think at this point is  
24 only speculation. But it is something that, obviously, we  
25 are interested in looking into further.

1           As to the two patients with sepsis in the ongoing  
2 study, I know that one of them had mixed gram-negative  
3 urosepsis. The other one I don't know, but I don't believe  
4 it was a fungal infection.

5           DR. VOSE: Dr. Kaye, were there any quality of  
6 life studies done in either of the pivotal trials  
7 specifically related to looking at the effects of edema or  
8 other side effects that were a concern?

9           DR. KAYE: Not to date.

10          DR. BROUDY: I would like to ask whether either in  
11 your preclinical studies or normal volunteers you have  
12 quantitated the number of progenitor cells in the Neumega-  
13 treated patients compared to the controls, or using the  
14 patient as his or her own control. I guess the reason I am  
15 asking this is because I would like to make sure that  
16 Neumega doesn't impair erythropoiesis in any way, although  
17 you have certainly convinced me that expanded plasma volume  
18 is one issue.

19          DR. KAYE: In the Phase I study marrows were done  
20 before and after the two weeks of dosing and we saw  
21 increases in megakaryocyte progenitors and no significant  
22 changes in other progenitors between the higher doses and  
23 the 10 mcg/kg dose, which is a minimal active dose in that  
24 setting.

25                 In animal studies I think we have good data

1 showing, for example in a mouse model in which carboplatin  
2 irradiation is used to myelosuppress, that there is  
3 accelerated recovery of erythroid cells as well as platelets  
4 in that model. This is an observation that has been made  
5 with several thrombopoietic growth factors. So I don't  
6 believe that in clinical studies it is really possible in  
7 the setting where we have studied patients to make any  
8 conclusions. I think the preclinical in vitro evidence and  
9 the evidence from the Phase I study does not suggest that  
10 there is any impairment of erythroid production.

11 DR. VOSE: Additional questions? Dr. Berman?

12 DR. BERMAN: In your handout you stated that you  
13 would recommend this for nonmyeloid tumors, but has it been  
14 tested at all in patients with leukemia, or is the degree of  
15 thrombocytopenia so profound that you do not want to test  
16 it?

17 DR. KAYE: The question is what data there are on  
18 acute leukemia, myeloid leukemia particularly I think. We  
19 are very interested in studying Neumega in AML patients and  
20 we are planning that now. But studies have not been done so  
21 far, mainly because we have been focused on the chemotherapy  
22 program that I presented this morning and trying to achieve  
23 the most rapid registration within that indication as  
24 possible.

25 In in vitro studies, as with a number of other

1 growth factors, there can be some augmentation of myeloid  
2 leukemia proliferation, usually in combination with IL-3.  
3 It has been very unusual to see direct stimulation of AML  
4 cells in vitro by Neumega. But, as you know, myeloid growth  
5 factors which have direct stimulatory effect on AML cells--  
6 one is approved already for use and another one is being  
7 discussed tomorrow. So I think the issue of safety of using  
8 growth factors that can potentially have those effects on  
9 AML cells in vitro is one that has been recognized and  
10 addressed in appropriate ways.

11 DR. AUCHINCLOSS: You have been talking about  
12 preventive use of IL-11. I am wondering about potential  
13 therapeutic uses. In particular, obviously the low risk  
14 group of patients that you have been talking about, a number  
15 of them would not need the drug. Would it be possible, or  
16 do you have information about how quickly it acts so that  
17 you could potentially use it in just a subset of people as  
18 platelet counts begin to fall or come to a certain level?

19 DR. KAYE: The question is how quickly does  
20 Neumega act and would it be possible to intervene directly  
21 when a patient is thrombocytopenic during their nadir.

22 (Slide)

23 The best information about the time course of the  
24 activity of Neumega on stimulating platelet production comes  
25 from our Phase I study, the study conducted by Dr. Gordon.

1 These are the mean platelet counts for each of the cohorts  
2 from 10-75 mcg/kg over time during that study.

3 First of all, what you can see is that the  
4 increase in platelet counts was roughly dose related from 10  
5 mcg/kg up to 75 mcg/kg groups. But notice that the real  
6 increase doesn't begin until after 5-7 days of treatment.  
7 This is, interestingly, exactly what has been observed, as  
8 far as I know, with all of the agents that have had some  
9 effect on thrombopoiesis. There seems to be an inherent  
10 biologic limitation of the megakaryocyte development  
11 process.

12 Notice also that in this study patients were dosed  
13 for 14 days. Notice also that the platelet counts continued  
14 going up for several days even after dosing was stopped. So  
15 there seems to be a delay in the off effect, if you will,  
16 because once the megakaryocyte development program is revved  
17 up it continues running, and there are other endogenous  
18 growth factors that are present normally, particularly in  
19 myelosuppressed patients, which are known to synergize with  
20 IL-11.

21 So I think the answer to the question is that we  
22 haven't studied that but the time course of the effect on  
23 thrombopoiesis that we have observed in non-myelosuppressed  
24 patients and also in preclinical studies would suggest that  
25 beginning treatment during the nadir is probably not the

1 most effective strategy. But we haven't studied this  
2 specifically.

3 DR. SWAIN: Could you please comment on the total  
4 percent of patients that had to stop receiving Neumega  
5 versus placebo because of adverse effects? I think it was  
6 in the briefing papers but I don't remember seeing it in  
7 your presentation this morning.

8 DR. KAYE: Right. Let me just come back to the  
9 other question that was asked for a moment. All deaths over  
10 all cycles in 9308, 7 of the patients were white and there  
11 was one registered as "other" in terms of the racial  
12 background.

13 In 9416 there were 7 deaths total. This includes  
14 the patients who died of disease progression. There were 5  
15 whites and 2 African American patients.

16 I am sorry, the question was?

17 DR. SWAIN: The percent of patients who  
18 discontinued because of adverse events.

19 DR. KAYE: Right. In the two studies I presented  
20 this morning a total of 12 patients discontinued due to  
21 adverse events. We have slide that shows what those adverse  
22 events were.

23 (Slide)

24 This is the list. What you can see is that there  
25 is the one patient in the placebo group and two in the

1 Neumega group who discontinued because of atrial  
2 arrhythmias. There is one patient who was coded as  
3 discontinuing because of the aortic stenosis who also  
4 experienced atrial arrhythmia while in congestive heart  
5 failure, which actually began after the completion of cycle  
6 2 but was still coded as a reason for discontinuation.

7           Of the other events, there really is only one of  
8 various things here and there. So I think it is fair to say  
9 that there is no common adverse event that precipitated  
10 discontinuation in the studies. There is some difference  
11 between the groups but it is not any particular event.

12           DR. AUGUST: I have two questions which are not  
13 really related. The first is, the subcutaneous injections  
14 are obviously being given to patients who are  
15 thrombocytopenic. Was there evidence of hematoma formation  
16 or bleeding at the injection site? The reason I am asking  
17 this is that I was taught as a fellow and I continue to  
18 teach that absorption is perturbed when there is a hematoma  
19 that forms at the injection site. You can't know whether  
20 absorption is going to be increased or decreased, and that  
21 could have a confounding effect on the intent to administer  
22 a certain dose of your drug.

23           Also I would just comment that, as I recall, most  
24 of the studies that have been published on G- and GM-CSF,  
25 the earliest ones were all given intravenously, or many of

1 them were given intravenously.

2 DR. KAYE: Yes. The question has to do with  
3 subcutaneous dosing and whether there were any local  
4 reactions, hematoma or other local reactions, and also the  
5 question about intravenous dosing.

6 We decided early in the program that because of  
7 the high bioavailability, and because of the greater  
8 convenience to patients, and because we thought the risks of  
9 local bleeding problems would be relatively small with the  
10 low volume of injection that is required, we would use the  
11 subcutaneous route of administration, and that is what we  
12 have done in all of our studies. We have not studied  
13 intravenous use.

14 The number of local injection site reactions has  
15 been fairly small. Usually, if there is a reaction it is  
16 mild in duration or sometimes with erythema at the site.  
17 These can occur even several days into the course of  
18 treatment but are not serious. I am reminded that in the 50  
19 mcg/kg the exact incidence is 7 percent and in the placebo  
20 group the exact incidence is 7 percent, in the 2 randomized  
21 studies, of injection site reactions of any sort.

22 So I think that is a relatively minor problem.  
23 Probably in the studies that we did the prophylactic  
24 transfusion policy helped some because I think, certainly,  
25 what we do know is that of the patients who had a nadir

1 below 20,000 in our studies, half of them got down to 10,000  
2 or less. Half of the patients got down to 10,000 or less if  
3 they got below 20,000. If patients are allowed to sit at  
4 that level and continue having any sort of trauma, bleeding  
5 is likely to occur, as we saw in the first part of the  
6 presentation. So probably prophylactically transfusing  
7 platelets helped.

8 DR. AUGUST: My second question is about  
9 premenopausal women with cancer who are getting  
10 chemotherapy. They are frequently advised not to become  
11 pregnant and many go on birth control pills and that, it  
12 would seem to me, would constitute a risk of patients in  
13 your studies who would be at special risk from complications  
14 of Neumega, particularly in light of what we have already  
15 heard about the increase in fibrinogen and other acute phase  
16 reactants. I am just wondering how you plan to deal with  
17 that, and if you think that it is a real risk.

18 DR. KAYE: Well, we have no direct evidence. As I  
19 mentioned, we have looked at our clinical trial data for  
20 incidence of thrombotic events and seen very few. So we  
21 have not been able to identify an association with any  
22 particular other confounding medications. But I think this  
23 is something that we would certainly discuss further with  
24 FDA in terms of general precautions.

25 DR. VOSE: I think we are going to need to stop at

1 this point to take a break, and we will re-initiate with the  
2 FDA discussions at 10:30. Thank you.

3 (Brief recess)

4 DR. VOSE: Go ahead with the FDA perspective on  
5 the IL-11 trials now, Dr. Steffen.

6 **FDA Perspective, Richard O. Steffen, M.D.**

7 (Slide)

8 DR. STEFFEN: Dr. Vose, members of the Committee,  
9 these are the members of the CBER review team for this  
10 license application.

11 (Slide)

12 In studying Neumega, the sponsor put together a  
13 really very nicely coordinated set of clinical trials. What  
14 weaknesses there are, are that the pivotal trials stem  
15 solely from the fact that these were actually designed as  
16 Phase II studies. As a result, they are moderate in size.  
17 The maximum number of patients in one arm was 40.

18 They were, as we have heard, conducted in two  
19 different, certainly related but different settings of  
20 primary and secondary prophylaxis. The protocol for both  
21 studies called for the primary analysis to be done on  
22 evaluable patients, which certainly is a reasonable thing  
23 for Phase II studies. For the purposes of licensure we  
24 prefer the analysis to be done on the intent-to-treat  
25 patients, which was also done and I will be presenting our

1 results of that analysis only.

2           The protocols didn't identify certain of the  
3 important analytic decisions prospectively, and then the  
4 study was not designed to obtain data on tumor response but,  
5 rather, the hematopoietic effects of Neumega.

6           (Slide)

7           Certainly, these trials did have some strengths.  
8 They were well designed studies, as were all the studies in  
9 their clinical development program. They were randomized,  
10 double-blind and placebo-controlled, as were the majority of  
11 all the studies they conducted, including the normal  
12 volunteer studies.

13           Investigator compliance was quite good with the  
14 protocol. Even though the analytic decisions were not made  
15 prospectively in the protocol, these were made and committed  
16 to writing prior to unblinding the studies.

17           Finally, they did put together a follow-up  
18 registry looking at the question of tumor response, which  
19 actually captured data on all but two patients, 99 percent  
20 of the patients that were enrolled in the three randomized  
21 studies in patients.

22           (Slide)

23           I will be going over just briefly the design of  
24 each since they are a little different, starting with study  
25 9308.

1 (Slide)

2 The primary objective of this study was to compare  
3 each of two doses of Neumega with placebo. The primary  
4 endpoint was the need for platelet transfusion, a simple yes  
5 or no, did the patients receive transfusion or not. There  
6 was a series of secondary endpoints that had to do with the  
7 hematopoietic performance of Neumega, which Dr. Kaye has  
8 presented.

9 (Slide)

10 To be eligible for this study patients could have  
11 any documented solid tumor or lymphoma. They had to be  
12 undergoing chemotherapy, and had to have had an episode of  
13 severe thrombocytopenia in the cycle immediately preceding  
14 entrance into the study. That was designated as cycle X.  
15 Severe thrombocytopenia was defined as a platelet count less  
16 than 20,000 and the receipt of a platelet transfusion.  
17 Patients had to recover to a platelet count of 100,000 to  
18 enter into the study itself.

19 As you have heard, they received the identical  
20 same chemotherapy in the study cycle, which was designated  
21 as cycle X+1. There was no dose reduction allowed.  
22 Supportive care was to remain as unchanged as possible. The  
23 exception was that patients would not receive a myeloid  
24 growth factor in cycle X but could receive G-CSF in cycle  
25 X+1. Patients receiving GM-CSF were not eligible.

1 (Slide)

2 Patients were stratified by the amount of prior  
3 therapy and the duration of chemotherapy to be given, and  
4 randomized to 25 mcg/kg or 50 mcg/kg of Neumega. Also they  
5 were randomized to placebo and to help maintain the study  
6 blinding patients randomized to placebo underwent a second  
7 randomization to one of two volumes on a per kilogram basis  
8 equivalent to the two volumes of the active study. The  
9 placebo group was, of course, combined for analysis.

10 (Slide)

11 The planned enrollment was 105 patients. It was  
12 prematurely terminated at 93 patients and, as we have heard,  
13 there was a wide variety of underlying malignancies in the  
14 patients who were enrolled in this study.

15 (Slide)

16 Again, there were 12 different cytotoxic agents  
17 used in 24 different combinations in this study. The most  
18 commonly used were the DiCEP and ICE regimens but they were  
19 actually used in a fifth or less of the patients, and then  
20 there were a few less common regimens and a smattering of  
21 much less common regimens.

22 (Slide)

23 This is the result of the sponsor's intent-to-  
24 treat analysis which was done, as we have heard, on all  
25 randomized patients, and 30 patients were randomized to the

1 placebo arm, 31 to the lower dose Neumega and 32 to the  
2 higher dose Neumega. In the placebo arm 7 percent avoided  
3 transfusion compared with 19 percent in the lower dose  
4 Neumega arm and 38 percent in the higher dose Neumega arm.  
5 There is certainly the appearance of a dose effect here and  
6 in comparison in the difference of the high dose Neumega arm  
7 and the placebo arm this was highly significant, with a p  
8 value of 0.005. The sponsor chose to adjust for the  
9 multiplicity of comparisons in this study using a bootstrap  
10 adjustment and their adjusted p value was 0.006.

11 (Slide)

12 We performed a series of exploratory analyses on  
13 the intent-to-treat population. For the purposes of our  
14 analyses, we reclassified one patient who was not transfused  
15 with a platelet count less than 20,000 as having been  
16 transfused. The primary endpoint was actually the number of  
17 patients requiring transfusion and we felt that this patient  
18 required it according to the protocol. This patient was in  
19 the higher dose, 50 mcg/kg, Neumega arm.

20 As was mentioned, there were 5 patients who  
21 withdrew their consent and never received study drug. The  
22 clinical data available on these patients was really quite  
23 minimal, just one page of a case report form that had to do  
24 with transfusion. Two of these patients had it recorded on  
25 that form that they had received platelet transfusion. Both

1 of these patients were in the 25 mcg/kg arm. Three patients  
2 on that form had it reported that they had not received  
3 transfusion. There was a single platelet count, as I  
4 remember, on each one of these that was above 20,000 but  
5 really that is all the data we had on these 5 patients who  
6 never received study drug, and these patients were in the 50  
7 mcg/kg arm.

8 (Slide)

9 This is the result of the first exploratory  
10 analysis that we did. For the purposes of our analysis, we  
11 considered all of those patients who withdrew consent and  
12 didn't receive study drug as having been transfused.  
13 Certainly, one of the advantages of the intent-to-treat  
14 analysis is that it is a conservative analysis, and we  
15 figured this was the most conservative thing to do with  
16 these patients since we really couldn't say for certain that  
17 they had not received a transfusion or did not require a  
18 transfusion under the terms of the protocol.

19 Four of these patients that were reclassified were  
20 in the higher dose Neumega arm. As a result, 7 percent of  
21 the placebo patients in this analysis avoided transfusion,  
22 19 percent in the lower dose Neumega arm and now 25 percent  
23 in the higher dose Neumega arm, and there was still the  
24 appearance of a dose effect. The p value in comparing the  
25 high dose arm to the placebo arm comes out somewhat to 0.08

1 unadjusted. For the purposes of our analysis we decided,  
2 just for simplicity's sake, to report unadjusted p values.

3 (Slide)

4 the next thing we did was just go ahead and  
5 eliminate those 5 patients who never received study drug.  
6 That left still 30 patients in the placebo arm and now 29  
7 patients in each of the two Neumega arms. The result of  
8 this analysis was that 7 percent of the patients in the  
9 placebo arm avoided transfusion compared with 21 percent in  
10 the low dose arm and 28 percent now in the high dose Neumega  
11 arm. In comparing the difference in the placebo and the  
12 high dose arm we got a p value of 0.04 unadjusted for  
13 multiplicity.

14 (Slide)

15 We attempted to do an analysis by center in this  
16 study. There were 20 centers and, as is common with multi-  
17 center studies, the contribution of the various sites varied  
18 quite a bit. There were two heavy contributing sites. They  
19 contributed 19 patients each. Three sites contributed 6 or  
20 7 patients each and then the remaining 15 sites contributed  
21 5 or less patients each. This was a 3-arm study so not all  
22 the sites randomized one patient to placebo and one patient  
23 to the high Neumega arm, which was the arm in which we were  
24 interested.

25 In looking at the transfusion rate, we found that

1 it varied quite markedly by site. In the two largest sites  
2 the transfusion rate was 100 percent and 89 percent. This  
3 site, in which all patients received transfusion, was the  
4 site that contributed all the DiCEP patients, a very  
5 myelosuppressive regimen. The site at which 89 percent of  
6 the patients were transfused was the site that contributed  
7 all the patients who were on the ICE regimen, again quite a  
8 myelosuppressive regimen. At the third largest site the  
9 transfusion rate was only 29 percent, which is really only  
10 2/7 patients. Then when we looked at the fourth and fifth  
11 largest sites and, again, the transfusion rate was 100  
12 percent.

13 So the treatment effect in this study was really  
14 being driven by this one site and a whole smattering of even  
15 smaller sites. We felt we really couldn't get a good  
16 analysis by center, and when we really thought about it  
17 certainly chemotherapy was another variable in this study.  
18 Different sites enrolled different patients with underlying  
19 malignancies. They had different institutional protocols  
20 for the chemotherapy and, in reality, any difference we saw  
21 by site might simply be a difference due to chemotherapy.

22 So what we tried to do was an analysis looking at  
23 treatment results, given a certain level of  
24 myelosuppression. There is, obviously, no good way to  
25 quantitate the myelosuppressiveness of any regimen. So we

1 decided to try using the time to ANC recovery with 500 as a  
2 surrogate for the myelosuppressiveness of the regimen.  
3 Ideally, we should have used data from cycle X for this but  
4 those data weren't available so we used the data from cycle  
5 X+1, realizing that there are statistical problems in doing  
6 this.

7           When we looked at the ANC recovery of 500 in this  
8 study, it varied between 0-20 days, with a mean of 11 days.  
9 It turns out that if we bisected the study population at  
10 that point into a group who had an ANC recovery at 11 or  
11 greater days or 10 or less days, in essence, we had two  
12 equal groups, 43 and 44 patients each, and that is how we  
13 did the analysis.

14           (Slide)

15           These are the results of the analysis of the  
16 patients that had a time of ANC recovery of 500 in 10 or  
17 less days, a group we just arbitrarily labeled our moderate  
18 dose-intensity group. As you can see, 13 percent of the  
19 patients in the placebo arm avoided transfusion compared to  
20 33 percent in the lower dose Neumega arm and now 46 percent  
21 in the higher dose Neumega arm. Again, there is appearance  
22 of a dose effect and certainly a strong suggestion of a  
23 treatment effect in this subpopulation.

24           (Slide)

25           When we looked at the population that had a time

1 to ANC of 500 in 11 or more days, a group that we called  
2 arbitrarily our severe dose-intensity group, we see very  
3 little evidence, if any evidence, of a treatment effect. No  
4 patients in the placebo group avoided transfusion and only  
5 1, or 7 percent, in the lower dose Neumega group and only 2,  
6 or 13 percent, in the higher dose Neumega group avoided  
7 transfusion.

8 (Slide)

9 These are the secondary endpoints that we looked  
10 at. We looked at this in all the patients who had received  
11 study drug, what we call our intent-to-treat populations.

12 So these are all 88 patients who received study drug. The  
13 median number of platelet transfusion events was 2.5 in the  
14 placebo arm, 2 in the lower dose Neumega arm and 1 in the  
15 higher dose, 50 mcg/kg, arm. Comparison of the placebo arm  
16 with the higher dose Neumega arm gave us a p value of 0.07.

17 There was less of a difference seen when we looked  
18 at the mean number of transfusion events, and there was  
19 really no difference in median days to platelet recovery of  
20 a platelet count of greater than 20,000.

21 (Slide)

22 These are the adverse events that were associated  
23 with Neumega in study 9308. By "associated" we mean with a  
24 p value of 0.1 or less. For those that have asterisks the  
25 value was the p value was 0.05 or less than 0.05. For the

1 purposes of the analyses, we combined both the Neumega arms  
2 since, as was said by Dr. Kaye, the incidence of events  
3 really wasn't any different in the two arms. In the Neumega  
4 arm 60 percent of the patients did report peripheral edema.  
5 Almost half or 48 percent reported dyspnea. Obviously,  
6 there is a fair percentage in the placebo group also.

7           In this study, anorexia, fever and headache  
8 happened to be associated with Neumega but this is the only  
9 controlled trial in which this happened. And 20-25 percent  
10 of the patients did report tachycardia or palpitations and  
11 14 percent of patients in this study were documented as  
12 having atrial fibrillation or flutter and none in the  
13 placebo group.

14           About half way through this study they started  
15 actually monitoring for atrial fibrillation with Holter  
16 monitor. About half of these patients were asymptomatic and  
17 were picked up on Holter monitor only. The other half were  
18 symptomatic and that did result in either hospitalization or  
19 prolongation of hospitalization.

20           (Slide)

21           One thing we have been concerned about when you  
22 use growth factors in combination, and that concern was  
23 echoed by this Committee a couple of years ago, is the  
24 potential for an adverse effect on another lineage. There  
25 really was no evidence of lineage steal in this study. The

1 median time to neutrophil recovery was similar in the three  
2 arms. The incidence of febrile neutropenia was also similar  
3 for the three arms. Essentially all the patients were  
4 receiving concomitant G-CSF and there was no evidence of any  
5 adverse interaction of Neumega and G-CSF.

6 (Slide)

7 Moving then to study 9416--

8 (Slide)

9 --the primary objective of this study was to  
10 assess the need for platelet transfusion over 2 cycles. So  
11 it was a 2-cycle study. The primary endpoint, again, was  
12 changed to be similar to that of 9308, the need for platelet  
13 transfusion, yes or no. It wasn't a decision that I made  
14 myself. We did discuss it at the divisional level with the  
15 Division of Biostatistics and we agreed that, given the  
16 circumstances, it was an appropriate change to be made at  
17 that point. The secondary endpoints were similar as in  
18 9308.

19 [Slide.]

20 To be eligible for this study, patients had to  
21 have high-risk stage 2, 3 or 4 breast cancer so, at least in  
22 this study, we are dealing with one single underlying  
23 malignancy, and they had to be undergoing dose-intense  
24 chemotherapy with the same cyclophosphamide-doxorubicin  
25 regimen so we are dealing at least with one chemotherapy

1 regimen in this study.

2 Patients with a history of atrial arrhythmias or  
3 conditions predisposing to atrial arrhythmias were not  
4 eligible for this study. The study consisted of two blinded  
5 cycles without dose reduction with crossover followed by  
6 four optional open-label cycles. All patients received  
7 concomitant G-CSF in the study as per protocol.

8 [Slide.]

9 The patients were stratified by investigator or  
10 site and whether or not they have had prior chemotherapy.  
11 They were randomized to 50 mcg/kg of Neumega or placebo.  
12 There were 77 patients enrolled. All were women. The arms  
13 were balanced for the usual demographic factors.

14 [Slide.]

15 37 patients were randomized to placebo, 40 to the  
16 Neumega arm. All entered cycle 1 and received study drug.  
17 13 patients did drop out of cycle 1. The dropouts were  
18 similar in both arms and the reasons for dropout were  
19 similar in both arms.

20 Five of these patients who dropped out of cycle 1  
21 were transfused prior to dropping out. Thus, they had  
22 reached a study endpoint. They were treatment failures.  
23 One of these was in the placebo arm and four were in the  
24 Neumega arm. However, that left eight patients who had not  
25 been transfused when they dropped out of the study and how

1 these eight patients are dealt with in an intent-to-treat  
2 analysis becomes one of the problems in analyzing this study  
3 for a couple of reasons.

4           One is that eight patients does account for  
5 10 percent of the study total and the second thing is there  
6 was a major imbalance with six of these being in the placebo  
7 group and only two in the Neumega group. All the patients  
8 that entered cycle 2, then, went on to complete the study.

9           [Slide.]

10           This is the intent-to-treat analysis as performed  
11 by the sponsor as was mentioned by Dr. Kaye for their  
12 intent-to-treat analysis. All the patients with the unknown  
13 outcomes, these eight patients, that dropped out of cycle 1  
14 without being transfused were considered treatment failures  
15 placed in the transfused group.

16           This was, again, a decision that was made  
17 prospectively prior to unblinding the study and prior to the  
18 realization that there was this major imbalance in the  
19 dropouts between the placebo and Neumega group. Certainly,  
20 it is the common thing that would be done in situations like  
21 this where, when you have to account for an outcome for  
22 patients for an intent-to-treat analysis, they are assigned  
23 the worst possible outcome vis-a-vis the primary endpoint  
24 which, of course, in this case, would be transfusion.

25           The result of this analysis was that 41 percent of

1 the patients in the placebo group avoided transfusion  
2 compared to 68 percent in the Neumega group. That result  
3 was statistically significant with a p-value of 0.02.

4 [Slide.]

5 We performed a series of exploratory analyses for  
6 this study also. Again, we reclassified one patient who was  
7 not transfused with a platelet count of 20,000. The  
8 transfusion trigger was 20 or less. That patient was  
9 reclassified as having been transfused for the same reason  
10 we did it for study 9803. We then dealt with those eight  
11 patients who dropped out of cycle 1 without being transfused  
12 by assigning them different outcomes for the intent-to-treat  
13 analysis.

14 The first thing we did was simply proportion them  
15 50/50. The rationale for that was that slightly less than  
16 50 percent of the patients in this study required platelet  
17 transfusion. It was about 45 percent depending on what you  
18 use for your denominator. So it seemed to be a reasonable  
19 thing to do is just to go ahead and proportion them 50/50.

20 The next thing we did was just simply carry the  
21 last observation forward which, of course, means that these  
22 were then placed in the "no transfusion" group because they  
23 were not transfused in cycle 1. So they would be all  
24 considered treatment successes.

25 Then the last thing we did was what we called our

1 worst-case scenario where we just decided to bias the  
2 analysis as much as possible against Neumega by placing the  
3 six patients in the placebo group in the non-transfused  
4 category and the two patients in the Neumega group in the  
5 transfused category.

6 [Slide.]

7 These are the results of these exploratory  
8 analyses. Here I am just giving data now for those patients  
9 who avoided platelet transfusion. The top row is the  
10 sponsor's intent-to-treat analysis. There was a 27  
11 percentage difference between the incidence of avoidance of  
12 platelet transfusion in the placebo group and Neumega group,  
13 and that was statistically significant with a p-value of  
14 0.02.

15 As we progressively reassigned these eight  
16 patients, we can see that that difference narrows  
17 considerably. It doesn't go to zero. It doesn't go away.  
18 And the p-value obtained in analyzing that difference  
19 progressively increases.

20 [Slide.]

21 We again did an analysis by center. In this  
22 study, two sites contributed 13 patients each, three sites  
23 contributed 8 or 9 patients each, and nine sites contributed  
24 5 or less patients each. But at least here, we are only  
25 dealing with two arms, so many of the sites did randomize a

1 patient to both arms.

2           Again, we saw, kind of surprisingly, the  
3 transfusion rate did vary quite a bit by site even though we  
4 were only dealing with one disease and one chemotherapy  
5 regimen in this study. When you looked at the sites with  
6 five or more patients, only one really showed an appreciable  
7 treatment effect.

8           In the other sites, the effect was borderline or  
9 even but, as was commented on in Dr. Kane's analysis, in no  
10 site, in none of the 14 sites, did the placebo patients ever  
11 fare better than the Neumega patients in this study.

12           [Slide.]

13           We also looked at the effect of prior chemotherapy  
14 since that was one of the stratification elements in this  
15 study. Again, these are the data for the avoidance of  
16 platelet transfusion. We used the last observation carried  
17 forward for dealing with the patients in missing data in  
18 this analysis, so all the patients would have been placed,  
19 then, in the no-transfused arm.

20           In looking at the patients who had not received  
21 prior chemotherapy, really, there is not a great difference  
22 in the incidence of those who avoided transfusion. Most  
23 patients did quite well. Certainly, in those patients who  
24 had prior chemotherapy, there was a strong suggestion of a  
25 treatment effect. 30 percent of the patients in the placebo

1 arm avoided transfusion compared with 62 percent in the  
2 Neumega arm.

3 We have to be a bit cautious, however, because in  
4 this group, we are dealing with less than a third of the  
5 patients in the study.

6 [Slide.]

7 These are the adverse events that were associated  
8 with Neumega in Study 9416. Again, "associated" means with  
9 a p-value of less than 0.01 and the asterisk denotes those  
10 where the p-value was less than 0.05. For the purposes of  
11 this analysis, we combined both cycles. Again, edema and  
12 dyspnea lead the list with percentages that are essentially  
13 identical to those percentages that were seen in Study 9308.

14 Probably related to the dyspnea, patients with  
15 cough noted more increase in cough in the Neumega arm.  
16 Here, in this study, we do see this peculiar conjunctival  
17 injection which does sort of sign like the plethoric changes  
18 you see in people with P. vera. A quarter of the patients  
19 were found to have this.

20 18 percent of the patients did have pleural  
21 effusions in this study. Again, this was a study in women  
22 with breast cancer and a high percentage of women did have  
23 Stage 4 breast cancer. I think about half of these were an  
24 increase in pleural effusion, I think by our count. The  
25 other half seemed to be de novo effusions.

1           Again, the one death that could be associated with  
2 study drug occurred in a woman with Stage 4 breast cancer  
3 who did have an effusion that was noted to increase while on  
4 study and she did expire and was felt to have a  
5 cardiopulmonary arrest.

6           [Slide.]

7           In summarizing our impressions from the data  
8 presented, we would say that, certainly, Study 9308 did  
9 consistently differentiate the Neumega 50 mcg arm from  
10 placebo. I think all the exploratory analyses we did were  
11 supportive of a treatment effect in this study.

12           In looking at the data, there is at least a  
13 suggestion that the treatment effect may be minimal in  
14 patients who are receiving myelosuppressive regimens. I  
15 think this is born out by the result of the randomized,  
16 double-blind, placebo-controlled study of Neumega following  
17 myeloablative chemotherapy where all patients, regardless of  
18 study-drug assignment, required platelet transfusion.

19           I think Study 9416 was less supportive. The  
20 analysis of this study was complicated by the fact that we  
21 had to account for 10 percent of the patients in doing the  
22 intent-to-treat analysis and, certainly, how those patients  
23 were classified for the analysis was important in the  
24 results received or the particular p-values obtained.

25           But, again, I think it should be mentioned that at

1 none of the 14 sites was placebo ever superior to Neumega in  
2 this study.

3           Finally, I think we would have to say, at least on  
4 the basis of these two studies which were of widely  
5 different design, that the treatment effect seen was modest.  
6 In Study 9308, the median number of platelet transfusion  
7 events was 2 1/2 in the placebo group and 1 in the higher-  
8 dose Neumega group. In 9416, the median number of  
9 transfusion events was 0 in both arms.

10           [Slide.]

11           In looking at the side effects, certainly side  
12 effects were common with Neumega in this study. Most  
13 patients did report at least one adverse event, although  
14 that was true of the placebo patients also. The majority  
15 of adverse events reported were Grade 2 and I think that was  
16 especially true of the ones that were actually statistically  
17 associated with Neumega.

18           In spite of what we saw in Study 9308, Neumega  
19 doesn't really seem to be associated with the toxicities  
20 common to many cytokines. There were actually five  
21 randomized placebo-controlled trials if you include the two  
22 in the normal volunteers. 9308 was the only one that  
23 reported any association of fever or any of the cytokinelike  
24 side effects.

25           Certainly, there is no evidence that there is any

1 adverse effect on neutrophil recovery, no evidence of  
2 lineage steal nor was there any evidence of an adverse drug  
3 interaction with G-CSF. We have absolutely no data,  
4 however, clinical data anyway, on the use of Neumega with  
5 GM-CSF.

6 I haven't reported it here, but we did review the  
7 long-term follow-up registry data and we could see no  
8 evidence of tumor stimulation or any actual adverse effect  
9 on the underlying tumor. Again, we didn't report it, but  
10 antibody formation does not seem to be a problem with this  
11 recombinant protein.

12 [Slide.]

13 Neumega is associated with some major side  
14 effects, however, and certainly fluid retention seems to be  
15 the mechanism of most, if not all, of them. About 60  
16 percent of the patients did report peripheral edema. About  
17 half reported dyspnea. In those patients who had underlying  
18 malignancies that might predispose to effusions, effusions  
19 occurred in about 20 percent of patients.

20 In these studies, these were almost all women with  
21 breast cancer but I think we would have to assume the same  
22 thing might happen, let's say, in women with ovarian cancer  
23 and ascites and so forth.

24 How much of a problem this dilutional anemia may  
25 be when given with chemotherapy is hard to say. Certainly,

1 it was something that was identified very early in the pre-  
2 IND meeting on the basis of the preclinical studies that  
3 Neumega appeared to cause a dilutional anemia. It was seen  
4 in the initial dose-escalation study and very nicely studied  
5 in two randomized, double-blind, placebo-controlled studies  
6 in normal volunteers.

7           However, in these studies, anemia wasn't more of a  
8 problem than it was in the placebo arm. If you look at the  
9 actual percent of decrease of hemoglobin from baseline, it  
10 was pretty similar in the patients receiving Neumega and the  
11 patients receiving placebo, maybe a few percentage points  
12 more in the patients receiving Neumega but certainly not  
13 anything that would lead to any kind of clinical  
14 significance.

15           The hemoglobin decrease seemed to nadir a little  
16 earlier in both studies in the Neumega patients than it did  
17 in the placebo patients, but recovery to baseline or even  
18 above baseline was pretty similar in both groups and there  
19 was no difference in red-cell transfusion requirements in  
20 the patients receiving Neumega or the patients receiving  
21 placebo.

22           Certainly, Neumega does appear to cause cardiac  
23 rhythm disturbances. 20 to 25 percent of the patients did  
24 report tachycardia or palpitations and 15 percent, at least  
25 of the unselected patients, did have documented atrial

1 fibrillation or flutter. About half of these were  
2 asymptomatic and picked up on Holter monitor alone. The  
3 other half were symptomatic, however, and did lead either to  
4 hospitalization or maybe prolongation of hospitalization.

5 Finally, there is the kind of peculiar  
6 conjunctival injection that was seen in about 25 percent of  
7 the patients but was actually seen in up to 80 percent of  
8 the normal volunteers who received this. The exact  
9 mechanism is unknown, but it certainly doesn't appear to be  
10 of clinical significance.

11 I think I will stop there and take any questions.

12 DR. VOSE: Thank you.

13 Does the committee have any questions for Dr.  
14 Steffen?

15 DR. AUCHINCLOSS: I guess it is not probably  
16 surprising that you can come up with a chemotherapeutic  
17 regimen that knocks the platelets down so far and so  
18 completely that this drug can't prevent effective  
19 transfusion. But it could still be a benefit, obviously, if  
20 it decreased the need for subsequent transfusions.

21 It seemed like it did but not in a dramatic way.  
22 And if it created a faster regulatory. The most surprising  
23 data to me was that the time-to-recovery at 20,000 is 13  
24 days in each case in the slide that you showed. Can you  
25 comment on that? Why would that be?

1 DR. STEFFEN: No. I guess it surprised us, too,  
2 other than I would assume, if it prevents severe  
3 thrombocytopenia, that is probably somewhat of a different  
4 mechanism than stimulating recovery.

5 DR. AUCHINCLOSS: Why?

6 DR. STEFFEN: Why? I don't know.

7 DR. VOSE: Other questions?

8 DR. SWAIN: Can you just comment on the  
9 papilledema that was seen in the studies and in your review  
10 of the toxicities because it wasn't mentioned.

11 DR. STEFFEN: This is something that I think we  
12 are not really certain what it means. There were, I think,  
13 four cases of papilledema reported. Three of them were in  
14 patients who had central-nervous-system malignancies. What  
15 is a little more of a concern is that two of them were in  
16 the children that were treated in the dose-escalation study  
17 so that it is 2 of something like 40 patients or something  
18 like that. I can't remember how many were in that study.

19 Again, we really don't know the exact mechanism of  
20 it. It didn't seem to be a problem but I think it is,  
21 certainly, something that bears watching, at least.

22 DR. SWAIN: I think it was also in one of the  
23 breast-cancer patients.

24 DR. STEFFEN: It was in two adult patients. I  
25 think one did have a CNS malignancy, I think. I can't

1 remember now.

2 DR. WEISS: I was wondering of the sponsor has a  
3 more complete dataset on the papilledema because I also  
4 thought I saw that it was in some of the children with  
5 amegakaryocytic thrombocytopenia also as well as a patient  
6 or two with brain tumors.

7 DR. KANE: The question was, again, about the  
8 clinical incidence of papilledema. Let me just begin with  
9 the preclinical background to this. We are going to switch  
10 computers so we can show our slides.

11 [Slide.]

12 In non-human primate toxicology studies, animals  
13 treated with the dose of 1000 mcg/kg, so about 20-fold  
14 higher than we are using in our clinical studies we are  
15 requesting for approval in the clinical application,  
16 developed papilledema during the course of dosing up to four  
17 weeks. About half the animals did.

18 This was fully reversible after a four-week  
19 recovery period. It was not associated with any  
20 histopathologic changes. There was no inflammation or other  
21 histopathology associated with other than mild edema seen in  
22 the sections.

23 [Slide.]

24 The next slide, P2, there were four out of the 242  
25 patients who had any Neumega exposure in our oncology

1 studies, so this includes the adult studies, the five adult  
2 studies and the pediatric trial, had papilledema. Three of  
3 the four, as Dr. Steffen mentioned, had CNS tumor and that  
4 includes both of the children who had papilledema.

5           The adult woman with breast cancer in 9416 who had  
6 papilledema had a C2 cervical spinal metastasis that was  
7 documented to be compressing the spinal cord. The fourth  
8 patient had very mild papilledema that was asymptomatic,  
9 picked up only by ophthalmologic exam on a routinely  
10 scheduled examination, actually picked up by the same  
11 examiner who saw the papilledema in the patient with the C2  
12 tumor at the same site.

13           So this, when it did occur, was mild and it was  
14 found after several cycles of treatment.

15           [Slide.]

16           PO4 shows that there were two patients who were  
17 reported to us in an investigator-sponsored study of  
18 children with a rare disorder, amegakaryocytic  
19 thrombocytopenia which causes severe thrombocytopenia who had  
20 papilledema reported during the course of their  
21 participation in the study.

22           This was a study in which there was inpatient  
23 dose escalation, so these patients were being treated  
24 monthly with increasing doses over the course of each  
25 progressive month of Neumega. One ten-year-old child was

1 reported to have visual blurring after a total cumulative  
2 dose of 4200 mcg/kg at which time she was being treated at  
3 the 100 mc/kg dose level and was found to have papilledema  
4 on examination.

5 Another child, an eight-year-old with the same  
6 diagnosis, had visual blurring and decreased acuity after a  
7 similar cumulative total dose. This patient also had signs  
8 of viral retinitis on examination, so it is really not clear  
9 whether what was being observed was part of that  
10 pathophysiology or something potentially related to the  
11 study drug.

12 DR. VOSE: Thank you.

13 DR. BERMAN: As 20 percent of the patients had  
14 pleural effusions, did this result in any patient having a  
15 thoracentesis to rule out progressive disease which might,  
16 in fact, be problematic in someone with low platelets?

17 DR. KANE: The question was about patients with  
18 pleural effusions, did any undergo thoracentesis. The  
19 answer is I don't believe so. We can double check that but  
20 I don't recall any patients who underwent thoracentesis  
21 while on our study for that reason.

22 DR. O'FALLON: The early termination of the  
23 clinical trial usually generates more reaction than I have  
24 heard from either group.

25 DR. STEFFEN: I think it was slow accrual, wasn't

1 it? When you really look at this, it is a tough study to do  
2 because the patients are hard to come by and to get them  
3 into the protocol. So I think it was just slow accrual.

4 DR. MILLER: Would you like to comment on either  
5 the FDA or the sponsor's feeling about the concomitant use  
6 of diuretics in the IL11. One, the one study where maxzide,  
7 I think, was used to try and prevent the fluid of the edema,  
8 even though that was a potassium-sparing diuretic and I  
9 suspect the patients were closely monitored, given that it  
10 was being used as part of the clinical trial, two patients  
11 died.

12 I guess my concern maybe is if the drug is  
13 approved and available and people will see edema, one of the  
14 things that people will do may give diuretics. I guess I am  
15 concerned that there maybe needs to be some pretty  
16 significant education that this may not be best thing to do  
17 because if you have two deaths in a very closely monitored  
18 clinical trial, especially if the deaths appeared to occur  
19 after the was already one dose reduction in the maxzide for  
20 the hypokalemia, I think you may need to be pretty strong  
21 about saying you shouldn't use diuretics in this patient  
22 population.

23 I would like both of your comments on that.

24 DR. STEFFEN: We discussed that incorporation into  
25 that trial. It was used in one of the normal volunteer

1 studies and there was really no problem in the normal  
2 volunteers. We had the discussion mainly on what is the  
3 best way. At that time, we were a little more concerned  
4 that the dilutional anemia that is seen may be a problem and  
5 may complicate any of a variety of clinical-management  
6 problems.

7 I think the patients in the other trials who had  
8 edema and dyspnea, about half of them were managed with  
9 furosemide, I think, as I remember--about a third. There  
10 was really no problem there. Whether it is related to the  
11 fact that this is a chlorathiazide thiampterine combination  
12 diuretic or not, I don't know. I think certainly something  
13 like that would be very prominently displayed in any  
14 labeling.

15 I think, certainly, we don't have evidence that  
16 non-potassium-sparing diuretics have caused the same  
17 problem.

18 DR. MILLER: Why would potassium-sparing diuretics  
19 make that problem worse than better?

20 DR. STEFFEN: We don't know. Again, it is the  
21 combination. I am not quite sure. I think that may be one  
22 reason why these kinds of combination products are kind of  
23 falling out of favor.

24 DR. KANE: My comment is that we began the  
25 systematic use of diuretic in that study because of

1 observations in the normal volunteers. If I could see 52.

2 [Slide.]

3 In a very carefully controlled setting, we found,  
4 as we had seen suggested in the other studies, that Neumega  
5 treatment was associated with decreased hemoglobin  
6 concentration which is the dilutional effect, mild weight  
7 gain and sodium and water retention equivalent to about the  
8 volume of normal saline which distributed between the  
9 intravascular and interstitial extracellular fluid would  
10 account for this degree of hemoglobin decrease.

11 There was no effect on blood pressure, creatinines  
12 or potassium excretion. This was a three-armed study in  
13 which the subjects either received placebo, Neumega by  
14 itself or Neumega with the combination diuretic, potassium-  
15 sparing and hydrochlorothiazide.

16 The diuretic did improve the dilutional anemia  
17 associated with Neumega.

18 [Slide.]

19 On the next slide, the actual curves are shown for  
20 hemoglobin concentration over time during the course of this  
21 study. The patients or the normal volunteers who received  
22 Neumega by itself had this decrease of about 2 g/dL in  
23 hemoglobin, from about 14 1/2 to 12 1/2. The placebo group  
24 had a relatively constant hemoglobin over the course of the  
25 study and the Neumega-diuretic group actually had an

1 increase in hemoglobin concentration initially because of  
2 the diuretic effect.

3 By the end of the study, their hemoglobin  
4 concentrations were somewhat below the placebo group but  
5 certainly well above the maxzide group. If you sort of  
6 integrate the area above this curve and this curve, which is  
7 the placebo and the combination Neumega-maxzide, you can see  
8 that there really is a substantial blending of the  
9 dilutional anemia that this diuretic can achieve.

10 We didn't see increases in potassium excretion in  
11 the Neumega-alone arm, but a combination diuretic that  
12 includes hydrochlorothiazide can certainly result in a net  
13 potassium excretion whether or not someone is receiving  
14 Neumega.

15 So we agree that there should be prudent  
16 monitoring of fluid and electrolyte balance, in particular  
17 potassium, if a diuretic is used in the patient receiving  
18 Neumega as would be common practice in general.

19 DR. MILLER: Do you know of those patients  
20 received cisplatin and had preexisting potassium wasting  
21 from something like cisplatin?

22 DR. KANE: That is a very good question. Both  
23 patients were on regimens of iphosphamide by itself. As you  
24 know, iphosphamide has also been associated with a renal  
25 tubular defect which results in increased potassium and

1 other electrolyte losses and has even been reported in the  
2 literature as causing fatal hypokalemia.

3 So there were a series of, I think, complications  
4 with these patients which, together, resulted in developing  
5 severe potassium depletion.

6 DR. MILLER: Thank you.

7 DR. VOSE: Are there additional questions for Dr.  
8 Steffen and the sponsor.

9 DR. STEFFEN: I was just going to say, I think the  
10 thing is, too, that this was chronic diuretic  
11 administration. I certainly think, given the data, that  
12 there really isn't that much of a difference in anemia in  
13 patients on placebo and Neumega because of the effect of  
14 chemotherapy.

15 I don't know that these patients are going to be  
16 on chronic diuretic use, so I don't know that we would  
17 necessarily limit intermittent diuretic use, one shot of  
18 lasix, that sort of thing.

19 DR. AUCHINCLOSS: What are the limitations on  
20 dose? What happens when you go to 100 mcg?

21 DR. KANE: In the phase I study, we treated three  
22 patients with 75 mcg/kg and only a single patient with 100.  
23 At 75 mcg/kg, the patients began complaining of some aches,  
24 myalgia and one patient, actually, although it was  
25 considered grade 2 by the investigator, withdrew from the

1 study for that reason.

2 At 100, there was one patient treated in the  
3 prechemotherapy cycle. This patient was a woman in her 60's  
4 with a history of stroke which we weren't aware of at the  
5 beginning of the study, had a small thrombotic cerebral  
6 event on day 4 of treatment.

7 Whether this was related to Neumega, we don't  
8 know, but we decided, because of the adverse events at 75  
9 and that single-event in 100, that we wouldn't pursue higher  
10 doses.

11 I should also mention that in 9206, in the  
12 chemotherapy cycles--if I can see 25.

13 [Slide.]

14 We looked very carefully at dose relationship for  
15 platelet nadirs during the two cyclophosphamide-adriamycin  
16 chemotherapy cycles in this study. I mentioned this in the  
17 presentation, but these are graphs showing the actual data.  
18 For the four dose groups in the two chemotherapy cycles,  
19 their platelet counts over time--and these are displayed on  
20 a logarithmic scale here.

21 What you can see is that the patients in the  
22 10 mcg/kg cohort had a platelet nadir of 67,000 in the first  
23 cycle where patients in the other three dose groups all had  
24 nadirs above 150,000 and there didn't appear to be any dose  
25 relationship within this range.

1           Similarly, in the second cycle, patients in the 10  
2 mcg/kg cohort had nadirs on average of 44,000 while all  
3 three of the other dose groups were above 100,000 on  
4 average. These nadirs in the 10 mcg/kg group were similar  
5 to what had been seen previously at Indiana with patients  
6 receiving this chemotherapy regimen without any growth  
7 factor.

8           So we really thought that we were seeing a pretty  
9 good effect and that there wasn't reason to go to a higher  
10 dose. That is why we decided to focus on 25 to 50 in the  
11 randomized trials.

12           DR. VOSE: Thank you.

13           Additional questions? If not, I think we will go  
14 ahead and go on to the discussion questions.

15                           **Committee Discussion**

16           DR. VOSE: The first question; "Given the clinical  
17 data, does Study 9308 provide evidence that Neumega is  
18 effective for the presentation of recurrent severe  
19 thrombocytopenia after an episode of severe thrombocytopenia  
20 in a previous chemotherapy cycle or so-called secondary  
21 prophylaxis?"

22           Who would like to start the discussion on this  
23 issue?

24           DR. BROUDY: I am always willing to comment. I  
25 would say yes to this question. It seems to me that about

1 one-third of the patients treated with Neumega avoided  
2 platelet transfusions above those in the placebo group who  
3 avoided platelet transfusions. So, of all the ones treated  
4 with Neumega, about a third of them benefitted in a sense in  
5 that they avoided a platelet transfusion in comparison to  
6 having required a transfusion during the previous course of  
7 chemotherapy.

8           These differences were statistically significant.  
9 There was not the problem of reassigning of patients that  
10 complicates the second trial. So I would answer yes to  
11 question no. 1.

12           DR. SWAIN: I would totally agree with that and I  
13 would say yes, also. The only concern I have and I don't  
14 know how to really enter this, when you looked at the slide  
15 that he just put on. At the end, the 25 and 50 mcg dose  
16 were the same. I guess these patients hadn't had that much  
17 chemotherapy but you don't see that difference in the  
18 randomized study at all.

19           As I mentioned before, there is a difference in  
20 the patients who got carboplatin and that is the drug with  
21 which we would want to use this. So, with some reservation  
22 there. But I agree with Dr. Broudy that I would vote yes  
23 for this.

24           DR. VOSE: I think, certainly, from my  
25 perspective, this study shows benefit and is not complicated

1 by some of the issues related to the primary prophylaxis  
2 issue. I think it has a pretty strong indication.

3 Any other comments? If not, why don't we move on  
4 to the second question, then. "Given the clinical data,  
5 does study 9416 provide evidence that Neumega is effective  
6 for the prevention of severe thrombocytopenia when  
7 administered, starting with the initial of therapy or so-  
8 called primary prophylaxis."

9 There was quite a bit of difference related to  
10 patients that had no prior therapy and those that had prior  
11 therapy and the amount of prior therapy was an issue, and  
12 some of the other complicating issues we discussed.

13 DR. LEITMAN: Could I ask a procedural question?

14 DR. VOSE: Yes.

15 DR. LEITMAN: From experience on other committees,  
16 I thought we would come to a vote after each discussion.

17 DR. VOSE: I am combining this with question no. 4  
18 which is actually going to be the voting question.

19 DR. BROUDY: I was much less convinced by the  
20 second study. I think there were a lot of problems with it  
21 and I think the critical issue of how those patients were  
22 reassigned--and it seemed to me that, in a sense, there was  
23 no way of knowing how to assign those 10 percent of the  
24 patients in a sense.

25 In basic science research, which I do, we can't

1 create data to fill in missing data and so I could certainly  
2 agree with reassigning the one patient who was not  
3 transfused who had achieved the trigger point for a  
4 transfusion as having been transfused.

5 But I am quite uncomfortable with the reassigning  
6 of the other, I think it was eight patients. And that very  
7 strongly affects the outcome of the trial. So I was much  
8 less convinced that IL11 has shown benefit for primary  
9 prophylaxis in patients who have not previously required a  
10 platelet transfusion.

11 DR. MILLER: I agree that the primary prophylaxis  
12 trial was difficult to evaluate because of the difference in  
13 patients receiving or not receiving previous chemotherapy.  
14 When the whole study is looked at, I don't think that this  
15 can support the endpoint of primary prophylaxis. So I  
16 agree.

17 DR. AUCHINCLOSS: I don't agree with that  
18 assessment. I think that it is a false distinction that we  
19 are looking at primary versus secondary prophylaxis. I  
20 thought that the study, while obviously having problems in  
21 conjunction with the first study, basically supported the  
22 notion that this drug can prevent thrombocytopenia in a  
23 group of patients.

24 The question is which group of patients. I don't  
25 know the answer to that still. To a degree, it is a

1 function of what their condition is like before you start,  
2 it would appear, and, to a degree, it is a function of how  
3 strong the chemotherapeutic program is.

4           So I don't think we have data here to make a  
5 distinction in my own mind between primary and secondary  
6 use. I would actually suggest that it be licensed as a drug  
7 that can prevent chemotherapy-induced thrombocytopenia.

8           DR. VOSE: Dr. Dutcher, do you have any comments?

9           DR. DUTCHER: I actually agree with Dr.  
10 Auchincloss about that. I think that we don't have  
11 sufficient data to say it is not something that can,  
12 perhaps, over time, prevent a degree of thrombocytopenia. I  
13 would like to actually see some more long-term studies in  
14 terms of using it in conjunction with chemotherapy over a  
15 period of time and look at the number of platelet  
16 transfusions that are required and see if the whole spectrum  
17 of its effect will limit the need for transfusion and,  
18 perhaps, help us limit our transfusion threshold.

19           But that is the future, I think.

20           DR. BROUDY: I guess I would like to point out  
21 that a licensing decision has to be made on the basis of  
22 data that is convincing that shows a significant difference  
23 between the treated patients and the control patients. I  
24 really don't believe that Study 9416 showed that.

25           In a practical sense, if it is licensed for

1 secondary prophylaxis, it will be available and then  
2 additional studies can be done or it could be used in a  
3 practical sense. But I would certainly vote against  
4 licensing it for primary prophylaxis and that the data do  
5 not convince me that it benefitted these patients.

6 DR. VOSE: I have to agree with Dr. Broudy. I  
7 think it is a concern that the data, as far as looking at  
8 the patients that have been previously treated and  
9 untreated, leaves very few patients in that subset that did  
10 show some benefit. I am concerned that the data that we  
11 have to work with does not really support that issue  
12 although certainly you are right, with a multicycle and a  
13 lot more patients, that may be the case. But we have to  
14 work with the data that we have available right now.

15 DR. AUGUST: I think whichever way we go, it is  
16 important to somehow require the company to collect more  
17 data in this regard. I think, number one, that a number of  
18 patients that were treated were few, number two, the  
19 chemotherapy regimens were quite diverse.

20 It is quite possible that embedded in the  
21 oncologic world, the primary therapy out there, there will  
22 be groups of patients who will benefit significantly from  
23 this treatment. I think we should oblige the company to  
24 continue that search. I would hate to think that if we  
25 voted no, we would be throwing the baby out with the bath

1 water.

2 DR. VOSE: I think that, certainly, there is a  
3 hint of efficacy here for a certain patient population. As  
4 Dr. Broudy pointed out, if it is approved for other uses,  
5 that doesn't preclude that future studies will be done to  
6 try and point that out and to give that patient population  
7 additional benefit.

8 DR. BROUDY: I would also like to commend the  
9 company. I think they have done a tremendously good job of  
10 studying this drug in a normal patient population trying to  
11 really understand the mechanism of the plasma volume  
12 expansion, the possible toxicities associated with this  
13 drug. The data were very, very clearly presented on the  
14 studies and the normals treated with placebo or Neumega or  
15 plus or minus the diuretic.

16 Also, they have achieved 99 percent follow up on  
17 their patients long term, which is remarkable. I would just  
18 like to say I think they will be responsible and do that. I  
19 have been impressed by the quality of this application, the  
20 quality of the studies they did in the normals.

21 DR. NEEMAN: Excuse me. I am the statistician for  
22 the FDA, Terry Neeman. I wanted to comment on your charge  
23 of creating data and analysis of creating data.

24 DR. BROUDY: Not a charge, just a comment. It was  
25 certainly not an accusation.

1 DR. NEEMAN: Certainly, what Dr. Steffen  
2 presented, we did create data and then do an analysis based  
3 upon assigning or imputing data or assigning patients'  
4 outcomes. I just wanted to comment that the analysis that  
5 the company did in the last week that wasn't part of your  
6 briefing package was an analysis that did not create data in  
7 which every patient's information was used in an intent-to-  
8 treat analysis.

9 Their reported p-value was 0.04 and they report to  
10 me that when we take this disputed patient that we  
11 classified as a failure and they classified as a treatment  
12 success, that the p-value was 0.11. Now, that analysis is a  
13 valid analysis under the assumption that those patients who  
14 are so-called missing are missing at random.

15 We didn't mean to imply that the true p-value was  
16 0.49 or the true p-value was--in fact, we are prepared, if  
17 you want a p-value that you want to live with, it is  
18 probably, by the FDA, someplace in the neighborhood of 0.1  
19 and 0.15 and by the sponsor's analysis in the neighborhood  
20 of 0.05.

21 DR. VOSE: I think that just points out that one  
22 patient here or there makes a huge difference and so that  
23 the trial size is a little bit difficult as far as trying to  
24 do some of these analyses in the patients that dropped out.

25 DR. NEEMAN: That is certainly one of the problems

1 that we pointed out earlier, one of the problems we had with  
2 the data, that it was not very robust.

3 DR. VOSE: Any further comments?

4 DR. AUCHINCLOSS: Just to say that I don't believe  
5 we ought to license drugs either on the basis of absence of  
6 data. My only point is that I think it is a false  
7 distinction, primary versus secondary prophylaxis. I am  
8 sure there are secondary chemotherapy programs for which  
9 there will be no benefit for this drug, so why do you say  
10 that that is the one that we should go for when it is, I  
11 think, just as likely--my point is that we should just leave  
12 that issue out altogether.

13 I certainly agree there ought to be future trials,  
14 but you know once this drug is out there, there will be lots  
15 of future trials trying to find who really gets benefit and  
16 which patient population should be using it.

17 DR. MILLER: Primary versus secondary has nothing  
18 to do with the chemotherapy. Primary prophylaxis means all  
19 comers who get started on this regimen will get the drug and  
20 secondary prophylaxis means that only patients who have  
21 already shown that they have the event.

22 So you are taking a very wide patient population  
23 and narrowing it down until you have the data that it is  
24 effective in the wide population. It is not that patients  
25 who initially get chemotherapy should get it. It is based

1 on whether or not they have proven that they have a  
2 significant enough risk of thrombocytopenia to then be able  
3 to continue therapy. They need the support and that is the  
4 difference.

5 DR. AUCHINCLOSS: Yes. I stand corrected on that,  
6 but I still think the issue is not a false one.

7 DR. LEITMAN: What this comes down to is the  
8 patient won't get it on the first cycle of chemotherapy but  
9 will get it on the second cycle of chemotherapy for  
10 indication no. 1 if for indication no. 2--you are not really  
11 restricting use.

12 DR. MILLER: At the most, 25 percent of the  
13 patients who are getting chemotherapy will require platelet  
14 transfusion with the initial cycle of chemotherapy. So,  
15 yes, of the 25 percent of patients who get it with the first  
16 cycle, then they could be treated. So it is a major  
17 difference.

18 I think that there may be very well a valid role  
19 in certain regimens for primary prophylaxis. I think that  
20 the primary-prophylaxis studies are actually much easier to  
21 do than the second-day prophylaxis studies. I think we need  
22 to better pick primary-prophylaxis trials in patients who  
23 have been treated before--you know that is a high-risk  
24 group--and show that, in that patient population, it is  
25 effective at preventing transfusion in that patient

1 population.

2 So there are major differences.

3 DR. BERMAN: But, practically, those major  
4 differences, once the drug is licensed, really are of not  
5 significance if we are to learn anything from the G or GM.  
6 In clinical practice, it may be licensed for the use of  
7 documented neutropenia but, in fact, many oncologists,  
8 myself included, use it in the setting where we anticipate  
9 neutropenia.

10 So I think if it is licensed, that distinction  
11 will be moot.

12 DR. VOSE: Typically, post-marketing studies will  
13 be very helpful in trying to clarify these issues. I think  
14 that is really the area where this is going to have to be  
15 clarified.

16 MS. MEYERS: Number one, FDA can request post-  
17 marketing studies but the manufacturer doesn't have to do  
18 them. There is no requirement. So post-marketing studies  
19 are--sometimes companies do them, sometimes they don't. The  
20 issue, from the perspective of patients, is if you license  
21 it for secondary, it may not get reimbursed for primary.

22 The reimbursement problem for a sick cancer  
23 patient who may not have very good insurance is a big  
24 problem. So I would urge you to be as liberal as possible  
25 on the labeling of this to make sure everybody gets

1 reimbursed whether it is primary or secondary.

2 DR. VOSE: I think we all understand that, but we  
3 also have to go with the data that is available and what we  
4 feel is appropriate.

5 DR. SIEGEL: Just a further comment on whether it  
6 is a distinction with impact. While the labeled indication  
7 will not necessarily completely, and maybe even not at all,  
8 impact the breadth of use, aside from reimbursement, it also  
9 will distinctly impact the allowable marketing.

10 The allowing marketing often secondarily impacts  
11 what trials get done. In other words, if a company doesn't  
12 have something on their label, they can't make claims about  
13 it, they can't promote that use. There is a certain  
14 incentive to do that study. So the labeling can have an  
15 impact in that regard.

16 I also wanted, just for clarity of structure here,  
17 we are getting some very useful comments on two separate  
18 issues. I think some of the disagreements are because  
19 people are talking about different issues. In questions 1  
20 and 2, we are asking about two different studies and the  
21 extent to which they support efficacy.

22 In question 4, we are asking about primary and  
23 secondary use. It may be that, for those of you who think  
24 you can make the distinction between the usage, you might be  
25 able to make the distinction between the studies. Of

1 course, the studies are linked to the uses, but there are  
2 two different types of issues we are interested in here,  
3 your impression of the quality of the efficacy data and,  
4 then, in question 4, which as you indicated will come to a  
5 vote, the implications regarding the indication.

6 Finally, as quick clarification of your comment,  
7 we do also want to vote on question 3 when you get to that.

8 DR. BROUDY: I would just like to make one more  
9 brief comment and that is on the regulatory history of G-CSF  
10 and GM-CSF in which the FDA has seen a sequence of  
11 applications, one that got its initial licensure and then  
12 more detailed studies that demonstrated its use in other  
13 settings.

14 I think if we vote to approve this for the study  
15 which we are jointly convinced it shows some benefit, but we  
16 don't approve it for the other study, the company can still  
17 come back with additional studies defining other subgroups  
18 of patients in which it is effective and then get an  
19 extended license at a later date which may help with your  
20 question, Abbey.

21 DR. MILLER: Could I ask a question, a  
22 clarification from the FDA, about the use of this as an  
23 orphan drug. I can understand the orphan drug for the  
24 secondary prophylaxis, but if it is approved for primary  
25 prophylaxis in patients receiving chemotherapy, that is

1 clearly not an orphan drug. There are huge numbers of  
2 patients. So can the FDA clarify that for the committee?

3 MS. MEYERS: I might be able to shed some light on  
4 it. They would get the orphan-drug designation for the  
5 smaller population, but there would be no exclusivity, no  
6 tax credits, for the larger population.

7 DR. MILLER: Thank you.

8 DR. WEISS: Unfortunately, I don't think we have  
9 representation here from the Office of Orphan Drugs. I  
10 would have to look at just the specific letter that is sent  
11 out from that office. Even though there is a good amount of  
12 communication, I don't know specifically what the orphan  
13 designation is.

14 MS. MEYERS: Interferon has 12 or 14 different  
15 orphan-drug designations for specific rare cancers. But on  
16 the cancers that are above 200,000 people, there is no  
17 benefit to that. There is no orphan-drug designation.

18 DR. MILLER: Thank you for clarifying that.

19 DR. SWAIN: I just wanted to make a comment. I  
20 think it gives a false message to approve it for primary  
21 prophylaxis when we don't have the data. It really does. I  
22 mean, we just don't have it. It was mentioned that someone  
23 here uses G-CSF for prophylaxis, but I think you treat  
24 leukemia patients. For breast-cancer patients, it is not  
25 done and for a lot of solid-tumor patients.

1           So I think there is a difference there. Even ASCO  
2 guidelines don't recommendation it. So I would feel very  
3 strongly that it would be a false message to approve it for  
4 the primary prophylaxis.

5           DR. VOSE: I think we have to go with the data we  
6 have available and, hopefully, future studies will clarify  
7 that.

8           Additional comments on the primary prophylaxis  
9 issue? I think Dr. Freas wants to clarify things before we  
10 take a vote on an issue.

11          DR. FREAS: On the next statement, we will be  
12 taking a vote. Because the voting status of the members at  
13 the table changes with each topic, I would like to clarify,  
14 for the purpose of the record, that, for this topic, all  
15 members sitting at the table, that is 18 of us, temporary  
16 voting members and representatives will have the power of  
17 voting.

18          DR. VOSE: We are going to skip to question no. 4  
19 because I think that more closely relates to 1 and 2,  
20 really, and then go back to no. 3. "If licensed, should  
21 Neumega be indicated for the presentation of chemotherapy-  
22 induced thrombocytopenia and the reduction of the need for  
23 platelet transfusions after myelosuppressive chemotherapy in  
24 patients with non-myeloid malignancies as it relates to  
25 secondary prophylaxis?"

1 All members in favor, please signify by raising  
2 your hand.

3 [Show of hands.]

4 DR. FREAS: 18 votes in favor.

5 DR. VOSE: The same question related to primary  
6 prophylaxis. Everyone in favor, please raise your hand.

7 DR. AUCHINCLOSS: I am sorry. I am not clear what  
8 you are saying.

9 DR. VOSE: It would be the same question as above  
10 but related to an indication of approval for primary  
11 prophylaxis.

12 DR. AUCHINCLOSS: So we are not doing it quite  
13 like question 4 reads here. I think I understand. Yes; I  
14 think it should be licensed for primary prophylaxis.

15 [Show of hands.]

16 DR. FREAS: Three votes in favor.

17 DR. VOSE: Any other comments?

18 DR. DUTCHER: I abstain.

19 DR. VOSE: Dr. Dutcher abstains.

20 DR. LEITMAN: Do you not take no votes and  
21 abstentions after you take yes votes?

22 DR. VOSE: Okay. We took the abstention. Number  
23 voting no?

24 [Show of hands.]

25 DR. FREAS: 14 no's.

1 DR. VOSE: We are going to go back to question  
2 no. 3 now for discussion and voting purposes. "In both  
3 studies, a significantly higher incidence of edema was  
4 reported in the Neumega arm than in the placebo. In study  
5 9308, three were significantly higher. There were also  
6 significantly higher rates of tachycardia, atrial  
7 arrhythmias and palpitations in the Neumega arm versus  
8 placebo. The benefit of Neumega is a decrease in the need  
9 for platelet transfusions. One alternative to Neumega would  
10 be chemotherapy dose reduction.

11 "Do the potentially effects of Neumega therapy  
12 outweigh its toxicity?" Who would like to start the  
13 discussion on this issue?

14 DR. MILLER: I think, in appropriate patients,  
15 yes, the potential benefits outweigh the toxicity. The  
16 toxicity is generally mild and if watched, it can be of no  
17 major clinical significance. So I feel yes.

18 DR. VOSE: It seems as though the toxicity is very  
19 well outlined and, with appropriate indications on the  
20 insert that they have, it should be very well monitored.

21 Dr. Swain, any comments or concerns?

22 DR. SWAIN: No.

23 DR. VOSE: Any concerns about the papilledema that  
24 we want to discuss further? If not, we will go ahead and  
25 take a vote on this issue, then. "Do the potential benefits

1 of Neumega therapy outweigh its toxicity?" Everyone signify  
2 by raising their hand if they think the potential benefits  
3 outweigh the toxicities.

4 [Show of hands.]

5 DR. FREAS: 18 votes in favor of the benefits  
6 outweigh the toxicity.

7 DR. VOSE: Any other discussion? If not, we are  
8 going to skip to question no. 5, then. This question  
9 concerns the labeling, as far as trying to discourage the  
10 usage in specific subpopulations where there may be  
11 increased potential to experience adverse events such as  
12 patients with congestive heart failure and/or arrhythmias,  
13 patients with preexisting pleural effusions or ascites or,  
14 as we discussed earlier, perhaps prior doxorubicin therapy  
15 or concern of age as has been outlined by the sponsor.

16 Would anyone like to discuss any of these issues?

17 DR. BROUDY: I just think it should be commented  
18 on in the package insert that patients with preexisting  
19 pleural effusion may experience an increase in the size of  
20 their pleural effusion and, certainly, the frequency of the  
21 atrial arrhythmias and its use with caution with previous  
22 atrial fibrillations certainly be outlined.

23 DR. HONG: Is there any age restriction on this  
24 approval?

25 DR. VOSE: I believe as it is currently outlined,

1 there is no age restriction. That is a question, since it  
2 was brought up earlier, that age did have something to do  
3 with the toxicity in a discussion question.

4 DR. HONG: Then, perhaps, there should be  
5 information that there is inadequate information on the  
6 study in pediatric populations.

7 DR. SIEGEL: We will have a chance to discuss that  
8 in question 7.

9 DR. AUGUST: I wonder if brain-tumor patients  
10 shouldn't be at least mentioned as being candidates for the  
11 subsequent development of papilledema. That wasn't regarded  
12 as being clinically very significant, but, certainly, that  
13 finding scares clinicians when they find it and I think  
14 should be noted.

15 DR. LEITMAN: I just think that, perhaps, the  
16 message should be even stronger in the label than just  
17 mentioning it. If you label the increased incidence of  
18 arrhythmias, atrial arrhythmias, congestive heart failure  
19 and pleural effusions and the confusion in therapy when  
20 those occur weighed against the low possibility of one or  
21 two platelet transfusions, I think that, in my mind, the  
22 toxicity would weigh in favor of the platelet transfusions  
23 rather than this increased risk.

24 So I just think it should be stronger than just  
25 mentioned.

1 DR. SWAIN: I think that is a clinical judgement  
2 and just having the information there is what is necessary.

3 DR. DUTCHER: I would just like to say that they  
4 really have done a good job of presenting these toxicities.  
5 I think it really should be very well outlined. We talked  
6 about even some having a table of everything that is there  
7 and the patient populations that have problems. But I think  
8 I agree with Dr. Swain that people can use their judgment  
9 with their patients when they see these problems.

10 DR. VOSE: I agree that it is very well outlined  
11 and very well documented as far as the side effects. I  
12 think, hopefully, the oncologist who use this would be able  
13 to use that information appropriately in the patient  
14 population.

15 DR. WEISS: I had a question which was you added  
16 in the question, which I am glad you did, about prior  
17 doxorubicin therapy. Would the committee then feel that is  
18 also something that should be, particularly because a lot of  
19 the studies were done in a big population, maybe women with  
20 breast cancer, where doxorubicin therapy is very common.

21 I was just wondering if there are any comments on  
22 that and, also, whether or not there are any data even from  
23 the sponsor--if there is some issue with doxorubicin,  
24 whether there is an amount of doxorubicin as opposed as to  
25 just prior doxorubicin therapy.

1 DR. BROUDY: I wouldn't want to rule out prior  
2 doxorubicin therapy in that so many of our patients getting  
3 myelosuppressive chemotherapy get regimens that do include  
4 doxorubicin.

5 DR. VOSE: I agree. I don't think it should be  
6 there as a contraindication. But, since some of the  
7 information, and certainly we know those patients can be  
8 prone to congestive heart failure after a certain dosage,  
9 that that just needs to be kept in mind by the treating  
10 physicians.

11 DR. BERMAN: I think I agree with Dr. Leitman that  
12 it really is going to be very important in the package  
13 insert to state that in patients who do have fluid  
14 accumulation which is up to 20 and 30 percent of patients  
15 that when diuretics are used, that they be monitored very  
16 closely for potassium because that is where the two deaths  
17 were seen.

18 So I think this should be a warning very clearly  
19 stated. Evidently, people who have no prior history of  
20 heart disease but who have this fluid overload can  
21 apparently easily enter an atrial arrhythmia. So I think  
22 that, perhaps, some warning about prior heart disease is not  
23 all that is necessary but also in patients who have  
24 excessive fluid gain.

25 DR. VOSE: I think that was most clearly pointed

1 out probably in the transplant studies. That really isn't  
2 what we are talking about today, but the volume overload is  
3 a lot more in those patients and those patients had a higher  
4 incidence of atrial arrhythmia. So, again, all that  
5 information needs to be presented.

6 Any other discussion issues?

7 DR. HARTIGAN: Does it need to say anything about  
8 GM-CSF on the labeling, that it hasn't been tried in  
9 combination with that drug?

10 DR. VOSE: Is that a procedural question for Dr.  
11 Weiss or Dr.--

12 DR. WEISS: I'm sorry. Could you repeat the  
13 question.

14 DR. HARTIGAN: Does the labeling need to say  
15 anything about GM-CSF rather than the fact that it has been  
16 tried with G-CSF and not GM? We don't know what is going to  
17 happen, if anything.

18 DR. WEISS: Oftentimes, we will put in labeling  
19 that the combination or the interaction of this product with  
20 CM-CSF has not been studied, just to let people know what we  
21 do know and what we don't know as opposed to anything  
22 stronger than that.

23 DR. VOSE: Any additional comments, questions?

24 We will go on to question no. 6, then. "The data  
25 from the transplant setting indicate Neumega has little

1 impact on the myeloablative setting. In Study 9308, a post-  
2 hoc analysis based on the degree of myelosuppression of the  
3 chemotherapy regimen indicated patients treated with the  
4 more dose-intensive regimens derive less benefit following  
5 Neumega therapy. Should the sponsor be encouraged to  
6 further study Neumega in the dose-intensive setting?"

7 Personally, I would say yes.

8 DR. AUCHINCLOSS: What does "encouraged" mean,  
9 because I guess the answer is we would all say yes, if  
10 "encouraged" means what I think it does.

11 DR. VOSE: I believe that means post-marketing  
12 studies would be highly recommended in those areas.

13 DR. AUCHINCLOSS: Does it mean require post-  
14 marketing studies, or does it mean, "Gee, we would love to  
15 see more studies to figure out where this drug is really  
16 useful?"

17 DR. SIEGEL: We negotiate and receive written  
18 signed commitments for post-marketing studies on a regular  
19 basis often with review of protocols, even, prior to  
20 approval. We can make the approval contingent upon  
21 acceptable design and commitment to do those studies.  
22 Outside of the realm of accelerated approval, with our  
23 normal approvals, we have relatively little ability to  
24 enforce those commitments in the post-marketing situation.

25 We recently conducted a review over the last five

1 years of the status of post-marketing commitments to  
2 clinical trials. The experience is somewhat mixed, but more  
3 favorable than not. Most trials that are committed to be  
4 done, or most questions that are committed to be addressed,  
5 get addressed.

6           Sometimes, the trials vary because new drugs come  
7 aboard, new findings come along. Sometimes you can  
8 question, are they done as quickly as we would have liked,  
9 as well as we would have liked. It is not easy to answer  
10 the question, but we do get commitments and some significant  
11 number of those commitments are kept by many sponsors.

12           DR. ANDERSON: I guess just following up on that,  
13 the only thing I would feel strongly about is that post-  
14 marketing studies in this case not be tied to licensing.  
15 The data at least for secondary is sufficiently convincing  
16 that this agent is going to be studied and it is a decision  
17 by the company how quickly and how thoroughly they do post-  
18 marketing my feeling is in this case.

19           DR. BROUDY: I would agree with that. I think it  
20 is probably in the company's best interest to do some  
21 additional studies in the myeloablative transplant setting.  
22 I am sure there is no shortage of investigators who would  
23 like to collaborate on those studies. I would hate to  
24 require them to do that as a contingency on recruiting this  
25 drug today.

1 DR. NEEMAN: They have already done a study, 9313,  
2 in the myeloablative setting. It showed really nothing. In  
3 fact, I guess the trend was against Neumega. I don't know  
4 why such a study would want to be repeated.

5 DR. BROUDY: That was a very small study. Again,  
6 we are not going to approve the drug--we have recommended  
7 approval of the drug today, but we wouldn't be approving it  
8 in that setting. So if the sponsor wants to seek approval  
9 in that setting, they would certainly need to do some  
10 additional studies or maybe look at Neumega in combination  
11 with other cytokines or find some other way to use it.

12 That study would not be sufficient for approval,  
13 certainly.

14 DR. SIEGEL: Let me ask a question to clarify or  
15 extend your comments, Dr. Anderson. It seems to be the  
16 advice of the committee to approve for secondary prophylaxis  
17 and I believe you just said that the data are sufficient and  
18 there ought not to be other studies.

19 Often, post-marketing commitments involve--

20 DR. ANDERSON: Wait a minute, Jay. That is not  
21 quite what I meant to say. What I meant to say is there  
22 certainly might be additional post-marketing studies that  
23 could be done on secondary prophylaxis but simply that the  
24 licensing shouldn't be tied to a requirement of the company  
25 to do it. That is all I meant to say.

1 DR. SIEGEL: I understand that. What I was about  
2 to ask is that often we talk about post-marketing  
3 commitments in uses that are not part of the indication but  
4 likely to be done simply because regardless--in a case such  
5 as this, if there weren't an indication for primary  
6 prophylaxis, one would be largely motivated to seek that in  
7 any case. However, in this or other cases, one would ask if  
8 that use is going to be done and if more information is  
9 needed about its safety and efficacy and risk benefit, we  
10 often ask for studies applicable to indications not exactly  
11 within the labeled use.

12 Would your comments also apply similarly, then, to  
13 primary prophylaxis or do you think that is something that  
14 really there ought to be a commitment for further study.  
15 You had a different opinion about the labeling in the first  
16 place?

17 DR. ANDERSON: Right. My vote for approval of  
18 primary prophylaxis was based on that sort of grey area of  
19 really taking seriously what Abbey Meyers said in terms of  
20 reimbursement and perhaps a faith in leukins that, perhaps,  
21 is still gray but, nonetheless, positive.

22 If the data for secondary had been what the  
23 primary was, so that it was a question of licensing, period,  
24 I would have voted against it because that wouldn't have  
25 been strong enough as the initial licensing.

1           Now, the question you just asked me is should  
2 there be a commitment for studies for primary prophylaxis.  
3 I guess my feeling remains the same, and that is that the  
4 decisions on what studies to do and what studies the company  
5 should pay for really has to be a decision of the company.

6           Now, if this were a Merck or a Novartis, that is a  
7 little different because they clearly have resources.  
8 Biotech companies do not, even one like GI, necessarily have  
9 the means to be able to carry out all the studies that they  
10 are being asked to do. Investigators are going to do them,  
11 anyway so it is not that primary prophylaxis is never going  
12 to be studied by anybody ever.

13           It is simply is it done as a post-marketing  
14 commitment. My feeling stays the same unless argued  
15 convincingly otherwise by you folks and that is that in most  
16 cases, where there is a clear evidence of support for  
17 licensing for an indication that post-marketing commitment  
18 prior to licensing by FDA should not be done.

19           Was I sufficiently fuzzy that I didn't answer your  
20 question?

21           DR. VOSE: Dr. Petricciani, did you have a comment  
22 to make?

23           DR. PETRICCIANI: Just a brief comment to  
24 the committee, perhaps, in understanding where we are as  
25 company. As you know, we have concentrated all of our

1 efforts on trying to establish safety and efficacy for the  
2 indications that were presented to you this morning. This  
3 is not to say that we are uninterested in pursuing other  
4 avenues for IL11, other therapeutic areas.

5 In fact, we have under serious consideration at  
6 the present time, a study in dose-intense dicep and we are  
7 talking about other ones. So I think the message that I  
8 would like to leave you with are two, actually. One, we  
9 presented data this morning, some of which you find  
10 convincing. We would really ask that you look at that in  
11 and of itself and, also, take into consideration that we are  
12 pursuing, in an early stage, additional studies and we will  
13 be doing more with IL11 in this area.

14 DR. VOSE: Thank you for that comment.

15 Are there any other comments?

16 DR. LEITMAN: While we are on question no. 6, and  
17 this relates to question no. 5, too, the small phase I-II  
18 trials of use of IL2 in autologous transplantation were very  
19 problematic. I think most of us would agree that, in those  
20 studies, what is reported in our briefing papers, the  
21 incidence of the toxicity outweighed the benefits. In fact,  
22 there were no benefits seen between the placebo versus the  
23 study groups.

24 I think that if we are recommending licensure, a  
25 comment in the labeling stating that preliminary data

1 suggest that toxicity outweighed benefits in this setting,  
2 just to deter off-study use in that setting would be  
3 helpful.

4 DR. VOSE: The transplant trial was very small.  
5 It was 21 patients or something like that so I think it is  
6 of a concern to actually say that one way or the other if it  
7 is good or bad because I think that would give the wrong  
8 impression. I think that appropriate randomized trials  
9 would be the only way to really test that.

10 In the transplant population, especially, that is  
11 really a difficult area to try and look at toxicities like  
12 that. So I would have a concern about saying one way or the  
13 other.

14 DR. LEITMAN: It is just off-study use. On-study,  
15 clearly, further data is necessary but for clinicians who  
16 don't have access to what we are looking at here, not to  
17 encourage use in that setting.

18 DR. VOSE: I think most of the information will be  
19 available for the physicians who look at the information.  
20 Certainly, I know that that has been published information  
21 so they will have that available to make their own use of  
22 that information.

23 Any other comments?

24 Why don't we go to question no. 7. This concerns  
25 the use in pediatric patients. "Regulations permit labeling

1 for pediatric use based on adequate and well controlled  
2 studies conducted in adults together with other information  
3 supporting pediatric use--for example, PK data, safety data  
4 and pharmacokinetic data--when the course of a disease and  
5 the effects of the drug both are beneficial and adverse are  
6 sufficiently similar in the pediatric and adult populations  
7 to permit extrapolation.

8 "Does the committee feel that thrombocytopenia in  
9 the pediatric population following myelosuppressive therapy  
10 is similar to that in adults so that it could be  
11 extrapolated in those circumstances?"

12 DR. KLEINERMAN: First, I would like to commend  
13 the company because I think that this is the first time that  
14 we have ever seen any pediatric data. I would like to  
15 commend them for attempting those studies. Clearly, more  
16 information is needed but we do experience severe  
17 thrombocytopenia following chemotherapy so I think this is a  
18 problem in pediatric oncology and I think this drug would be  
19 very useful.

20 The only thing is clearly, from the data, the  
21 limited data that we have, dosage required may be higher for  
22 the pediatric population since the excretion seems to be  
23 higher. So, perhaps, something in the labeling could  
24 suggest that if inadequate results are achieved that maybe  
25 consideration for increase in the dose, then maybe to

1 contact the company for the latest data on the pediatric  
2 dosage.

3 But I suspect probably the MDT is going to be  
4 higher for the kids based on what we have seen.

5 DR. VOSE: Certainly, a lot of the chemotherapy  
6 regimens used in children are very dose intense and there is  
7 a concern about thrombocytopenia in that patient population.  
8 Since we have no other drugs currently that are useful, I  
9 think it is a very important population to look at with  
10 additional studies.

11 Any other comments? Just to finish up, then, the  
12 second part of that question. "Are there specific safety  
13 concerns for the pediatric population related to volume  
14 expansion, the need for careful monitoring of fluid status  
15 and the concern about the papilledema that should be  
16 highlighted in the labeling for pediatric patients."

17 DR. KLEINERMAN: Again, I think there should be  
18 some indication in terms of brain-tumor patients, the same  
19 as we talked about with adults. But fluid retention is  
20 usually not as big a problem as in adults. The pediatric  
21 kidney seems to do a lot better. So I don't think any  
22 special indications, but, again, I think patients with brain  
23 tumors who are going to potentially receive this drug, the  
24 same caution should be exercised.

25 DR. AUGUST: I may be missing something here but

1 the data that was presented by the company that had to do  
2 with pediatrics was mostly a defense of its safety and an  
3 explanation as to who got papilledema and why. It really  
4 didn't discuss efficacy at all. There is no data about  
5 numbers of patients who needed transfusions and not.

6           So I think you have to either ask Dr. Bleyer to  
7 tell us if his group study is showing efficacy and go on  
8 that or just say that the work is half done and we don't  
9 really know whether it is as effective as the studies in the  
10 secondary patients have shown us it is.

11           DR. VOSE: I believe they didn't actually present  
12 all the data because of time limitations. But, please, if  
13 you have some additional data.

14           DR. BLEYER: Thank you, Dr. August. The work is  
15 half done, I think is the bottom line. I think there is  
16 sufficient concern that the primate model demonstrates that  
17 papilledema can occur in most subjects if you reach a high  
18 enough dose regardless of the presence of a brain tumor or  
19 the presence of amegakaryocytic thrombocytopenia which is a  
20 small group of patients six of whom--one of those six also  
21 has had evidence for optic-disk edema and blurred vision and  
22 the other one had retinal changes, not papilledema but  
23 retinitis thought to be viral.

24           I think with those two out of the six  
25 amegakaryocytic thrombocytopenic patients and the two brain-

1 tumor patients among the 28 children on the trial does  
2 warrant further investigation.

3           Although we can easily discount the brain tumors  
4 being the primary basis for the increased evidence for  
5 papilledema, that can happen in any child, or any patient,  
6 particularly with increased pressure to begin with, and the  
7 fluid retention, the sodium retention, may also tip some of  
8 these patients over.

9           So I think the question is warranted but the  
10 answer is only half in. Did that answer your question?

11           DR. AUGUST: What I was most curious about was  
12 efficacy and whether that exists.

13           DR. BLEYER: The efficacy question regarding the  
14 data to date in 28 children who have been elevated in  
15 cohorts from 25 to 50 to 75 and now 100, and we now know  
16 there are five children who have had 100 mcg/kg for 14 or  
17 more days, and they go on to successive cycles, does imply  
18 that there is increased efficacy with the five being the  
19 basis for this implication at 100 versus 75 and 50.

20           So that study will continue to accrue patients.  
21 It will probably go up again in the next dose level soon.  
22 Looking for additional evidence for a higher dose  
23 relationship in children than in adults.

24           The data, Dr. August, is basically this, that  
25 whereas children at lower doses or historically who had no

1 IL11 had a median platelet transfusion event of between 6  
2 and 12, depending on G-CSF dose that was used. But let's  
3 average that to nine platelet-transfusion events for the  
4 first cycle, have had a reduction to two platelet events  
5 with both the 75 and 100 mcg/kg dose.

6 There are four children in the 75 per kilo and  
7 five children in the 100 per kilo, nine altogether. But,  
8 certainly, that is a dramatic decrease from our historical  
9 experience and also at the lower doses of IL11 studied to  
10 date.

11 Also, being able to resume chemotherapy on time,  
12 the question that was asked about dose intensity by you,  
13 also, Dr. August, is that 67 percent of the children at the  
14 75 and 100 mcg/kg doses were able, by day 21, to recover  
15 their platelet count about 100,000 and go on with the next  
16 cycle of chemotherapy.

17 At lower doses, and also historically, 80 percent  
18 are not ready. At most 25 percent can go on at day 21  
19 having not achieved the platelet count of over 100,000 by  
20 then. So dose intensity seems to be increasing with IL11  
21 although that study, especially on a randomized basis which  
22 we are prepared to do, would be a far better answer.

23 DR. VOSE: Thank you. Does that sufficiently  
24 answer your questions?

25 DR. AUGUST: Yes.

1 DR. VOSE: Dr. Auchincloss, did you have a  
2 comment?

3 DR. AUCHINCLOSS: I was going to make a comment.  
4 I have a lot of confidence in the FDA people that they will-  
5 -they already make the point that I am going to make but I  
6 am going to make it anyway. When I read labeling in chronic  
7 descriptions, I often get lost for the bizarre, the rare,  
8 the occasional event for what is really significant.

9 As I understand this agent, there is one clear-cut  
10 major adverse event; namely, fluid retention, which is not  
11 trivial and it probably happens in every patient and has  
12 very significant clinical impact in lots of ways, as we have  
13 heard.

14 Somehow, you need to make sure, as you work on the  
15 labeling, that that point emerges and doesn't get buried in  
16 the list of runny noses.

17 DR. VOSE: Additional comments or questions? Have  
18 we answered all your questions that you need to have  
19 answered, Jay.

20 DR. SIEGEL: Yes.

21 DR. VOSE: With that, then, I think we are going  
22 to break. We are going to start this afternoon at 1:15  
23 instead of 1:30 since we are going to have a lot of  
24 discussion this afternoon. Thank you.

25 [Whereupon, at 12:10 p.m., the proceedings were

at

1 recessed, to be resumed at 1:15 p.m. the same day.]  
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1 Kathy, would you please come to the microphone and  
2 address the committee at this time.

3 MS. GILL: Good afternoon. My name is Kathy Gill.  
4 The Baxter Isolex machine was used in my treatment for  
5 breast cancer at the Medical College of Virginia in  
6 Richmond.

7 When a person is diagnosed with cancer, life  
8 expectancy is a large item on their mind. I was diagnosed  
9 with breast cancer in April of 1966. In visiting with  
10 medical personnel undergoing tests, approving treatment  
11 plans, and making all the decisions necessary, the one thing  
12 that I found lacking was hope, hope that I could beat this  
13 disease, hope that it was not as bad as the doctor said it  
14 was, hope that my treatment was the best available and the  
15 right one for me, and hope that I would live.

16 My treatment plan combined prayer with the God-  
17 given talents of the medical community at the Medical  
18 College of Virginia. My treatment included a stem cell  
19 transplant in February of this year. While preparing for  
20 the transplant, I was asked to participate in a random  
21 sample for the study of the Isolex machine.

22 After consideration, we decided that it could  
23 nothing but increase my chances for complete recovery. It  
24 gave renewed hope. The use of methods, machines, and  
25 medications that increased survival rates for patients are

1 all tools, not only necessary to the physical recovery of a  
2 patient, but also the emotional recovery.

3 I never saw the Isolex. Until I decided to come  
4 here today, I had no real direct knowledge of it, but I am  
5 glad I was selected to participate in the study.

6 I had a friend who, when randomized for the same  
7 study with the same disease, was not chosen to participate  
8 and tried her best for another chance, so she could take  
9 advantage of what she saw as another tool for complete  
10 recovery.

11 You learn to take advantage of the best there is  
12 to offer, continue to examine new methods and procedures. A  
13 cure is out there. We believe it is a combination of the  
14 medical and spiritual healing, but each is necessary.

15 Thank you for hearing my comments.

16 DR. FREAS: Thank you, Kathy. Before you sit  
17 down, in the interest of fairness, we ask for all  
18 participants in the open public hearing to address any  
19 financial involvement they may have with the sponsor or  
20 competing firms, and if you have such an interest, would you  
21 please make it part of the record?

22 MS. GILL: I have no financial affiliation with  
23 the Baxter Company. They have agreed to reimburse my  
24 expenses for coming up here today. That's all.

25 DR. FREAS: Thank you very much.

1 Is there anyone else at this time who would like  
2 to address the committee during this open public hearing?

3 [No response.]

4 DR. FREAS: I see none. If anyone would like to  
5 address the committee tomorrow, please see me at the close  
6 of the session, and we will make sure that you are part of  
7 the meeting agenda.

8 Dr. Vose, I turn the microphone back to you.

9 DR. VOSE: Thank you, Dr. Freas.

10 We will go ahead with the Topic No. 2 now, which  
11 will be the Baxter Isolex application, and we will go ahead  
12 with the presentation from the company at this point in  
13 time.

14 **OPEN COMMITTEE DISCUSSION: TOPIC II**

15 **Premarketing Approval Application 97-0001**

16 **Isolex 300, Baxter Healthcare Corporation**

17 **Presentation by Baxter Healthcare Corporation**

18 **Introduction**

19 DR. GRIFFITH: Thank you very much.

20 On behalf of Baxter, it is my pleasure to  
21 introduce today's presentation of the Isolex 300 System.  
22 Before doing so, I would like to thank Dr. Freas and Gail  
23 Dapolito for their help in preparing for today's  
24 presentation. We would also like to thank the FDA reviewers  
25 of our submission for their help in the preparation, and

1 also the advisory committee members themselves for their  
2 time today.

3 Today's presentation will involve three primary  
4 presenters.

5 Dr. Kenneth Cornetta, who is a transplantation  
6 medicine expert from Indiana University, will discuss the  
7 clinical utility of stem cell selection.

8 Dr. John McMannis is from Baxter, has spent a  
9 great deal of time implementing the technology in the field,  
10 has worked with investigators around the world with this  
11 technology, and he will talk about the system and tell you a  
12 little bit about how it works.

13 Finally, Dr. Bonnie Mills, who has coordinated the  
14 clinical trials for this presentation, will talk about the  
15 pivotal trial and the device performance.

16 We also are very fortunate today, in addition to  
17 Dr. Cornetta, to have two additional investigators with us  
18 who have participated in our pivotal trial, Dr. Chabannon  
19 from Marseille, France, and Dr. Yanovich from the Medical  
20 College of Virginia.

21 We have five other stem cell experts joining us  
22 today to answer questions: Dr. Kuer Civin from Johns  
23 Hopkins, Dr. Bill Bensinger from Fred Hutchinson, Dr. Bob  
24 Preti from Hackensack University Medical Center, Dr. Harry  
25 Mallech from NIH, and Dr. Elizabeth Shpall from the

1 University of Colorado.

2 Finally, we have two additional technical experts,  
3 Dr. Mike Loken, who is an expert in cell selection, cell  
4 characterization, from Hematologics in Seattle, and Mark  
5 Munsell, who is our statistician from Applied Logics.

6 Finally, our expert in regulatory affairs from  
7 Baxter, Tung Koh.

8 With that, I will turn it over to Dr. Cornetta.

9 **Clinical Utility of Stem Cell Selection**

10 DR. CORNETTA: Thank you and good afternoon.

11 I have been asked to share my perspective on CD34  
12 selection devices and their utility in the setting of marrow  
13 and peripheral blood stem cell transplantation. My goal is  
14 to present a clinician's viewpoint in regards to the  
15 potential uses of this technology and share my expectations  
16 for device performance. Hopefully, this perspective will be  
17 useful as we review the clinical trial which will be  
18 presented in greater detail here today.

19 [Slide.]

20 Now, I will apologize to a number of members on  
21 the panel, but I do have some introductory slides since this  
22 is a varied audience today. What we are talking about this  
23 afternoon is the discussion of the Isolex 300, which is a  
24 device designed to enrich for CD34+ cells.

25 [Slide.]

1           Now, CD34 is a cell surface glycoprotein whose  
2 function is yet unknown. We believe it may be important in  
3 cell trafficking, and its expression, though, is fairly  
4 restricted throughout the body.

5           We can find it in some endothelial cells, but the  
6 area where it seems to be most important or of most interest  
7 is in the bone marrow, and it is expressed on approximately  
8 1 percent of bone marrow cells.

9           As we analyze the cells that express CD34, we find  
10 that they are a population of hematopoietic progenitors, and  
11 within this sort of heterogeneous population of cells that  
12 express CD34, there are important cells which we term stem  
13 cells.

14           [Slide.]

15           Now, what are stem cells and why are they  
16 important? Well, we believe stem cells are the most  
17 primitive of hematopoietic progenitor cells and they have  
18 two very important and unique characteristics.

19           First, they have the ability to differentiate into  
20 the mature blood cells of all the various blood lineages.  
21 In addition, these stem cells retain the capacity for self  
22 renewal. Now, during development, we believe stem cells  
23 arise in the yolk sac, then move to the fetal liver, and in  
24 the adult they can be found mostly in the bone marrow.

25           We know a small percentage of these cells also

1 circulate in the peripheral blood, and we can increase their  
2 number by giving cytokines or chemotherapy. We also now  
3 know that cord blood is a source for stem cells that can be  
4 used in transplantation.

5 Now, the real importance to us as transplanters in  
6 regards to stem cells is that we believe these are the cells  
7 responsible for sustained engraftment of donor cells after  
8 bone marrow transplantation.

9 [Slide.]

10 Now, in this cartoon, which I know many in the  
11 audience have seen a number of times, we try to depict the  
12 differentiation of stem cells from marrow of populating  
13 cells here to form the blood lineages. Here, we have sort  
14 of depicted the cell in the marrow microenvironment or  
15 stroma.

16 As you can see, as it moves, these cells actually  
17 differentiate into a variety of progenitors, CFU-GM, BFU-E,  
18 and they eventually form our mature blood cells,  
19 neutrophils, macrophage, red blood cells, and platelets, and  
20 not shown here, they also differentiate into lymphocytes,  
21 such as B cells and T cells.

22 Now, the point I would like to make -- and,  
23 hopefully, you can see this at the very bottom of the slide  
24 -- is that if we look at CD34 expression, it is really,  
25 mainly found in this early stem cell and early progenitor

1 population, and decrease and is not expressed in more mature  
2 blood cells.

3           The other thing to note in here is the cell cycle  
4 activity, and it is most notable in this area here, and that  
5 results in a great expansion of the number of cells, and  
6 that is why if we look at percentagewise, only about 1  
7 percent of cells in the bone marrow comprises this  
8 compartment over on the left of our slide, and the vast  
9 majority of a more mature precursor cells and later  
10 progenitors do not express CD34.

11           It ends up this is the population that we like to  
12 capture and use in transplantation, and this is the  
13 population we hope to isolate with the CD34 selection  
14 device.

15           Now, on the next three slides I would like to go  
16 over some applications where I believe CD34 enrichment may  
17 have clinical implications.

18           [Slide.]

19           The first is an autologous transplantation and the  
20 applications in this area, again by reducing the numbers of  
21 cells very significantly by CD34 enrichment, we are  
22 decreasing the number of cells going back into our patient,  
23 we can decrease their DMSO exposure which, while I think it  
24 can be done relatively safely, certainly is unpleasant, it  
25 also will decrease our storage requirements.

1           Now, as a clinician, I think there is an area  
2 where I am particularly much more interested in this  
3 technology, and that is in the ability to reduce tumor cells  
4 in the autograft. We know a large variety of hematologic  
5 and non-hematologic malignancies do have circulating cancer  
6 cells, and they can be present in the autograft.

7           A number of investigators, including ourselves,  
8 have shown that you can have a 2 to 3 log reduction in tumor  
9 cells within an autograft product by using CD34 enrichment.  
10 One of the advantages is that since the majority of  
11 malignancies do not express CD34, we can apply this  
12 technology to a wide variety of cancer patients.

13           Now, I think it is important to note that we still  
14 are unclear what the contribution of tumor cells in the  
15 autograft play in disease relapse. We do know from gene  
16 marking studies performed by Dr. Malcolm Brenner and Dr.  
17 Diesseroth that leukemia cells in an autograft can  
18 contribute to disease relapse after autologous  
19 transplantation for AML and CML.

20           We also know that in transplants where the  
21 autograft is contaminated with lymphoma cells or breast  
22 cancer cells, there is increased incidence of relapse  
23 associated with that contamination.

24           I think that as we approach our patients with  
25 malignancies, we are going to have to deal with two

1 problems. One is residual disease of tumor cells within the  
2 patient and we need to better increase our ability to kill  
3 these malignant cells through different preparative  
4 regimens, but I think as we deal with that problem, we will  
5 also have to deal with contamination of tumor cells in  
6 autografts, and I believe this is one of the methods that we  
7 can use in that approach.

8           Now, I think there are other applications of this  
9 technology in regards to autologous transplantation, and I  
10 think it may be important in helping us develop novel  
11 approaches to autoimmune diseases and also in developing  
12 protocols for ex vivo expansion.

13           [Slide.]

14           Another clinical situation where I see CD34  
15 enrichment playing a role is in the setting of allogeneic  
16 bone marrow transplantation. As many of you know, T cells  
17 within an allograft can contribute to graft versus host  
18 disease, a disease which can be severe and lethal.

19           We can decrease the incidence of graft versus host  
20 disease by depleting the graft of T cells and we and others  
21 have shown that CD34 enrichment is an effective method at T  
22 cell depletion giving us a 2 to 3 log depletion in T cell  
23 number.

24           Now, prior to our use of CD34, we had done a  
25 technique for T depletion called soy bean lectin sheep red

1 blood cell agglutination, and what we found in this  
2 procedure versus our previous procedure is that we were  
3 getting a more consistent product. This system allowed us  
4 to use a closed system with more defined reagents, and again  
5 gave us a well-characterized product.

6 I also think that this technology in regards to  
7 allogeneic transplantation will have the applications as we  
8 develop future protocols for tailored products. One, it  
9 would allow us to give more specific T cell dosing, and that  
10 also may be very important to allow us to give specific  
11 amounts of CD34 cells.

12 Now, I think there is two applications where you  
13 would want to give more CD34 cells. Both experimental and  
14 now some clinical evidence indicates that increasing CD34  
15 number may help us overcome some of the histocompatibility  
16 antigen barriers that prevent us from transplanting folks  
17 who do not have an exact HLA match.

18 In addition, there is also evidence now that  
19 increasing CD34 will allow us to decrease the preparative  
20 regimen, and most of our patients undergoing allogeneic  
21 transplant require high doses of chemotherapy and total body  
22 irradiation, both which are considerably toxic, and if we  
23 can decrease that, we can hopefully impact on the toxicity  
24 associated with these preparative regimens.

25 As we do that and increase our CD34 dose, we also

1 want to be able to tailor the number of T cells we are  
2 giving back to the patient, and I think this device will  
3 help us in that area.

4 [Slide.]

5 The final area of application I would like to talk  
6 about is the relation to gene therapy, and there are a  
7 number of protocols and a number of diseases in which  
8 investigators are targeting the bone marrow stem cells with  
9 various genes, and this technology allows us to enrich the  
10 target cells which we are trying to treat with our gene  
11 vectors.

12 This allows us to reduce our vector requirements.  
13 Why that is important is something that I deal with actually  
14 fairly regularly, because not only do I serve as director of  
15 bone marrow transplant at Indiana University, I am also  
16 director of our vector production facility, and recently I  
17 have been coordinating the National Gene Vector Lab.

18 Now, as we look at Phase I trials that come into  
19 our center and estimate the cost of producing vector, for a  
20 bone marrow study using CD34 enriched marrow, we estimate  
21 the cost of vector production just for supinate to be about  
22 40- to \$50,000.

23 With CD34 enrichment, you are allowing us to treat  
24 about 1 out of 50 potential cells in the bone marrow.  
25 Without that enrichment process, we would have to increase

1 the number of cells treated by 50-fold. As you can see,  
2 even with enrichment, our cost is 40- to \$50,000. It would  
3 not be economically feasible to go ahead and perform most of  
4 the clinical gene therapy protocols currently underway or  
5 proposed without this technology.

6           There are a number of applications at many  
7 centers. I have just included here for folks the trials  
8 that are either ongoing or will be started in the next year  
9 at Indiana University, and we are looking to try to increase  
10 the ability of bone marrow stem cells and progenitor cells  
11 to tolerate chemotherapy using retroviral vectors expressing  
12 the multidrug resistance gene or the MGMT or methylguanine  
13 methyltransferase gene, and we are also looking to treat  
14 patients with genetic diseases, with chronic granulomatous  
15 disease, adenosine deaminase deficiency, and Fanconi's  
16 anemia.

17           I know there is folks like Dr. Mallech and Dr.  
18 Anderson here today who are also involved with trials in  
19 these diseases, and again, this is just represented from IU,  
20 but there are many centers exploring this technology, and  
21 this CD34 enrichment is a vital part of that.

22           [Slide.]

23           Now, as I looked at CD34 enrichment and a device  
24 that is going to do this, I do not see this as a treatment  
25 for cancer or genetic diseases. This is really an enabling

1 technology, and that technology has implications both in  
2 tumor cell reduction, T cell depletion, gene therapy, ex  
3 vivo expansion, and component therapy.

4 [Slide.]

5 On my last slide, I would just like to show you  
6 what my expectations were when we started our clinical  
7 trials looking at CD34 selection.

8 I was looking for a device that provided  
9 consistent products in regards to purity and yield, that  
10 maintained cell viability, that decreased unwanted cells  
11 whether they be tumor cells or T cells, that they provide  
12 acceptable engraftment kinetics both for short-term  
13 engraftment and for long-term engraftment, that they provide  
14 comparable reconstitution to what we were seeing with  
15 unmanipulated cells, and that did not increase the toxicity  
16 of our procedure.

17 So far at least at Indiana University, the Isolex  
18 300 has met our expectations and appears to be serving our  
19 patients well.

20 I hope this discussion has been helpful and will  
21 be helpful in your deliberations this afternoon.

22 Thank you.

23 **Description of Isolex 300 System**

24 [Slide.]

25 DR. McMANNIS: Dr. Cornetta has talked to you

1 about some of the clinical applications of CD34 cells. Now  
2 what I would like to do is introduce you to the Isolex 300  
3 Magnetic Cell Separator System, and specifically, I would  
4 like to talk about some of the technical aspects of the  
5 process.

6 [Slide.]

7 The first thing to note with regards to this  
8 system compared to other systems is that it is an  
9 immunomagnetic based selection one. It is an indirect  
10 system in which the primary antibody is directed against the  
11 CD34 epitope itself.

12 The secondary antibody is directed against the  
13 mouse IgG, and it is covalently attached to paramagnetic  
14 beads. Once these rosettes have formed, they can be  
15 separated from the non-target cell by their ability to be  
16 attracted to and retained by the magnet.

17 Once these rosettes are selected, a releasing  
18 agent can be added to separate the antibody bead complex  
19 from the selected cells themselves.

20 [Slide.]

21 The Isolex 300 System consists of three parts.  
22 The first part is the instrument itself, which we do have an  
23 example in the back of the room which during any of the  
24 breaks we can show you specifically parts of it.

25 In addition, I would just like to point out some

1 of its main features, the first being an IV solution pole,  
2 where you can hang your various fluids plus your cells, an  
3 array of primary magnets, which are used to retain the  
4 rosettes once formed, a rocking mechanism not shown in this  
5 picture, which allows the cells to remain in suspension  
6 during the incubations, a secondary magnet which will trap  
7 any beads that escape from the primary chamber, and then a  
8 keypad that prompts the operator through the various steps  
9 of the procedure.

10 [Slide.]

11 In addition, the system consists of a sterile  
12 disposable set and a reagent kit consisting of one vial of  
13 antibody, one vial of beads, and one vial of releasing  
14 agent.

15 [Slide.]

16 The procedure for selection of CD34 cells can be  
17 divided into three steps. The first step is the  
18 sensitization of the peripheral blood stem cell product with  
19 the murine monoclonal antibody.

20 The second step is rosetting of these CD34 coated  
21 cells with beads, and then finally, it is the release of  
22 these CD34 cells from the beads. A more detailed  
23 description is given in the next slide, and I will try to  
24 walk you through the various procedures.

25 [Slide.]

1           As I mentioned, peripheral blood stem cells are  
2 stained with the murine monoclonal antibody 9C5. The cells  
3 are then allowed to drain into the primary chamber which  
4 already contains the sheep antimouse immunoglobulin which  
5 has the paramagnetic beads.

6           During a 30-minute incubation, these rosettes  
7 form, at which point the magnet will come in close proximity  
8 to the chamber, attracting any rosettes that have formed,  
9 keeping the non-CD34 cells in suspension.

10           The non-CD34 cells are then drained out into a  
11 collection bag here. After extensive washing, the releasing  
12 agent is added, and during an additional incubation, the  
13 releasing agent replaces the antibody or separates the  
14 antibody from the CD34 cells.

15           The magnet will then come out again, the bead  
16 antibody complexes are attracted to the magnet, whereas, the  
17 CD34+ cells remain in suspension this time. These 34-  
18 positive cells then pass by the secondary magnet into a  
19 final collection bag.

20           [Slide.]

21           A representative example of a FACS analysis from  
22 one selection is presented here. The starting product,  
23 apheresis product contained about 1 percent CD34 cells and  
24 99 percent of the cells were non-CD34s, which could consist  
25 of tumor cells or T cells.

1           After selection, analyzing a similar number of  
2 events, 95 percent of the cells express the CD34 antigen and  
3 less than 5 percent did not express the CD34 antigen.

4           There is two points I would like to make on this  
5 slide. First, the Isolex system results in a very high  
6 purity of CD34 cells, and the second point is that there is  
7 about 100-fold reduction in non-target cells. Obviously,  
8 you can see from here that there is inverse relation or  
9 direct relation between purity and non-target cell  
10 reduction. The higher the purity, the more reduction of  
11 non-target cells occurs.

12           [Slide.]

13           We have also tried to characterize at the cell  
14 surface of these isolated cells. CD34 cells were isolated  
15 using the Isolex 300 technology, and then cells were stained  
16 with a rat antimouse immunoglobulin that was conjugated to  
17 gold.

18           Scanning electron microscopy was performed to see  
19 if any of the rat antibody bound to the surface,  
20 demonstrating that there was still murine antibody on the  
21 cell surface. As you can see, none of the rat antibody  
22 bound to the cell surface, whereas, in the positive control,  
23 what we did was first stain the cells with the murine  
24 antibody directed against the CD34 epitope, and then came  
25 back with the rat immunoconjugated gold particles, and you

1 do demonstrate that the CD34 epitopes are there.

2 We conclude from this that there is no murine  
3 antibody left on the cell surface, however, the integrity of  
4 the cells and the expression of the CD34 epitopes are still  
5 present.

6 [Slide.]

7 In conclusion, the Isolex technology is an  
8 immunomagnetic based technology. The procedure is a  
9 consistent, well-defined process resulting in high CD34 cell  
10 purity and unaltered cell surface.

11 Now we would like Dr. Mills to come up to present  
12 some of the clinical studies.

13 **Clinical Results and Device Performance**

14 DR. MILLS: Good afternoon. Thank you for the  
15 opportunity to present our data.

16 My talk will be divided into two parts, which I  
17 will address the expectations that you heard from Dr.  
18 Cornetta for the performance of such a device.

19 First, I would like to present data from a pivotal  
20 randomized controlled study which adequately demonstrates  
21 acceptable rapid and sustained engraftment using selected  
22 CD34 cells in the absence of any unexpected or unusual  
23 toxicities, and in the second part of my talk, I will  
24 address the device performance and, in fact, show you device  
25 performance data that supports the conclusion that these

1 cell products have high purity and that there is a  
2 significant reduction in the non-target cells associated  
3 with the positive selection procedure.

4 [Slide.]

5 I apologize. This is a rather busy slide that  
6 summarizes the study design of the pivotal study. I am not  
7 going to read you the details of the slide, but rather I  
8 would like to use this as an outline slide to go through the  
9 various phases in the treatment scheme.

10 Eligible patients included patients with high risk  
11 or metastatic breast cancer, and this included Stage II,  
12 III, and IV patients who were eligible for institutional  
13 transplant protocols.

14 Patients were mobilized with chemotherapy plus  
15 growth factor or growth factor alone, and successful  
16 mobilization was defined as the detection of greater than or  
17 equal to 20 CD34 cells per microliter in the circulating  
18 peripheral blood.

19 I would like to use the next slide to explain the  
20 randomization that was used here.

21 [Slide.]

22 Patients who met most of the eligibility criteria  
23 -- and this is prior to the mobilization criteria -- were  
24 enrolled in the study. Following successful mobilization,  
25 as defined by greater than or equal to 20 CD34 cells per

1 microliter of peripheral blood, patients then proceeded to  
2 randomization to one of two arms - a test arm or a control  
3 group.

4           The test group were patients intended to be  
5 transplanted with selected CD34 cells, and the requirement  
6 for this arm for the apheresis procedures was the collection  
7 of products that contained at least 5 million CD34 cells per  
8 kilogram before selection in addition to a nonselected back-  
9 up product.

10           For the control group, the target collection  
11 requirement was 2.5 million CD34 cells per kilogram in the  
12 apheresis products, and this target collection in the test  
13 group was based on the desire to have a transplant product  
14 after selection of approximately 2 million CD34 cells per  
15 kilo, and the expected 40 percent yield of the device.

16           So there are three groups of patients which you  
17 will see in the following slides summarizing the results of  
18 the analysis.

19           First, there are a group of 71 patients were  
20 enrolled, 24 of these patients did not proceed to  
21 randomization. These will be referred to as non-randomized  
22 patients. The majority of these patients were not  
23 randomized because they did not meet the 20 CD34 cell per  
24 microliter mobilization criteria.

25           All patients who were randomized then are included

1 in the intent to treat analysis. There were, however, 4  
2 patients in the test group who failed to meet the 5 million  
3 per kilo target collection criteria. These patients were  
4 therefore discontinued from the study and were transplanted  
5 with unselected PBSC, as well as any selected cells that had  
6 been obtained.

7           There is one additional patient in the test group  
8 who met the target collection criteria, but in whom the  
9 final CD34 cell dose following selection was considered to  
10 be not acceptable by the investigator, and the patient was  
11 then removed from the study and unselected back-up was also  
12 infused at transplantation.

13           So the total test group of 26 patients is included  
14 in the intent-to-treat analysis, and a subset of the test  
15 group comprising the 21 patients who received selected CD34  
16 cells only were also used for some of the key analysis, and  
17 you will see these in some of the subsequent slides.

18           The remainder of the 47 randomized patients, or 21  
19 patients, were randomized to the control group, and there  
20 were no patients in the control group who failed to meet the  
21 target collection for that group.

22           [Slide.]

23           Briefly, the statistical analysis of the study was  
24 based on published literature which demonstrates that one  
25 can detect differences in engraftment as small as three

1 days, statistically significant differences as small as  
2 three days with groups of patients less than 20 each.

3 In fact, the reason for this is because the  
4 kinetics of engraftment following PBSC transplant does not  
5 follow the exponential distribution. If you look at a  
6 Kaplan-Meier plot of the engraftment kinetics, what you will  
7 see is that the initial portion of the Kaplan-Meier curve is  
8 flat to approximately day 9, and during this time no  
9 patients engraft.

10 Following this, then, is a steep slope during  
11 which most or all patients engraft, and this is then  
12 followed again by a plateau.

13 Based on these kinetics, and using data from  
14 unselected PBSC transplant kindly provided by Dr. Bensinger,  
15 we developed a model and found that, in fact, the gamma  
16 distribution provided a good fit to these kinds of kinetics.

17 Based on this fit, an additional 2,000 simulations  
18 were performed to assess the characteristics of the log-rank  
19 test in this model. These simulations revealed that with 20  
20 patients per arm, we, in fact, had greater than 80 percent  
21 power to detect a three-day difference with a level of  
22 significance of 0.056.

23 [Slide.]

24 This slide summarizes the characteristics of the  
25 patients in each group with the most important point being

1 that there were, in fact, no differences between the control  
2 and test group with respect to age, weight, stage of disease  
3 at enrollment, or previous chemotherapy. In fact, there was  
4 also no difference between the groups of randomized and non-  
5 randomized patients with respect to these characteristics.

6           There was a significant difference between the  
7 randomized patients and the non-randomized patients, and  
8 that the patients who were randomized successfully had a  
9 higher proportion of patients who were mobilized with  
10 chemotherapy plus growth factor compared to the use of  
11 growth factor alone.

12           Finally, the only significant difference between  
13 the control and test groups is illustrated in the bottom  
14 here, and that is that the number of apheresis required to  
15 reach the target collection was significantly higher in the  
16 test group, and this is, in fact, not surprising since the  
17 target collection number was more than double for that  
18 group.

19           [Slide.]

20           Further demonstrating the similarity between the  
21 patient populations, this slide summarizes the distribution  
22 of patients in the different treatment regimens, and the  
23 patients I should emphasize were stratified by site for  
24 randomization to provide appropriate balance in  
25 institutional variations in treatment regimens.

1           You can also see here that, in fact, most of the  
2 patients in both groups received one of two regimens here.

3           [Slide.]

4           Again, my outline slide. Following conditioning,  
5 patients were infused with either unselected PBSC or  
6 selected CD34 cells depending on the arm to which they were  
7 randomized, followed by the administration of growth factor.

8           The primary endpoints, clinical endpoints of the  
9 study included demonstration of adequate engraftment and  
10 engraftment for neutrophils was defined as the first of  
11 three days when neutrophils were greater than 500 per  
12 microliter, and for platelets it is the first of three days  
13 where platelets were greater than 20,000 per microliter  
14 without transfusions, as well as the demonstration that  
15 there are no unusual or unexpected toxicities associated  
16 with the use of selected CD34 cells.

17          [Slide.]

18          Again, the key endpoints are shown here, analyzed  
19 for the control group of 21 patients, the test group of 26  
20 patients, as well as the subset of 21 test patients who  
21 received CD34 selected cells only.

22          On the left you can see the doses that were given  
23 for these groups, and the point here is that, in fact, the  
24 test and test subsets both received significantly lower  
25 doses of CD34 cells per kilo when compared to the control

1 group. In fact, the control group received almost double  
2 the number of cells as the test subset.

3 Despite the almost twofold difference in dose of  
4 CD34 cells, in fact, the time to neutrophil engraftment was  
5 the same in these groups with a median of 10 days in the  
6 control group and 11 days in the test and test subset.

7 Likewise, the time to platelet engraftment was the  
8 same for three groups, with a median of 10 days in the  
9 control group and 12 days in the test and test subset, and  
10 in addition, which you will see as a secondary endpoint  
11 later, there was, in fact, no difference in the platelet  
12 support needed for these populations.

13 [Slide.]

14 This slide shows you the confidence intervals that  
15 were calculated based on the statistical model that I  
16 described. With respect to neutrophil engraftment, as I  
17 indicated, the median time to neutrophils of 500 in the  
18 control group was 10 days, and in the test group was 11  
19 days, a difference of 1 day.

20 The 95 percent confidence intervals for this  
21 parameter, in fact, demonstrated that the difference between  
22 the control and subset is no greater than 2 1/2 days. When  
23 a similar analysis is done for the test subset of patients  
24 who received CD34 selected cells only, again, the difference  
25 in median time to engraftment is one day, and the 95 percent

1 confidence intervals demonstrate that the difference is no  
2 more than two days.

3           With respect to platelet engraftment, a similar  
4 analysis was performed, the median time to platelets of  
5 20,000 in the control group was 10 days and 12 days in the  
6 test group, a difference of 2 days, and the 95 percent  
7 confidence intervals demonstrate, in fact, that the  
8 difference is no greater than 3 days between these two  
9 groups.

10           When this analysis is performed for the test  
11 subset, again, the median time to platelet engraftment was  
12 12 days, and the 95 percent confidence interval illustrates  
13 that the difference is no greater than 4 days between the  
14 test subset and the control group.

15           [Slide.]

16           Lastly, with respect to primary engraftment  
17 parameters, this shows you the kinetics of engraftment, the  
18 Kaplan-Meier curves for the recovery of ANC and platelets,  
19 and again, the three groups that were analyzed, the control  
20 group in orange, the test group in blue, and the test subset  
21 in yellow, and you can see that these curves are all  
22 overlapping.

23           [Slide.]

24           Now, the second primary clinical endpoint was that  
25 there was no significant toxicities associated with the use

1 of these cells, and again I would like to remind you of the  
2 list that Dr. Cornetta showed you at the end of his talk in  
3 terms of expectations, and this was also a major  
4 expectation.

5           What is illustrated here is the number of adverse  
6 events reported at each grade of severity, I through IV, for  
7 the control group and the test group. In absolute numbers,  
8 you can see here were not very different between the two  
9 groups, and below the absolute numbers is shown in  
10 parentheses the number of events per patient, that is, the  
11 total number of events divided by the number of patients in  
12 each group, and again there is no difference at any level of  
13 severity between the two groups.

14           Without going into detail -- and this is in your  
15 packet, in fact, summarized on the bottom of the slide --  
16 are the 12 Grade IV events that were reported in the two  
17 groups, and the main take-home message here is, in fact,  
18 that the 6 Grade IV events reported in the test group  
19 occurred either prior to transplant during conditioning and  
20 were associated with chemotherapy, or long after transplant  
21 and were associated with progressive disease.

22           Now, secondary endpoints that were evaluated  
23 included the requirements in these groups for transfusion  
24 support, days on antibiotics, hospitalization days, as well  
25 as secondary engraftment parameters and infusional

1 toxicities, and those are summarized in the next series of  
2 slides.

3 [Slide.]

4 First, with respect to secondary engraftment  
5 parameters, although the p values aren't shown on here,  
6 there were, in fact, again no significant differences  
7 between any of the three groups in any of the secondary  
8 engraftment parameters, and, in fact, all patients in the  
9 control, test, and test subsets achieved ANC of 1,000 and  
10 platelets of 50,000.

11 Of note is that there were two patients in the  
12 control group, 19 of 21, and three patients in the test  
13 group, 3 of 26, for whom platelets greater than 100,000 were  
14 demonstrated. All of these were, in fact, associated either  
15 with death prior to achieving this parameter or with  
16 additional chemotherapy that was administered due to  
17 progressive disease.

18 With respect to infusional toxicities, one of the  
19 ways that was looked at was by looking at vital signs  
20 including respiration, pulse, temperature and systolic and  
21 diastolic blood pressure before and after infusion. We  
22 assessed the greatest change in each of these from before  
23 infusion to after infusion, looking at vital signs taken  
24 during the 24 hours following infusion, and then performed  
25 an analysis of variance on the maximum change that was

1 detected in this period.

2           There are two points here. First, comparing the  
3 control group and the test group with respect to the  
4 differences in these parameters. There were, in fact, no  
5 significant differences between the two groups in the  
6 changes measured in these vital signs from before to after  
7 infusion, and secondly, that, in fact, the changes that were  
8 detected were, in fact, very small and not clinically  
9 important.

10           [Slide.]

11           Now, this slide summarizes other safety parameters  
12 that were assessed as secondary endpoints, and, in fact,  
13 addresses Dr. Cornetta's expectation that there are not  
14 increased risks or toxicities associated with this, and also  
15 demonstrates clinically that time to engraftment is, in  
16 fact, for platelets, associated with no difference in the  
17 number of transfusion products required in the two groups.

18           This is also true for transfusion requirements for  
19 red cells with a mean of 5 and 6 in the control and test  
20 groups with the number of days patients were on antibiotics,  
21 14 and 15 respectively, and with respect to the days of  
22 hospitalization associated with the transplantation, 26 and  
23 23 for the two groups.

24           Now, last, long-term follow-up was assessed by  
25 documenting time to relapse and time to death, and that is

1 shown on the next slide.

2 [Slide.]

3 These are the Kaplan-Meier curves for time to  
4 relapse and time to death. Again, for the three groups that  
5 were looked at, the control group in orange, the test group  
6 in blue, and the test subset of the 21 patients that  
7 received selected cells only in yellow, again demonstrating  
8 that there is no detectable difference with respect to  
9 either time to relapse or time to death, and the curves are  
10 essentially the same for the three groups.

11 [Slide.]

12 In summary, the controlled randomized pivotal  
13 study provides data that, in fact, demonstrates the rapid  
14 and stable engraftment that is achieved with the use of  
15 selected CD34 cells when compared to unselected peripheral  
16 blood cells in the absence of any unexpected or unusual  
17 toxicities.

18 In fact, we have not been able to demonstrate any  
19 increased risk with respect to any of the parameters that  
20 were examined, and these included regimen-related  
21 toxicities, infusional toxicities, engraftment, transfusion  
22 requirements, antibiotic use and infections, days of  
23 hospitalization, and time to relapse or time to death.

24 [Slide.]

25 Now, there are some other supporting studies which

1 I will refer to in the subsequent part of my talk, where I  
2 will summarize the device performance, and although I am not  
3 going to present the clinical analysis of these studies, I  
4 think is important to point out that, in fact, when one  
5 looks at the primary endpoints for engraftment, these  
6 studies which include a multi-site study of autologous  
7 transplanted patients with B-cell malignancies and a single-  
8 site study of a similar group of patients, as well as an  
9 allogeneic PBSC transplant study, in fact, demonstrates  
10 similar engraftment parameters that were shown in the test  
11 group of this study I just described, with median times to  
12 neutrophil engraftment of 11, 9, and 14 days in the three  
13 studies, and to platelet engraftment of 13, 12, and 12 days  
14 in the three studies.

15 [Slide.]

16 The second part of my talk then I would like to  
17 show you some of the data related to the device performance,  
18 and, in fact, the ways that we assess the device performance  
19 are listed here - purity, and as John indicated, we achieved  
20 very high purities, and this is assessed by looking at the  
21 percent of CD34 cells in these selected products, and, in  
22 fact, is directly correlated with the reduction of non-  
23 target cells in these products, which we also assessed.

24 Secondly, we looked at the yield of the CD34 cells  
25 in the final cell product and the quality of the cells in

1 the CD34 selected cell product can be assessed by looking at  
2 the expression of the CD34 intensity, the viability of the  
3 cells, and the sterility of the cell product.

4 [Slide.]

5 First of all, these next series of slides now  
6 summarizes the data from approximately 280 selection  
7 procedures that were performed on products from  
8 approximately 120 patients across the studies that I have  
9 just described.

10 This slide illustrates the CD34 cell purity that  
11 is both high and consistently achieved across a wide number  
12 of studies. Now, on the left, the yellow bars, which you  
13 probably cannot see very well, in fact, represent the  
14 starting percentage of CD34 cells in the apheresis products,  
15 which is typically less than 1 percent, and the blue bars  
16 represent the median purity in the selected CD34 cell  
17 products across these studies with a number of selections in  
18 each study shown in the bar at the bottom.

19 In fact, the median purity typically is on the  
20 order of 89 to 90 percent across all of these studies.

21 [Slide.]

22 Secondly, this illustrates the yield of CD34  
23 cells, and likewise, the associated recovery of total  
24 nucleated cells following positive selection. Again, the  
25 yellow bars, which are barely visible here, represent the

1 recovery of total nucleated cells, and you can see again in  
2 each case it is less than one representing greater than 100-  
3 fold reduction in the number of total nucleated cells from  
4 the starting product to the selected product.

5           The blue bars illustrate the median CD34 cell  
6 yields, and again these are relatively consistent across a  
7 variety of studies and are typically on the order of about  
8 40 percent.

9           [Slide.]

10           Next, the quality of the cells, as I indicated,  
11 can be addressed by looking at a number of characteristics  
12 of the selected cells. Illustrated here is the intensity of  
13 CD34 staining representative of the expression of CD34 on  
14 the cell surface with intensity increasing along the y axis.

15           In the middle panel, you can see a CD34 cell  
16 selected product, which includes a range of intensities of  
17 CD34 cell expression, and most importantly, includes the  
18 very highest CD34 cell expressors which, as Dr. Cornetta  
19 indicated, are thought to be the most immature progenitor  
20 cells and those which include the population responsible for  
21 long-term and stable engraftment.

22           This is similar to the range of CD34 cell  
23 intensity seen in the apheresis product, but, in fact, when  
24 you look at the non-target cells or the cells that are left  
25 after selection, you can see that, in fact, the most highly

1 expressing CD34 cells are, in fact, selectively depleted and  
2 are retained during the selection procedure.

3 [Slide.]

4 With respect to viability, in this case measured  
5 by dye exclusion, the CD34 cell selected products typically  
6 have the same viability as the starting products and almost  
7 always greater than 95 percent.

8 [Slide.]

9 Lastly, with respect to sterility, of 314 CD34  
10 cell selected products in all of these studies that have  
11 been tested for sterility, 2 tested positive, 1 was a fourth  
12 of the total transplant product from an autologous patient,  
13 and 1 was a fourth of the total transplant product for an  
14 allogeneic patient. In neither case were there any  
15 associated clinical infections or symptoms associated with  
16 these positive cultures.

17 [Slide.]

18 As I have indicated, the purity is also an  
19 assessment of the reduction of non-target cells, and these  
20 are directly related with high purities correlating with, in  
21 fact, good depletion of non-target cells.

22 One can look at depletion of non-target cells in  
23 different ways, but the most convenient way to assess the  
24 depletion of non-CD34 cells is by picking a representative  
25 cell population that is present both with high frequency in

1 the products and in almost all products, thus, facilitating  
2 the ease with which one can follow the depletion of the  
3 cells through the selection procedure.

4 That is illustrated on this slide by looking at  
5 the depletion of CD3 and CD19 cells in a positive selection  
6 procedure again across a variety of studies.

7 In each case, the blue bar represents the number  
8 of CD3 cells in the apheresis product, and the green bar  
9 represents the number of CD3 cells in the selected CD34  
10 product. Likewise, the yellow bars represent the starting  
11 CD19 cells, and the purple bars, the CD19 cells in the  
12 selected products.

13 Again, fairly consistent results were obtained  
14 with approximately a 3.5 log reduction consistently seen for  
15 T cells, and about a 2.5 log reduction for B cells.

16 [Slide.]

17 Alternatively, when available, one can use  
18 specific tumor cell markers, and there are a variety of ways  
19 in which can do this. Some examples follow on the next  
20 couple of slides.

21 [Slide.]

22 Using FACS analysis, sometimes it is possible to  
23 identify a tumor cell population by the unique co-expression  
24 of surface antigens, in this case, an NHL patient, whose  
25 tumor cells co-expressed CD5 and CD20, and the presence of

1 those cells in the apheresis product is illustrated in the  
2 left panel here in the upper right quadrant by the co-  
3 expression of these two antigens.

4 On the right is shown a similar analysis of the  
5 CD34 selected product showing the absence of the co-  
6 expressing cells from this product, and, in fact, this was  
7 reported as no detectable tumor cells.

8 [Slide.]

9 Using even more sensitive techniques when there  
10 are appropriate available markers, such as T14:18  
11 translocation, in some tumor cells from patients with non-  
12 Hodgkin's lymphoma, one can do a similar analysis, and this  
13 slide illustrates PCR analysis of cells from a non-Hodgkin's  
14 lymphoma patient that was positive for the T14:18  
15 translocation.

16 The first three lanes respectively include the  
17 apheresis product in lane 2, the CD34 cell selective  
18 product, and in lane 3, the non-target CD34 cell negative  
19 fraction, and again showing the absence in the selected cell  
20 product of a detectable T14:18 translocation product.

21 Again, this was reported by the site as no  
22 detectable tumor cells in this product following positive  
23 selection.

24 [Slide.]

25 Thus, the device performance summary from a wide

1 variety of studies in a large number of patients illustrates  
2 the non-target cell reduction that is achieved by the high  
3 purities shown with the CD34 selection process which result  
4 in the reduction of total nucleated cells by greater than  
5 100-fold and the depletion of non-CD34 cells by 2.5 to 3.5  
6 logs.

7 [Slide.]

8 The proposed indication therefore for this device  
9 would be to concentrate CD34 cells thereby reducing the  
10 infusion volume and the volume of cryoprotectant solution in  
11 cryopreserved autologous peripheral blood stem cell products  
12 used for hematopoietic rescue.

13 This is achieved by the positive selection of  
14 CD34+ cells with the Isolex System, which reduces the non-  
15 CD34 or non-target cells in the infusion product by  
16 approximately 3 logs.

17 Thank you.

18 DR. VOSE: Thank you for the presentation.

19 We would now like to open it up to the panel for  
20 questions for the sponsor regarding the device.

21 DR. LEITMAN: I have a question. Our lab has some  
22 personal experience with the use of this device and what is  
23 problematic with it is the highly variable degree of CD34  
24 yield, percent of yield, and I would like to point out in  
25 one of the slide you just showed, where a mean yield was 40

1 percent overall within various populations, a range from 25  
2 to 44 percent.

3           You don't give the range of yields, but in the  
4 actual briefing document you did. For example, the B-cell  
5 study where the mean yield was 43 percent, the range was 3  
6 to 300 percent, which is our experience, too, a range that  
7 you can't count on that makes clinical processing and a  
8 prediction of number of apheresis procedures necessary, and  
9 prediction of yield impossible.

10           DR. MILLS: In fact, many of the characteristics  
11 that are assessed with respect to device performance are  
12 directly related to the starting cell product, and, in fact,  
13 the median yield -- those were medians, not medials that  
14 were shown across the studies. While they are consistent, I  
15 would agree that the range is very broad and that reflects,  
16 in fact, the broad range of starting products that are put  
17 into the process.

18           In fact, depending upon the content of CD34 cells  
19 in the starting product, and probably on a lot of other  
20 characteristics of the starting product, there is, in fact,  
21 variation in the final product.

22           DR. LEITMAN: Actually, if you look only at the  
23 breast cancer study, which was described extensively in the  
24 reading materials we received, eligibility was contingent  
25 upon the starting number of 6.5 million per kilo, so you

1 knew the starting number.

2           In that study, which I have right before me, on  
3 page 11, the starting median number was 8.1 million per  
4 kilo, and the disinfused was 2.3, and that is 29 percent  
5 recovery which is problematic.

6           DR. MILLS: The number collected, in fact,  
7 includes the unselected back-up.

8           DR. LEITMAN: So that that is not the actual  
9 processing yield, that's the overall yield. Okay.

10           DR. MILLS: That is not the actual number put into  
11 the procedure, correct.

12           DR. LEITMAN: A second question. I am not sure  
13 this is what the committee is supposed to be considering  
14 right now, but as you know and the manufacturer has  
15 mentioned in numerous places in the documents, there is a  
16 modification of the device, which makes its performance  
17 better, and it is given a different name, the 300i, and it  
18 performs much better.

19           In early trials, the amount of time needed for  
20 processing is reduced by one-half, from 5 hours to 2 to 2.5  
21 hours, and the yield is significantly better and more  
22 consistent, which makes it a much more attractive device in  
23 terms of practical use and the time of the day the end  
24 processing, the time of the day you go home and the number  
25 of pheresis procedures necessary.

1           How does the upcoming I suppose application for  
2 that impact on this?

3           DR. MILLS: That will be considered under a  
4 separate application and, in fact, we don't consider the  
5 time -- we consider the time required for processing to be a  
6 convenience issue, not a device performance issue. In fact,  
7 we think this device meets the performance requirements that  
8 have been required by the clinical people and have been  
9 demonstrated by the studies shown here.

10           All of the data that you have seen here was  
11 obtained with the SA device.

12           DR. VOSE: Dr. Auchincloss.

13           DR. AUCHINCLOSS: I wondered if the sponsor wanted  
14 to identify for us any clinically measurable benefit  
15 identified in any of your studies for any of the patients.

16           DR. MILLS: In fact, the primary efficacy endpoint  
17 analyzed in this study, was not to a therapy, because we  
18 don't believe this is, in fact, a therapy, but a support, a  
19 supportive tool that allows high-dose therapy to be applied,  
20 and was that the use of CD34 cells, in fact, results in  
21 engraftment comparable to unselected PBSC, which is the  
22 intent of the product.

23           With respect to other potential clinical benefits,  
24 I would rather defer to the clinicians who, in fact, have  
25 experience using these products.

1 DR. AUCHINCLOSS: That's right. I think you have  
2 made the point, and that is fine. I mean you are not  
3 claiming benefit, maybe there is a potential benefit, but no  
4 study here shows benefit to patients at this point. You  
5 have got a device that enriches 34 positive cells.

6 DR. MILLS: Correct.

7 DR. VOSE: Dr. Berman.

8 DR. BERMAN: Can you comment on the study in the  
9 B-cell malignancies where out of the 71 patients, 7 of them  
10 needed back-up?

11 DR. MILLS: Yes. In fact, 5 of those patients  
12 received back-up related to delays in engraftment, and 2  
13 patients received back-up for other reasons, 1 for a low  
14 yield following selection, and 1 for -- and I quote -- "the  
15 reported reason for use was that they tend to prevent risk  
16 of sepsis in a patient that had severe congestive  
17 cardiomyopathy."

18 There were 5 patients with engraftment delays, 5  
19 additional patients, excuse me, who received unselected  
20 back-up in that study related to engraftment delays.

21 Those included 1 patient that was, in fact, a  
22 collection target failure and should have been removed from  
23 the study after the apheresis, but was not; 2 delays in  
24 engraftment that were associated with pulmonary  
25 complications, and I can go into, you know, if you have

1 specific questions. Most of these delays, in fact, are  
2 platelet engraftment only.

3 One delay related to a cardiac -- no, excuse me,  
4 that was the patient with congestive cardiac failure.

5 Now, it summarizes 3 of those patients with  
6 delayed platelet engraftments were at one site, and had  
7 received Bactrim during the time as part of the treatment  
8 regimen, as part of the prophylactic antibiotics, and it has  
9 been suggested that this drug may have an effect on  
10 hematologic progenitors although we don't know that that  
11 affected it in this case.

12 Perhaps the clinical people would like to make  
13 more general comments on the frequency of engraftment  
14 delays. That was not a controlled study, that was a single  
15 arm study.

16 DR. CORNETTA: Our experience with B-cell  
17 malignancy has been restricted to patients with myeloma that  
18 had been entered on the multicenter trial. For those  
19 patients we have not seen any significant engraftment  
20 delays. They have actually acted very promptly in that  
21 study, so I don't know whether this was, I don't know, I  
22 can't say whether there is differences in the preparative  
23 regimen or the population used there, but at least for  
24 patients with myeloma in the study, our experience has not  
25 been that.

1 DR. MILLS: In only one of those patients was  
2 there a report by the investigator that the delay might have  
3 been related to the use of selected cells in the  
4 investigator's opinion.

5 DR. VOSE: Dr. Dutcher.

6 DR. DUTCHER: Could I just ask you to clarify  
7 something? You stated in the study design that you had  
8 certain targets, CD34 yields for the pheresis, total  
9 numbers, and it was 2.5 times  $10^6$  per kilo for the control  
10 and 5 times  $10^6$  for the test subject, and yet when you  
11 showed the data about recovery, you stated that the actual  
12 dose infused was less for the test subject.

13 Now, is that to follow up on Dr. Leitman's  
14 question, this variability in terms of the processing that  
15 is occurring, that you started with a target of double and  
16 then ended up actually giving back fewer?

17 DR. MILLS: Actually, we started with a target of  
18 double based on, as I indicated, the expectation of  
19 approximately a 40 percent yield and the desire to have a  
20 dose of about 2 million cells per kilo.

21 The target collection dose, the major difference  
22 was not based on a lower than expected dose in the test  
23 group, but rather a higher than expected dose in the control  
24 group, and the median dose in the control group was greater  
25 than 4 million cells per kilo, even though the target

1 collection was 2.5 million cells per kilo.

2           The presumed reason for this is that if they don't  
3 reach that target collection in one apheresis, they  
4 typically do another apheresis in which they far exceed it,  
5 and we did not restrict the number of cells that could be  
6 infused, but, in fact, allowed the infusion of all the cells  
7 that were collected.

8           DR. BERMAN: Just to go back to some of your  
9 clinical studies that you didn't describe in length in your  
10 presentation here, in two of your allogeneic transplant  
11 studies, the results seemed poor in the patients that had a  
12 matched unrelated donor using the CD34 product.

13           Are you pursuing those studies in the matched  
14 unrelateds?

15           DR. MILLS: Yes, but in a very careful and slow  
16 fashion. As you are well aware, in the data that you have  
17 in your packet, there is a very, very small number of  
18 patients that have been transplanted. In fact, there are a  
19 lot of considerations that have to carefully go into the  
20 design of such studies.

21           Yes, we are interested in pursuing those, but  
22 again at a very slow and careful pace. Again, maybe some of  
23 the people who are, in fact, involved in some of the  
24 allogeneic transplant studies might like to comment on that.

25           DR. CORNETTA: We have one center that is

1 interested in pursuing CD34 in unrelated. I have seen some  
2 of the data that Baxter had generated initially. I think in  
3 unrelated transplants using any type of T-cell depletion,  
4 the method that you use to prepare the patients are  
5 extremely important and variable.

6 I think as you pursue those studies, we certainly  
7 would use something similar to a soy bean lectin and sheep  
8 red blood cell type of preparative regimen, and I think the  
9 centers who are looking to try to do this technology need to  
10 be very careful for the preparative regimens because they  
11 can be associated with graft failure and other  
12 complications.

13 DR. VOSE: Dr. O'Fallon.

14 DR. O'FALLON: Perhaps I could ask a few  
15 statistical questions.

16 The null hypothesis is in a certain sense a  
17 negative one here because you really don't expect to find a  
18 difference. Was the study powered enough to feel  
19 comfortable about the fact that you then didn't find a  
20 difference? It is a truism that we won't find something we  
21 don't look for and if we only look at small numbers. I  
22 didn't find comments about power.

23 DR. MILLS: In fact, I would like to ask our  
24 statistician, Mark Munsell, to comment on that question.

25 MR. MUNSELL: One of the slides was about just

1 this question, the null hypothesis. We did a simulation  
2 study on the log rank test to assess the operating  
3 characteristics of that test under these distributions, and  
4 we found if we had 20 patients per arm, we would have just  
5 over 80 percent power with a significance of 5 percent to  
6 see at least a three-day difference.

7 I think more important than that are the  
8 confidence intervals that we came up with that were shown,  
9 and the confidence intervals are pretty uniform in showing  
10 that the differences we can be comfortable are less than  
11 three days.

12 DR. O'FALLON: Your simulation test was  
13 interesting and involved, as I recall, fitting a gamma  
14 distribution by I, which struck me as also kind of  
15 interesting. I guess I was worried about the implications  
16 of that particular simulation in the sense that fitting a  
17 gamma distribution could have been done more formally as the  
18 gamma distribution is the only one that you looked at --

19 MR. MUNSELL: No, we looked at a whole family of  
20 distributions in the log, I mean we looked at, of course,  
21 the exponential and the  $\gamma$ , the gamma, the log, normal log  
22 logistic, and we chose the gamma based on the likelihood,  
23 the value of the likelihood, and we actually have a graph to  
24 show how well the gamma fits to the data, if you would like  
25 to see that.

1 DR. O'FALLON: Are the choice of the three days  
2 clinically meaningful?

3 DR. SIEGEL: I would like to address those two  
4 questions from an FDA perspective. We don't generally, in  
5 companies that for a given endpoint, are seeking to show  
6 equivalence or non-inferiority, we don't usually recommend  
7 an approach of adequate power with a null hypothesis of no  
8 difference, but typically, rather look to a prospective  
9 hypothesis of a predetermined margin of inferiority or of  
10 equivalence, which then is excluded in the study's power to  
11 exclude and one looks at the confidence interval.

12 This particular trial, I believe was not designed  
13 with the specific intent of supporting licensure in  
14 consultation with the Agency, but our approach then looking  
15 at it in retrospect is not really to look at the power to  
16 exclude a difference, but rather, as the company said, to  
17 look at the confidence interval to see what size a  
18 difference could be there and whether that difference is an  
19 important one, and that is your second question.

20 We have gone to this committee in 1994 to discuss  
21 specifically that issue, how long a prolongation of  
22 engraftment, whether of neutrophils, of platelets is  
23 acceptable in a variety of different settings and to  
24 characterize hours of discussion oversimply, hours which we  
25 have reread many times and have a feeling for the answer,

1 but that is dependent on compared to what.

2           Regarding the issue of tumor purging, for example,  
3 you know, it was felt by many members that it would depend a  
4 lot on the anticipated benefit of the tumor purging, or if  
5 it is graft versus host disease, or whatever, how much  
6 benefit and how likely would be critical, is a week okay, is  
7 only half a day okay, so I think it is hard to really have  
8 an answer out of context.

9           But what I wanted to point out here is that there  
10 was no prospective margin set that, you know, we should  
11 power or design the study to show less than a two or three  
12 days, rather, as you saw, after the study had been done,  
13 there were some simulations to look at what would be  
14 adequate and what would be considered meaningful. I am sure  
15 you will hear a lot more discussion about how meaningful one  
16 or two or three days is.

17           DR. O'FALLON: Fair enough. Thank you.

18           DR. VOSE: Dr. Siegel, I just want to point out  
19 that from those discussions in 1994, however, we looked at  
20 the differences in delays as compared to some benefit, true  
21 benefit that was there as opposed to implied benefit, so I  
22 think that is an important issue that we will need to  
23 discuss later.

24           Dr. Auchincloss.

25           DR. AUCHINCLOSS: I think Dr. O'Fallon is really

1 bringing up the central issue, and we know we are going to  
2 come back to this, so maybe the company wants to address it.  
3 I guess the suggestion had been made to you that, all right,  
4 you had a Phase II study with 20 patients in an arm, you  
5 come back with a Phase III study and convince us that there  
6 is no difference, and you have come back with the Phase II  
7 data without doing the Phase III study.

8           Can you convince us as a committee that these 20  
9 patients are sufficient for us to be convinced that this is  
10 a safe product?

11           DR. MILLS: I believe the statistical analysis  
12 with respect to the primary endpoints does, in fact, support  
13 that there is no difference in the primary endpoints that  
14 were assessed, that is, engraftment and adverse events.

15           I think it is based on the statistical analysis of  
16 the data that we have shown that there is no difference.  
17 The power is there.

18           DR. BROUDY: I guess the other implied benefit is  
19 reduction in non-target cells, and the concern I have is  
20 that non-target cells, many people will think that includes  
21 tumor cells, and while you have certainly shown reduction in  
22 lymphocytes, there really isn't much convincing data that  
23 there is reduction in tumor cells. In fact, one of your  
24 studies, the CLL cells were actually enriched in the  
25 pheresis product.

1 DR. MILLS: That was, in fact, in one instance. A  
2 single patient, that was where the cells were thought to be  
3 nonspecifically binding to the beads, and that patient was  
4 removed from study, as indicated.

5 DR. BROUDY: Right, and you showed us single  
6 instances, as well, of lymphoma, individual lymphoma  
7 patients. Do you have any quantitative data on reduction in  
8 tumor contamination?

9 DR. MILLS: No, in fact, particularly with respect  
10 to the pivotal study, at the time the study was initiated,  
11 there was, in fact, not a particularly good assay available.  
12 We did try to assess that in the breast cancer study by  
13 providing both apheresis products and samples of selective  
14 products to a central lab for analysis BIS, using what were  
15 then the relatively standard techniques for assessing this,  
16 which was immunocytochemical assay of breast cancer tumor  
17 cells, and, in fact, there are a number of things that  
18 really contribute to the inadequacy of the kinds of results  
19 reported from these assays to do that kind of assessment.

20 One is that the bulk of apheresis products and  
21 CD34 selected products are, in fact, infused back into the  
22 patients, and not available for testing. The second one is  
23 that the relative frequencies that have been reported at  
24 least to us, and I think in general, using that kind of  
25 assay for breast tumor cells at least are on the order of

1 about 1 in 100,000 to 1 in several million, and that is  
2 right at or, in fact, below the limits of sensitivity of  
3 such an assay, so, in fact, the numbers of cells reported,  
4 if you look at the raw data, seen in any particular  
5 specimen, are on the order of less than 5.

6           We don't consider that adequate to base --  
7 although you can use those numbers and the total nucleated  
8 cell depletion and come up with some purging level, which,  
9 in fact, when you do that, approximates 2.5 logs, I don't  
10 think an n of 2 or 3 or 4 or 5 is very adequate to base  
11 numbers on, and so, in fact, that is why we did a lot of  
12 analysis of other cells thought to represent, in fact, the  
13 non-CD34 cells and which are readily available and easily  
14 allow looking at the depletion of non-target cells, and that  
15 is why the CD3 and CD19 data were shown.

16           There are, on a case-by-case basis, tumors where  
17 one can readily assess that, where there are specific  
18 markers identifiable, but, in general, at least in the  
19 breast cancer population, that kind of an assay was not  
20 available at the time the study was done.

21           DR. VOSE: Dr. O'Fallon.

22           DR. O'FALLON: Could we get back and look at those  
23 confidence intervals that you referred to. How did sort of  
24 the null target of 3 fit into the calculation of confidence  
25 intervals? Am I missing a point? I am looking at -- I

1 don't know how to relate this slide to your slide numbers,  
2 but it shows confidence intervals on engraftment.

3 I read it as for minus 1 day, which would be the  
4 bad direction, I believe, to plus.

5 DR. MILLS: That would be one day better than the  
6 control group.

7 DR. O'FALLON: Is that the right direction? So  
8 minus 1 to plus 2, so we are ruling out 3? Is that the  
9 idea, we are ruling out the possibility that we could be 3  
10 days worse?

11 DR. MILLS: Right.

12 DR. O'FALLON: Comfortably ruling it out it  
13 appears, so the only issue at least for those who have a  
14 less severe -- we are not ruling out 3 in the 1 example. So  
15 are we comfortable with that?

16 DR. NEEMAN: I think you should know that these  
17 confidence intervals are done by bootstrap simulation, so  
18 that, in fact, it is not really the same as the confidence  
19 intervals you get when the underlying data are normally  
20 distributed where you need lots of patients in order to see  
21 a small confidence interval.

22 In this case, you can have just 10 patients in  
23 each arm and see a very small confidence interval.

24 DR. O'FALLON: I am not criticizing how we got the  
25 confidence interval. I am trying to make sure I can

1 understand it.

2 DR. NEEMAN: Just that you understand that small  
3 confidence intervals in this case don't go along with large  
4 numbers of patients.

5 DR. O'FALLON: I do that. I mean I do understand  
6 that, but I still have to understand the confidence interval  
7 to make sure we have the -- so the purpose was to rule out  
8 3, but in one instance we don't rule out 3, the confidence  
9 interval runs from minus 1 to plus 4.

10 DR. MILLS: That is in the test subset for  
11 platelets to 20,000, correct.

12 DR. WEISS: Right. We are looking at both  
13 platelets and neutrophils, and 3 is an arbitrary number.

14 DR. O'FALLON: Oh, I understood that, absolutely.

15 DR. WEISS: There was a lot of discussion. It is  
16 not absolutely clear, but when we discussed things with the  
17 company at the time, we came upon the figure of being able  
18 to rule out a three-day delay in both neutrophil and  
19 platelet engraftment.

20 DR. O'FALLON: Okay.

21 DR. VOSE: Another concern when we look at the  
22 non-CD34 cell as far as decreasing the number of cells is  
23 getting rid of immune effector cells which may be very  
24 important as far as relapse rates and infectious  
25 complications, and issues such as that.

1           So, do you think the study as designed was  
2 adequate to look at that issue?

3           DR. MILLS: I think in terms of adverse events and  
4 infectious complications, yes, I think clearly the study was  
5 not designed to assess small differences in time to relapse  
6 and time to death, and, in fact, a study to do that would  
7 require very large numbers of patients, on the order of  
8 hundreds.

9           DR. VOSE: Right, but the concern is that it is an  
10 issue that is a big concern for all of the selection  
11 devices, and I think one that is very concerning to us as a  
12 board to try and address that issue.

13           Abbey.

14           MS. MEYERS: I would just like to know what is the  
15 rush, why are you submitting this study on 20 patients, why  
16 didn't you do Phase III? Why are you submitting this now?

17           DR. MILLS: We, in fact, decided to submit this  
18 data following a discussion with the FDA of a proposed Phase  
19 III study where the primary endpoint was infusional  
20 toxicity, and we came to the conclusion, in fact, that the  
21 major emphasis in a study like that was to demonstrate that  
22 this device, in fact, does what we say it will do, and that  
23 is provide a cell product which adequately provides stable  
24 and long-term engraftment, and, in fact, there is no  
25 indication of any increased risks in any of the parameters

1 that we looked at.

2 In fact, review of our Phase II data suggests  
3 that, in fact, we had adequate data with ample statistical  
4 power to demonstrate those endpoints, and that was the basis  
5 for this decision.

6 MS. MEYERS: Is this a rare disease that you had  
7 trouble getting patients to go into the clinical trial, or  
8 why is it so small?

9 DR. MILLS: In fact, this application is  
10 restricted to a selection system that was used in 1995 in  
11 this group of patients. The trials have been ongoing with  
12 modifications to the system, but, in fact, we do think it is  
13 important for the system to be approved and available to  
14 clinicians based on the kinds of considerations that Dr.  
15 Cornetta presented.

16 MS. MEYERS: Has FDA ever approved, do you know,  
17 have you ever approved a study of 20 patients, a device?  
18 Yes. Do you know if FDA has ever done this before? Some  
19 devices have been approved on studies of fewer than 20  
20 patients?

21 DR. SIEGEL: I think that PEG-ADA got approved on  
22 a smaller number of them for SCIDS. I think there were six  
23 patients.

24 DR. VOSE: But, of course, that showed some actual  
25 benefit for the patients.

1 MS. MEYERS: But the total population of SCID in  
2 the United States is about 40 patients or actually it is  
3 less than 40 patients, so one could probably understand  
4 that. I don't understand why more people were not put into  
5 this clinical trial.

6 DR. BROUDY: I guess the concern I have is that  
7 there is implied benefit, but no demonstrated benefit and no  
8 quantitation of tumor cells, and I don't think that being  
9 able to reduce lymphocytes is an adequate surrogate for  
10 being able to reduce tumor cells, and that is the concern I  
11 have.

12 DR. LEITMAN: Could I ask some of the clinical  
13 investigators for a brief summary? There is I think several  
14 years now of data on prospective randomized trials in  
15 autologous transplant using selected versus non-selected  
16 cells in breast cancer, non-Hodgkin's lymphoma, and myeloma.  
17 Maybe that is not published yet, but there is followup.

18 Is there any evidence for prolonged disease  
19 survival or prolonged overall survival, not using this  
20 device, in any immunoselected CD34 selected transplant  
21 versus again a controlled prospective population of non-  
22 selected autologous transplant?

23 DR. SHPALL: Elizabeth Shpall from the University  
24 of Colorado.

25 I can address the breast cancer issue. If you

1 look at randomized trials staged for breast cancer patients  
2 that weren't designed to look at purging, Stage IV patients  
3 for the most part relapse in sites of bulk disease. There  
4 is no way I think -- and these studies were 75 percent or  
5 more Stage IV patients. I think to answer that question  
6 obviously and fairly, it is going to have to be done in the  
7 adjuvant setting, the high-risk adjuvant setting where, in  
8 fact, the tumor burden is more minimal and the disease will  
9 be controlled. There is data from Duke where marrow  
10 specimens from patients harvested at transplant, adjuvant  
11 patients, in whom tumor was detected, they have a higher  
12 relapse rate.

13           Many of us believe that, in fact, tumor will be  
14 important there, but these studies just haven't been  
15 designed to address that, and I think that is the mission of  
16 at least the clinicians here, is to over the next several  
17 years look at that seriously.

18           DR. CIVIN: I am Kurt Civin from Johns Hopkins.  
19 Dr. Leitman, the way I see this, and I think a lot of  
20 clinicians see this and perhaps you do, too, is that this is  
21 a modification of a selected care mechanism, that this is  
22 hematopoietic rescue in the first place, that the  
23 chemotherapy or perhaps the immunologic surveillance and  
24 immunotherapy afterwards must cure the cancer, that the  
25 supportive care is going to give quick recovery, and that is

1 quick and sustained recovery is goal.

2           There are some studies, of course, as you know,  
3 that show that purging is better than non-purging, but they  
4 are very controversial and as was said before, I think by  
5 Dr. Cornetta, it will take a while and improvement in the  
6 conditioning regimens to really be able to show -- or the  
7 immunotherapy -- to really be able to show that this  
8 matters, but again, as you know, it has been shown in  
9 neuroblastoma, breast cancer, CML, other diseases, that  
10 infused cancer cells can contribute to relapse and can  
11 really impede our research in trying to get more effective  
12 conditioning regimens.

13           If we don't work in parallel on both these  
14 problems, and make an advance in one step in one problem,  
15 and then make an advance in another step in the other, we  
16 are never going to get to cure.

17           By the way, I should say that my university, Johns  
18 Hopkins, holds patents on CD34 monoclonal antibodies at  
19 related devices, and as inventor, I receive royalties on  
20 that, so I wanted to disclose that.

21           DR. LEITMAN: I think the point of my question was  
22 not that blood cell transplants aren't good because there is  
23 more hasty engraftment or the temporal engraftment is  
24 better. It is to get at the fact that I don't think there  
25 is any data yet, after several years of looking at this,

1 that a selected CD34 positive graft gives benefit to  
2 survival in populations that have been studied than an  
3 unselected graft still.

4 DR. VOSE: Additional questions? Comments for the  
5 sponsor? Dr. Anderson.

6 DR. ANDERSON: I am not concerned about that at  
7 the end of a Phase II trial, the company feels there is  
8 sufficient data to come forward. That is whether it is 20  
9 patients or 18 patients or 30 patients, that doesn't bother  
10 me. What I would like a little more discussion on is  
11 clearly what is important if there is only 20 patients, that  
12 the statistical analysis be adequate, and I am not a  
13 statistician. I understand the words, but I can't follow  
14 all the arguments.

15 I would like to hear more from the statisticians,  
16 both on the committee and the FDA, to see if, in fact, there  
17 is agreement that the statistical analysis is adequate,  
18 because that is where my vote comes from.

19 I mean I am not worried about this 20, that's  
20 okay, and I am also not worried about is there clinical  
21 benefit, because this is a device, what they want to do is  
22 to concentrate CD34 cells and show that those cells are okay  
23 to use, so that is fine. I am comfortable with all that,  
24 but I am a little bothered by the fact that the  
25 statisticians are using all these fancy words, but they

1 don't seem to be agreeing.

2 DR. O'FALLON: I honestly don't think the  
3 statisticians were in disagreement. I was trying to assure  
4 the statistician from the FDA that I understood the  
5 bootstrap methodology was a good methodology and probably  
6 absolutely essential.

7 We were talking about the differences in median  
8 values of some small numbers, and we know we didn't have the  
9 nice, wonderful Gaussian bell-shaped distributions that we  
10 all learned about in grade school, so I was satisfied. I  
11 wanted to be sure I was interpreting those confidence  
12 intervals from the standpoint of what they meant to the  
13 clinician. I am satisfied with the confidence intervals.

14 I was trying to get a picture of how people were  
15 looking at this as a consequence of stating a null  
16 hypothesis of this type, so I wasn't expressing  
17 dissatisfaction at all with the statistics now that I  
18 understood where we were headed.

19 DR. VOSE: Dr. Auchincloss.

20 DR. AUCHINCLOSS: I think we should have this  
21 conversation again after the FDA presentations. I think we  
22 are going to hear a lot more here. The concern that jumps  
23 out at you is that the endpoints were changed and then they  
24 come back in with the data that they already had in hand  
25 when the endpoints were changed.

1 DR. O'FALLON: We can certainly hear what the FDA  
2 has to say about it.

3 DR. MILLS: In fact, the endpoints were the same  
4 as the original endpoints. What was changed was the  
5 approach to statistical analysis when it was discovered that  
6 it was not an exponential distribution.

7 DR. O'FALLON: Which is perfectly appropriate. We  
8 are always trying to find the most appropriate and powerful  
9 methods.

10 DR. NEEMAN: I just wanted to clarify that I am  
11 not the FDA statistician on this project, but I just wanted  
12 to just clarify the fact that you can have five patients in  
13 each arm and show equivalence based upon the bootstrap  
14 methodology, and whether you consider a 10-patient study to  
15 be adequate to show equivalence. That is something that you  
16 have to consider. I am just saying that equivalence, this  
17 equivalence analysis using confidence intervals, you don't  
18 need big numbers, and whether that is important or not, I  
19 leave that to you.

20 DR. VOSE: I think we will come back to this  
21 later, but a clinical concern when we look at this is  
22 applying it to our own patients and do we feel that 20  
23 patients in each arm is really clinically adequate to prove  
24 that.

25 DR. NEEMAN: In fact, you are more likely to show

1 equivalence when you have five patients on each arm.

2 DR. VOSE: I am sure you are.

3 Additional questions for the sponsor?

4 [No response.]

5 DR. VOSE: We are going to take a 10-minute break  
6 and then come back with the FDA discussions. We need to  
7 change equipment. Let's come back at five after 3:00,  
8 please.

9 **FDA Perspective**

10 DR. CHANG: Thank you very much.

11 [Slide.]

12 I am here to present the FDA perspective on the  
13 clinical aspects of this device. I want to thank Dr. Mills  
14 for presenting a lot of the background material.

15 This is PMA 97-0001. The Review Committee was  
16 chaired by Dr. Amy Rosenberg. This is a very complex device  
17 with many components and there are a lot of biological  
18 reagents and electronics involved, so we had a large number  
19 of people from CBER, as well as some consultants from the  
20 Center for Devices, in on this review.

21 I think it is fortunate we didn't have to screw in  
22 any light bulbs for all these people. Don't laugh, I might  
23 end up doing this after the review.

24 [Slide.]

25 This is the regulatory history of the PMA. The

1 Phase I-II trial was initiated in October of 1984 and in  
2 December of 1995, there was a request to switch to the  
3 enhanced device, which was a 300i.

4 In March of 1996, a phase trial was proposed by  
5 Baxter and subsequently, they had a meeting with FDA at  
6 which time we discussed some of the infusional toxicity  
7 endpoints and the problems of measuring that particular  
8 endpoint, and so Baxter, through some telecons that we had  
9 through the fall of 1996, Baxter revised the primary  
10 endpoint and subsequently, we agreed to review the Phase I-  
11 II data, so that this data really consists of the patients  
12 in the initial trial from October of 1994 to December of  
13 1995. So, then the PMA was submitted in February of 1997.

14 [Slide.]

15 Now, some of you have a great deal more clinical  
16 experience than I, but I am going to try to review some of  
17 the problems with trying to convert a Phase I-II study to a  
18 pivotal trial, and I am going to use this Baxter example to  
19 illustrate some of the problems.

20 Phase I-II trials may be prototypic in nature, as  
21 was this trial. There was a modification of the device and  
22 procedures, such as the releasing agent used in the device,  
23 and also there was a modification of the endpoints, as I  
24 have mentioned.

25 The trial involved small numbers of patients and

1 there were some miscommunications with the investigators.  
2 For example, at some of the sites, they did not have a  
3 prestudy meeting, and there were some miscommunications  
4 about randomization and enrollment in the multi-tiered  
5 scheme, which Dr. Mills showed you.

6           Biomonitoring revealed a number of protocol  
7 violations and there were substantial missing data.

8           The trial again was an open label trial, and I  
9 might remind you that there is possible bias in reporting of  
10 adverse events during open label trial.

11           [Slide.]

12           This is a chart of the subject entry and  
13 completion status. Initially, there were 71 patients  
14 enrolled, of which 47 were randomized and 24 were not  
15 randomized. The bulk of these were patients who did not  
16 mobilize.

17           Out of the randomization scheme, there were 26  
18 entered onto the Isolex arm, and it was later discovered  
19 that 5 of the Isolex patients also had unselected progenitor  
20 cells infused on day zero, so the population that we wound  
21 up evaluating was only 21 Isolex patients versus 21  
22 unselected controls. So, this wound up to be a sort of  
23 smaller trial than initially we had hoped.

24           [Slide.]

25           Now, here are some institutional variables that

1 are worth mentioning. There were 5 patients who were  
2 randomized at 1 center, and those 5 had a prior unselected  
3 transplant. The mobilization regimen varied by site. As  
4 you have heard about, three-quarters of the patients had  
5 both chemotherapy and G-CSF and one-quarter had G-CSF alone.

6 The myeloablative regimen also varied by the site  
7 and post-transplant G-CSF use varied at one site.

8 [Slide.]

9 These are the original co-primary endpoints and  
10 the initial one really addressed the safety issue, which was  
11 the incidence and severity of unusual or unexpected side  
12 effects compared to the control, and the phrase "unusual or  
13 unexpected" reflects the exploratory nature of the trial,  
14 because we weren't quite sure what they were looking for.

15 The second endpoint was the time to engraftment  
16 for both neutrophils and platelets, the first of three days  
17 to the ANC count of 500 and the platelets of greater than  
18 20,000.

19 [Slide.]

20 These are the revised primary endpoints which were  
21 introduced in November of '96, and as was mentioned, the  
22 primary efficacy endpoint was no delay in myeloid  
23 engraftment, with the null hypothesis being the difference  
24 in time to the first of two consecutive days of ANC greater  
25 than 500 is no more than three days between patients

1 receiving CD34 selected and unselected cells.

2 [Slide.]

3 These are the secondary endpoints, and was shown,  
4 the time from transplantation to a higher neutrophil count  
5 of 1,000 plus now efficacy endpoint of platelet engraftment  
6 was now downgraded to a secondary efficacy endpoint, so as  
7 the time to the first of three days without platelet  
8 transfusions at platelet counts greater than 20,000, 50,000,  
9 and 100,000, and then finally, there was the incidence of  
10 infusional toxicities.

11 [Slide.]

12 Now, infusional toxicities also happened to be a  
13 safety endpoint, but in addition was added the incidence of  
14 infections, the incidence and severity of adverse events,  
15 and mortality.

16 [Slide.]

17 So, in addition to the analyses that the company  
18 performed, we also looked at some supplementary analysis  
19 involving the efficacy subset or 21 patients, and these are  
20 5 collection failures that were excluded from the Isolex  
21 arm, because in 4 patients, there were insufficient CD34  
22 cells in the apheresis, and in one patient there was  
23 insufficient cells loaded onto the device.

24 The reason for the exclusion was that all patients  
25 received unselected cells on day zero.

1 [Slide.]

2 An additional issue was that the day of  
3 engraftment was recorded as the day after the last  
4 transfusion in some cases, and there was no data on the  
5 alloimmunization or antiplatelet antibody formation  
6 provided.

7 We adjusted the time to platelet engraftment to  
8 three days after platelet transfusion and with a count of  
9 greater than 20,000 in the absence of this information.  
10 This affected some patients, but in both arms equally, and  
11 ultimately, had no effect on the difference between arms.

12 [Slide.]

13 This is the chart to time to engraftment as you  
14 have seen before. This is the neutrophil engraftment and  
15 this is the platelet engraftment. This is the control arm.  
16 This is the Isolex before the five patients were removed and  
17 the adjustment, and this is the Isolex arm after those five  
18 patients were removed.

19 As was mentioned, the difference between control  
20 and the Isolex arms was one day, and with the Isolex arm  
21 being no worse with 95 percent confidence that the Isolex  
22 arm would engraft more slowly than two days than the control  
23 arm.

24 Now, after the adjustment, however, the time to  
25 platelet engraftment lengthened to 95 percent confidence

1 interval of as much as four days slower than the control  
2 arm, so that this was a secondary endpoint, and this  
3 difference has actually been seen with other devices.

4 [Slide.]

5 This is just the graph of ANC engraftment, which  
6 has been expanded a little bit. The ordinate shows the  
7 proportion of patients engrafting, and the abscissa shows  
8 the days to engraftment.

9 The curve on the left is the control in green and  
10 the curve on the right is the CD34 arm. You can see that  
11 the curves have the same relationship all up and down the  
12 periods to engraftment.

13 [Slide.]

14 This is the similar kind of chart for the platelet  
15 engraftment. Again, the control arm is on the left and the  
16 CD34 arm is on the right, and throughout the engraftment  
17 period, the CD34 arm grafts more slowly.

18 [Slide.]

19 This is a breakdown of the engraftment by center  
20 and study arm. There were two major sites involved in the  
21 study, the Indiana University site and the site in  
22 Marseille, France. I have here the column headers showing  
23 the treatment arm, the number of patients, the median days  
24 to neutrophil engraftment and the median days to platelet  
25 engraftment.

1           One can see at the Marseille site, there were some  
2 outliers in terms of engraftment, and we think this is  
3 probably due to the fact that this site delayed its G-CSF  
4 administration after the transplant by about three days.  
5 For some reason their platelet engraftment also was a little  
6 bit different from the other centers, and we have no  
7 explanation for this.

8           There were some other outliers here at another  
9 Paris site in terms of median days of neutrophil engraftment  
10 and platelet engraftment here, but these are relatively few  
11 patients.

12           [Slide.]

13           This is a slide of infusional toxicities. I  
14 wanted to mention a little about why infusional toxicities  
15 are difficult endpoints to meet. For one thing, the vital  
16 sign measurements can be affected by patient anxiety and  
17 emotional status.

18           It can be affected by the volume and rate of the  
19 infusion, and the location of the catheter tip that is used  
20 to administer the infusion, and finally, that automated  
21 measurements may be needed to reduce bias.

22           There is some question about the frequency of  
23 measurements that are required because if you measure too  
24 infrequently, you might miss a major event, and one also  
25 needs to define, well, what is going to be a clinically

1 meaningful difference.

2           It turned out in this study that there was no  
3 difference found in infusional toxicities, and we suspect  
4 this might have been due to inadequate design of having too  
5 few patients and also having not captured enough data during  
6 the 24-hour period.

7           There were also some execution problems involving  
8 some investigators diluting or washing cells to anticipate  
9 toxicity.

10           [Slide.]

11           As far as adverse events goes, the control study  
12 was an open-label study that had an small sample size and  
13 database. There may have been some dispute about toxicities  
14 attributable to transplant as opposed to the device.  
15 However, overall, there appeared to be no differences in  
16 infusional toxicities as was shown, infections or  
17 transfusions.

18           There is no development of human antimouse  
19 antibodies and one patient had human antisheep antibodies  
20 which were observed both before and after the procedure.

21           [Slide.]

22           Now, as far as overall survival goes, there was a  
23 higher death rate observed in the Isolex arm. Four patients  
24 died in a six-month period, and three of these were in the  
25 Isolex arm. In one year, 11 patients total died and 7 were

1 in the Isolex arm. This is too small a sample size to  
2 conclude risk, but there has been a similar trend seen with  
3 other selection devices.

4 So this being the Food and Drug Administration, I  
5 am going to leave you with some food for thought here as to  
6 whether there might be some removal of tumor surveillance  
7 lymphocytes, such as the till cells that have been described  
8 by Dr. Rosenberg at NIH, which might be removed in the  
9 selection process, and there seemed to be little or no  
10 literature published about this.

11 [Slide.]

12 Now, this to some extent has already been shown  
13 and discussed. This is the time to engraftment in the  
14 supportive studies of autologous Isolex transplantation, and  
15 I present up here the study number and the median dose of  
16 CD34 cells, the median day of ANC engraftment, and the  
17 median day of platelet engraftment, and then the percentage  
18 of patients given back-up cells.

19 You have heard already that there were five out of  
20 six patients given back-up cells, not necessarily reflecting  
21 a delay in engraftment. In the supportive studies, which  
22 only involved the Isolex, there were more patients in the B-  
23 cell malignancy study and in the non-Hodgkin's lymphoma and  
24 chronic lymphocytic leukemia study.

25 You can see that the doses of cells that was given

1 was much higher, and there was a broader range of  
2 engraftment times, both for neutrophils and platelets, and  
3 there was a relatively high percentage of patients given  
4 back-up cells. Now, this has already been discussed by Dr.  
5 Mills and Dr. Berman, so I don't need to go into that, but  
6 it would be useful for our agency to know what percentage of  
7 autologous non-engraftment would be reasonable or  
8 acceptable.

9           This particular study was also a small study, and  
10 the data are pretty tight and pretty consistent with the  
11 pivotal study.

12           [Slide.]

13           This is a similar slide of allogeneic  
14 transplantation. The first study involves the peripheral  
15 blood transplantation, and there are two categories here of  
16 matched related donor and mismatched related donor or  
17 matched unrelated donor, and although we don't have the  
18 figures on the CD34 dose, I am assuming that it may be  
19 comparable to this dose here, but what is a little bit  
20 concerning is that four out of the five patients had delayed  
21 engraftment.

22           In the bone marrow transplant study, again, we had  
23 two out of three patients with delayed engraftment, but  
24 these are very small numbers.

25           [Slide.]

1           So now in the supportive studies, I am going to  
2 just go over some of the adverse events that were seen.  
3 There were 123 patients in the uncontrolled studies, 87  
4 patients with B-cell malignancies and autologous  
5 transplants, 36 patients with various hematologic  
6 malignancies and allogeneic transplants.

7           As I have shown, the engraftment rates varied  
8 particularly for the allogeneic transplants. The graft  
9 versus host disease was similar to published unselected bone  
10 marrow, but, of course, this has a very wide range in the  
11 literature.

12           There were two cases of EBV lymphoma seen in the  
13 allogeneic transplants, as well.

14           [Slide.]

15           Now, because of the implied clinical benefit, we  
16 looked at some of the tumor cell depletion data in the  
17 pivotal study. The breast cancer cells were detected with a  
18 panel of five antibodies, and we did not receive any  
19 validation data for this particular test.

20           Five out of 24 patients in the Isolex arm had  
21 tumor cells at apheresis, 2 out of the 5 had residual tumor  
22 cells after CD34 selection, and the remaining 3 out of 5  
23 patients were not evaluated.

24           So there seems to be some controversy in the  
25 literature regarding the importance of residual tumor cells,

1 and there is an issue of reduction of tumor cell burden  
2 versus total depletion of tumor cells, which is a matter to  
3 be addressed by the committee, I hope.

4 [Slide.]

5 Now, in the supportive studies, there was a study  
6 of B-cell malignancies involving 71 patients. Again, the  
7 validation data for the following tests were not submitted.  
8 This involved PCR, polymerase chain reaction detection of  
9 immunoglobulin heavy chain rearrangement, and 5 out of 6  
10 apheresis products had tumor cells, 3 out of the 5 had  
11 residual tumor cells after the CD34 cell selection.

12 Using flow cytometry, however, with monoclonal  
13 antibodies, there was one patient with non-Hodgkin's  
14 lymphoma that was assayed with anti-CD5 and CD20, and 3  
15 patients with myeloma who were assayed with anti-CD56 and  
16 BB4, and all these patients had undetectable tumors in CD34  
17 cell selected product.

18 [Slide.]

19 This last study is a study in non-Hodgkin's  
20 lymphoma, chronic lymphocytic leukemia involving 8 patients.  
21 There was a molecular disease marker required for entry into  
22 the study, and the study was going to be carried out with  
23 PCR detection of the T:14:18 translocation involving the  
24 bcl-2 gene.

25 Now, for some reason, at apheresis, the marker

1 disappeared in some patients, so 3 patients were studied,  
2 and they became PCR-negative after CD34 cell selection. One  
3 patient's CLL cells became enriched, as was mentioned, and  
4 this was before the specific peptide release procedure was  
5 adopted.

6 [Slide.]

7 So, in summary, then, this was a small controlled,  
8 open-label study. There is a 95 percent confidence that  
9 there is less than two-day delay in myeloid engraftment, and  
10 there is a less than four-day delay in platelet engraftment.  
11 There is about a 10 percent incidence of delayed autologous  
12 engraftment in the larger studies.

13 The data on tumor cell depletion are relatively  
14 sparse considering all these studies, and there appears to  
15 be an imbalance in the early deaths with selected CD34 cell  
16 infusions.

17 Thank you.

18 DR. VOSE: Thank you.

19 Are there any questions for the FDA with respect  
20 to their perspective on this or any additional questions for  
21 the sponsor? Dr. Swain.

22 DR. SWAIN: Yes, I had a question about Table 1.  
23 This may be a misprint, but did they have 3 patients with  
24 Stage I disease? Their table did not say that, and I can't  
25 believe that, because all these patients had previous

1 chemotherapy.

2 DR. CHANG: Right. It turns out that that was the  
3 staging at the beginning of their diagnosis, and when they  
4 actually enrolled in the study, I believe their stage had  
5 advanced to the eligibility criteria.

6 DR. SWAIN: I think it must have because they had  
7 all gotten chemotherapy.

8 DR. CHANG: But in the database, it was confusing  
9 to us, and that is why it wound up on your Table 1.

10 DR. SWAIN: I think it should be corrected,  
11 because I think that this company, I am sure would not  
12 promote it in Stage I disease.

13 DR. CHANG: Right.

14 DR. VOSE: Additional questions for Dr. Chang?  
15 Dr. Auchincloss.

16 DR. AUCHINCLOSS: Maybe the company wants to put  
17 up the survival curves. I didn't notice differences in  
18 their survival curves for patients, so I was unclear as to  
19 what the FDA was referring to the imbalance. You have both  
20 time to recurrence of tumor and time to patient death, and I  
21 didn't notice any particular difference.

22 DR. VOSE: The issue probably is that it was not a  
23 significant difference. There was a slight difference, but  
24 it is not statistically significant.

25 DR. AUCHINCLOSS: It is only that it ended up on

1 the FDA sort of final summary slide as something important.

2 DR. VOSE: Dr. Hartigan, did you have a comment?

3 DR. HARTIGAN: With small numbers you have to  
4 understand that you can get what looks like something scary,  
5 but it is just because it is by chance. So in the first six  
6 months, 4 patients died. Three happened to be in the Isolex  
7 arm, and that you would be worried about, you know, the 3  
8 out of 20 and 1 out of 20, went on to in 12 months, it was  
9 11, 7 in the Isolex arm.

10 The study is too small to be able to say whether  
11 that is meaningful or not. It is all still within the realm  
12 of chance. I mean obviously, whenever you have any excess  
13 deaths, you have to worry about it, but you can't say how  
14 much at this point, because the numbers are too small.

15 DR. SWAIN: Can I make a comment about that, too,  
16 that we discussed with the previous device, too, that the  
17 patients are mixed of Stage II, III, and IV, which are  
18 totally prognoses, so that makes the numbers even tinier, so  
19 I really wouldn't put any credence in the survival data, and  
20 I think it is admirable they put it there.

21 DR. AUCHINCLOSS: I agree. Neither would I.

22 DR. SWAIN: You can't say it is plus or minus  
23 basically.

24 DR. HARTIGAN: That is right. It is not giving  
25 you enough information to say it is good or bad. It just

1 happens to be in excess at the moment, which is why the FDA  
2 mentions it.

3 DR. SIEGEL: Actually, the reason we mention it is  
4 that the guidance of this committee was that there was sort  
5 of indication the company did not need to be held to be very  
6 rigorous criteria for failure to make survival worse or for  
7 survival improvement. This is again a consensus with some  
8 dissenting views.

9 On the other hand, there was a desire to see  
10 whatever data were available to look at it and make of it  
11 whatever could be made. We are certainly in agreement not  
12 much can be made, and one of our questions is going to be,  
13 you know, do we need more or is it really not a big enough  
14 worry, but we presented it because that is what we have, not  
15 to imply that we think it either proves or rules out a very  
16 important or no effect on survival.

17 DR. HARTIGAN: I have a question about the  
18 confidence intervals for the engraftment. When you  
19 calculated them, the FDA, did you use bootstrap procedures,  
20 or you just reported the sponsor's --

21 DR. CHANG: No, we checked the statistics  
22 ourselves.

23 DR. HARTIGAN: And did bootstrap analyses to get  
24 the confidence intervals?

25 DR. CHANG: Dr. Misra did the statistics analysis.

1 DR. MISRA: Satish Misra from CBER. I would like  
2 to make two points here. The first point relates to time to  
3 engraftment. It is consistently longer in Isolex arm,  
4 whether you look at ANC greater than 300, 500, or 1,000, and  
5 whether you look at platelets greater than 20,000, 50,000,  
6 or 100,000, and we declare that it's significant because  
7 sample size is too small to lead to that conclusion.

8 The second point I want to make is time to  
9 engraftment ranges from day 9 to day 15. That means by day  
10 15, 90+ have already engrafted. So detecting a difference  
11 of plus or minus three days median time to engraftment  
12 covers the entire range from day 9 to day 15.

13 What does it mean for clinicians to answer. I  
14 don't know what it means. So we actually don't need a  
15 larger sample size to detect a difference of plus or minus  
16 three days when the range of engraftment is from day 9 to  
17 day 15.

18 There are other approaches like multinomial  
19 distribution. If we look at multinomial/binomial  
20 distribution, binomial distribution, the sample size  
21 required to detect some difference goes up quite a bit. We  
22 have done that sample size analysis, and that is all I have  
23 to say.

24 DR. O'FALLON: Everything you say is correct, but  
25 some of the things that you all displayed here suggests that

1 there might have been a desire to adjust for other factors,  
2 which you certainly cannot do with such small sample sizes.

3 DR. MISRA: Well, we did try to adjust for  
4 baseline CD34s, and there again --

5 DR. O'FALLON: It is very difficult.

6 DR. MISRA: Yes, it is very difficult.

7 DR. O'FALLON: So you have to accept that it was a  
8 well-designed study, that it was carried out correctly, that  
9 all of the participants did their thing, and yet your first  
10 couple of slides suggested quite the contrary.

11 So we are not really arguing about the bootstrap  
12 working, it is just that the bootstrap was working on data  
13 that might have some flaws in it.

14 DR. SIEGEL: Satish, it is correct that we  
15 performed bootstrap analysis, is that correct?

16 DR. HARTIGAN: Yes, it is. It says so right  
17 there.

18 DR. SIEGEL: And the range wasn't exactly plus or  
19 minus three days, but you have seen the bandwidth is three  
20 to four days, not six days.

21 DR. HARTIGAN: The width of the confidence  
22 intervals is certainly less than half the range. I mean  
23 that means that it is probably okay.

24 DR. VOSE: Additional questions for the FDA or the  
25 sponsor at this point before we get on to the discussion

1 questions?

2 [No response.]

3 **Committee Discussion**

4 DR. FREAS: I would like to remind the audience  
5 that of the 18 people at the table, we have two temporary  
6 non-voting members, and they are the industry rep and our  
7 consumer rep.

8 DR. VOSE: Thank you.

9 We are going to be voting on Question 1 and  
10 Question 2 just for information purposes.

11 Question 1. In this controlled trial, patients  
12 were randomized to receive transplantation with either  
13 unfractionated peripheral progenitors or Isolex purified  
14 CD34 positive peripheral progenitors. The median time to  
15 neutrophil engraftment was 10 days for patients in the  
16 unfractionated arm and 11 days for those in the Isolex arm,  
17 the 95 percent confidence interval around the 1 day  
18 difference ranged from 2 1/2 days longer to 1/2 day shorter  
19 with the Isolex selected cells. The median time to platelet  
20 engraftment was 10 days for the control patients and 12 days  
21 for the experimental arm. The 95 percent confidence  
22 interval as noted.

23 The question as stated: Are these data adequate  
24 to establish that, in patients with breast cancer who  
25 undergo peripheral blood progenitor transplantation, Isolex

1 processing does not substantially impair the engraftability  
2 of a cell population, i.e., that it yields a cell population  
3 effective for transplantation and engraftment with the data  
4 that we have before us?

5 Let's have some discussion on these issues.

6 Dr. Auchincloss.

7 DR. AUCHINCLOSS: Can I ask you and other members  
8 of the committee what do you consider substantially to be,  
9 at what point would you get worried as a clinician trying to  
10 bring back cells after cancer chemotherapy, because it is  
11 not what I do.

12 I am not convinced at this point that the two  
13 groups are statistically equivalent, that the engraftment  
14 occurs as quickly in the Isolex procedure group, but what it  
15 looks like to me is that it happens pretty quickly and  
16 probably quickly enough for clinical purposes in 100 percent  
17 of patients, but I don't know. Is that true for those of  
18 you who actually take care of patients in this group?

19 DR. VOSE: Dr. Broudy, do you want to discuss  
20 that?

21 DR. BROUDY: I would say there is probably not a  
22 clinically meaningful difference in engraftment kinetics  
23 based on the data that we have in front of us, having heard  
24 the discussion from a number of statisticians present. I  
25 wouldn't say a two-day difference under these circumstances

1 probably are a very major difference, but there are a number  
2 of other issues, though, more phereses were required to  
3 achieve this difference.

4           The patients who had their cells processed through  
5 the device had one to several more phereses than did the  
6 patients who did not have their cells processed through this  
7 device, and from my calculations, in the two studies that I  
8 looked at carefully, Study 104, 25 percent of the patients,  
9 despite having more phereses, were not able to get enough  
10 CD34 cells to allow them to be processed through the Isolex  
11 device, and then in the pivotal study, 15 out of 21 were  
12 mobilization failures meaning they didn't mobilize enough  
13 cells to allow the cells to be processed through the device.  
14 So I think there are actually a number of issues beyond that  
15 mentioned in this question.

16           DR. AUCHINCLOSS: Wasn't that before  
17 randomization, though? That is just a failure of  
18 mobilization, that wasn't a failure of the device, or do I  
19 have it wrong?

20           DR. BROUDY: Right. What I am saying is not  
21 failure of the device, but what I am saying is this device  
22 can't be applied if you have a certain set criteria of  
23 number of cells you need to achieve before you put the  
24 product through the device. You are going to end up  
25 pheresing patients many more times, and in these two

1 studies, between 20 and 25 percent of patients, even with  
2 more phereses, do not achieve that target number of CD34  
3 cells prior to processing.

4 DR. VOSE: I would have to agree with Dr. Broudy  
5 that a two-day difference, as noted here, is really  
6 clinically significant, however, the concerns are as the  
7 information presented to us, 20 patients in each arm, I  
8 guess clinically, I am still concerned that maybe that is  
9 really not adequate to show us that that truly does or does  
10 not represent a difference, and also some of the other  
11 concerns that she pointed out and that we have discussed  
12 earlier with respect to other issues related to this, can we  
13 say just based on engraftment, that that is inadequate, that  
14 we should use this procedure in a larger patient population  
15 based on concerns of immune effector cells and some of the  
16 other issues that we talked about earlier.

17 Dr. Dutcher, would you want to comment on that?

18 DR. DUTCHER: I guess what we are all saying in  
19 many ways is that it is difficult to divorce the clinical  
20 efficacy from the fact that you can get CD34 cells off of  
21 this procedure, and the issues that you have brought up, Dr.  
22 Broudy, have to do with the wear and tear of collecting  
23 those cells and processing them, and over on this side we  
24 could say but five people had to get back-up cells in  
25 addition to the CD34 after they had had more phereses

1 procedures to collect double the number of cells, because  
2 you are going to lose 40 percent, and then even then you are  
3 going to have to add back cells that weren't selected, so I  
4 see that the whole process of getting these cells as being  
5 much more cumbersome than just a comparison of when they  
6 regenerate.

7 DR. VOSE: Dr. Kleinerman.

8 DR. KLEINERMAN: As somebody who isn't in this  
9 field, I am really very confused, because it seems to me  
10 what we are being asked to vote on is does this device  
11 select CD34+ cells that can engraft, not is it better than  
12 other devices or is it going to be the way we treat all  
13 patients, but does it provide a device and offer a choice of  
14 clinicians out there, and I think if it is an inferior  
15 device, that will be sorted out, just like people have their  
16 preferences of whether they use different stem cell factors  
17 to promote granulocyte engraftment.

18 So, I really have a hard time trying to separate  
19 the question that is being asked and saying well, yes, but  
20 this isn't a perfect product. It may not be a perfect  
21 product, but it may work in a patient population. It may  
22 offer investigators an alternative.

23 One thing that I was struck by the data, the  
24 fluorescent data, it looked like the cells that were being  
25 selected were very highly fluorescent. Maybe these cells

1 take longer to engraft, but maybe down the line, I don't  
2 know were any bleeding times done, any kind of immunologic  
3 tests done?

4 I mean further along the line they tend to be  
5 superior in terms of long term outcome, but I am confused as  
6 to what we are being asked, but I think in terms of whether  
7 this device selects CD34+ cells that can engraft, I would  
8 say it does.

9 DR. VOSE: Dr. Siegel, do you want to just clarify  
10 things for us?

11 DR. SIEGEL: I can try to clarify what you are  
12 being asked. Obviously, there is a series of questions.  
13 The first question is largely focused on -- and I think you  
14 are starting to get to opinions on that -- remember, we are  
15 not asking you to compare this to other devices, we are  
16 asking you simply to compare engrafting, using the device  
17 and engrafting not using the device.

18 The first question is, are these adequate data to  
19 show that if you use the device you get cells that engraft  
20 acceptably well, which it is hard to imagine what you would  
21 compare that to other than not using the device, so I think  
22 it is appropriate to make that comparison because if, in  
23 fact, using the device, not only as some people have pointed  
24 out, it creates certain inconveniences, more procedures, but  
25 in an important matter, impairs the ability to engraft.

1 That is obviously an important thing to know about the  
2 device in making a regulatory decision.

3           What we are going to ask, then, in subsequent  
4 questions, though, it gets to the other part of what you are  
5 asking, which is, is that if indeed these cells engraft  
6 adequately, so that we now know that you can use the device  
7 and the patients will not do significantly worse than if you  
8 don't use the device, on the whole, is that enough to  
9 declare the device to be effective, or ought there need to  
10 be some more direct evidence of patient benefit.

11           I think we have had a lot of discussion within the  
12 Agency as to what our regulations and laws say about  
13 requirements in that regard, and if we felt we had the  
14 answer there, we wouldn't be asking you the question.

15           I think although we have further discussion to go  
16 on, I think that in significant part, this is a question  
17 that requires scientific input from a public health  
18 perspective, is what is it that we need to know about such a  
19 device and do we know it in order to approve it.

20           MS. MEYERS: Less than a year ago, this committee  
21 advised FDA to approve another similar device. We voted yes  
22 to approve the device. Have you approved that device?

23           DR. SIEGEL: Yes.

24           MS. MEYERS: You have. Okay. So this is not the  
25 only alternative available for public health purposes, is

1 it?

2 DR. SIEGEL: Well, that device is approved for a  
3 different indication. It is for use with bone marrow,  
4 although it is used for this indication, which is --

5 MS. MEYERS: For separating --

6 DR. SIEGEL: For separating peripheral blood stem  
7 cells, but neither device -- there is no device approved for  
8 this indication. Both devices are out there in use, and  
9 which will be available when is actually a very complicated  
10 matter.

11 MS. MEYERS: So there is an alternative to this  
12 device. If this committee votes not to approve this device,  
13 there is another alternative, is that correct?

14 DR. SIEGEL: There is currently a device that  
15 selects CD34 cells on the market, Cell Pro, which is  
16 approved for autologous bone marrow transplantation, but has  
17 been used for this indication.

18 DR. VOSE: Dr. Auchincloss.

19 DR. AUCHINCLOSS: Jay, it seems to me that you  
20 answered the question for us. It seems to me the last time  
21 we were here, when you gave us your new guidelines for FDA's  
22 way of regulating autologous cell transplants, and the  
23 understanding I had -- and I understand I guess that they  
24 are still guidelines, and not yet approved -- was that the  
25 FDA was going to take the view that minimally manipulated

1 autologous cells would not be under your most rigid  
2 scrutiny, and so it sounds like you have already decided you  
3 don't want us to pass on the efficacy of a CD34+ stem cell  
4 transplant, and we end up just looking at a device here and  
5 saying does it make the cells in a safe way -- I think I  
6 would conclude yes -- and I don't think that at this point,  
7 it does anybody any good, but you have told us, it seems to  
8 me, that you don't want us to tell you whether we think it  
9 does any good.

10 DR. SIEGEL: Well, that is a very good question.  
11 I don't think that is exactly what that policy says. I  
12 thank you for noting it, and let me note that. That policy  
13 is, as you note, out for public comment -- it is not -- it  
14 represents our current best thinking. We are receiving,  
15 however, a lot of commentary. We had discussed it with this  
16 committee or approaches to stem cells with this committee  
17 about a year and a half ago, and got some very interesting  
18 advice.

19 That document addresses the regulatory approach to  
20 the cells, not specifically to devices or factors used in  
21 preparing or growing cells. If that were the policy, what  
22 that would mean would be, for example, that were this or  
23 another device approved to make this cell population, we  
24 would not require every oncologist who used that device to  
25 file as a manufacturer of autologous stem cell therapies to

1 get a license approval.

2           That decision, as I see it at least, although  
3 there is ongoing discussions within the Agency, and this is  
4 evolving policy, and I am not a lawyer, and with all those  
5 provisos, let me say this. That decision per se does not  
6 bear directly on whether or not this device would be  
7 regulated.

8           There are many medical devices, for example, that  
9 are used in the operating room where you might take out a  
10 blood vessel or something and sew on it and cut on it, and  
11 do all sorts of things, and we would regulate those devices  
12 and put it back in. We wouldn't regulate that blood vessel.  
13 That doesn't mean that we don't regulate the devices that  
14 are used.

15           So, in some very real sense, there is a separate  
16 question, although they do come together. I think another  
17 important part of that question is that there are other cell  
18 therapies that that policy would propose that we do regulate  
19 as products, some of which might use a CD34 selection  
20 device, including allogeneic cells, cells that might be  
21 grown up or expanded or genetically manipulated with  
22 factors, and I think we are having a lot of discussion and  
23 probably can put on the regulatory approach to the device in  
24 that setting, but, for example, in the simple case of  
25 allogeneic cells, even where efficacy data would be sought

1 and required, it may well make more sense rather than to  
2 have each investigator have to show the efficacy of their  
3 allogeneic cell, to look toward a device used to purify such  
4 cells or to purge such cells if somebody had a T-cell  
5 purging device as the appropriate place to rest their  
6 primary burden for showing the safety and efficacy of that.

7           So, I say that only to say that while they are  
8 intimately interconnected, the policy that we stated of our  
9 proposed regulatory approach to the cells is not  
10 inextricably linked to the proposed regulatory approach for  
11 the device that is used to approve the cells, and obviously,  
12 the fact that we are here discussing this with you reflects  
13 our current thinking at least that this device belongs to a  
14 class where both there is an appropriate legal framework and  
15 an appropriate public health need to have a policy where we  
16 do evaluate it.

17           DR. AUCHINCLOSS: I personally think that you  
18 would be wrong to think that you can maintain regulation of,  
19 for example, allogeneic bone marrow stem cell  
20 transplantation by regulating the device, because, in fact,  
21 there is already a licensed device out there, and we all  
22 know that lots of things happen off labeling, and so you  
23 lose control, in fact, of all of these other applications if  
24 you say the device is the way we are going to regulate them.

25           So I think you will need to continue to regulate

1 the procedure if you choose to do so, if you think that is  
2 the right thing to do, and I do think it is the right thing  
3 for you to do, and that the device should be regulated as  
4 the device doing safely what the device says it does, in  
5 this case, make CD34+ cells.

6 I actually think the problem with this whole  
7 discussion is that I don't think you should give up the  
8 regulation of even autologous stem cell transplantation  
9 because there is the hint that a lot of people have the  
10 sense that maybe that is not doing anybody any good, and so  
11 we feel uncomfortable about giving a sense of a green light,  
12 go on out there and do these kinds of transplants because  
13 they are wonderful by approving a device which does what the  
14 device says it should do.

15 So my sense is that your guidelines are wrong,  
16 your proposed guidelines are wrong, but that this device is  
17 sound for what it says it is doing.

18 DR. VOSE: Dr. Leitman.

19 DR. LEITMAN: We have tried to compare the two  
20 arms of the study, the clinical study that was just  
21 presented to us by the FDA, and we are making a judgment on  
22 the quality of the progenitor cells infused by the time to  
23 engraftment, but we can't do that because there is a  
24 difference in quantity, and it is a very critical  
25 difference. It is 4.4 million per kilo versus 2.3 or

1 something like that. That is right in the range where you  
2 see a 1 to 2 to 3-day polymerization of neutrophil and  
3 platelet engraftment, so you can't say that something  
4 qualitatively, there are more bright on flow or something  
5 like that, is at issue here, because there is a quantitative  
6 difference.

7           If you were infusing the exact same number, if you  
8 did 4 phoreses until you document -- their eligibility  
9 criteria was that they start with pre-cell processing, a  
10 count of 5 million per kilo. This study would have been  
11 better if they insisted on a minimum number following  
12 processing, and that number could be adjusted then in the  
13 non-processed arm to be roughly the same number.

14           Then, you could have compared the same quantity  
15 processed and the same quantity non-processed, and got at  
16 the question we are asking about, is there any difference in  
17 engraftment.

18           DR. KLEINERMAN: But by that token, then, you can  
19 infuse half this many cells and still get -- what I was  
20 referring to was the cells that were infused that were  
21 fluoresced pre-going through the device and after the  
22 device, and it seems to me there was in the non-selected  
23 population there were some CD4+ cells that were left, but  
24 the ones that were selected were much brighter it appeared.  
25 That is what I was referring to, not that there were more

1 brighter cells in the unprocessed cells versus the processed  
2 cells.

3 But by your argument, you can infuse half as many  
4 cells and still get the equivalent engraftment.

5 DR. VOSE: I think the concern still remains that  
6 the two arms are not equal with a number of respects, not  
7 just that. At least I still have a concern that clinically  
8 speaking, I would have a problem with 20 patients in each  
9 arm trial convincing me that really, statistically, that was  
10 a valid comparison.

11 DR. BROUDY: I think the major concern that I  
12 have, that has not been brought out yet in this discussion,  
13 and that is, I don't think any clinical benefit has been  
14 shown.

15 Probably they do engraft within a comparable day  
16 or so in terms of neutrophils and platelets, but that is at  
17 a cost, it is at a cost of more phereses and more time and  
18 more effort, and I don't think any benefit has been shown in  
19 decreased infusional toxicity or decreased in number of  
20 tumor cells, and so I am very hesitant to approve a device  
21 that I can't see any clinical benefit that has been  
22 demonstrated in a trial presented to this committee, and  
23 that is my major concern.

24 DR. VOSE: Just to follow up on that a little bit,  
25 the other concern I have is that we have no information

1 regarding long term outcome as long term toxicities or long  
2 term concerns, and with a 20-patient trial, it is going to  
3 be very difficult to show anything related to that.

4 Dr. Anderson.

5 DR. ANDERSON: I just want to say that these are  
6 complex issues, and that is why the FDA asks specific  
7 questions, and my feeling is we should go through the  
8 questions, because we are really talking very broadly about  
9 lots of things, and definitively vote on each question.

10 The first question is, is there a delay in  
11 engraftment, and you just said what gets back to what I had  
12 asked earlier, and that is, do the statisticians agree that  
13 there is or is not (a) a significant study, and (b) a  
14 difference, and if they agree that it was a statistically  
15 significant study and that there is no difference, then, we  
16 should vote on the first one, but if the statisticians don't  
17 agree on that, then, we need to know that before we vote.

18 So I want to ask again -- because you just  
19 expressed concern about whether this is a statistically  
20 significant study.

21 DR. VOSE: I am also concerned about the last  
22 statistician that spoke -- I am sorry, I didn't get his name  
23 -- but he seemed to have much more concern about that than  
24 previously.

25 DR. SIEGEL: Let me comment as a non-statistician.

1 I talk to a lot of statisticians, though, I like them.

2 [Laughter.]

3 DR. SIEGEL: Maybe I can help translate some of  
4 the concern here.

5 You are not going to find a statistician who is  
6 going to tell you that this is a significant study that  
7 showed that there is no difference because you can't do a  
8 study that shows that there is no difference.

9 You can do a study that either looks for a  
10 difference of a given size with adequate power and fails to  
11 find it, or the way we prefer to think of it, you can do a  
12 study designed to make sure there isn't a difference of a  
13 size of concern and then show that the difference, if there  
14 is one, is less than that size. That is really what you can  
15 do with a clinical trial.

16 Now, there are two issues I think that bear on  
17 this question that you have heard bandied about, and I am  
18 going to try not -- I don't want to give answers -- but just  
19 to try to translate what the issues are.

20 One is that we have confidence intervals which, if  
21 they are correct confidence intervals -- and I will come  
22 back to that -- suggest that -- well, the point data suggest  
23 there is a day or so of longer engraftment, it is not  
24 statistically significant. It may well be that there is no  
25 difference.

1           Then, you have a confidence interval which  
2 suggests, depending on which one you look at -- that it  
3 could be a day or so shorter, it could be two to three days  
4 longer for engraftment.

5           What a confidence interval would purport to tell  
6 you is that based on the data you observe, that the true  
7 difference, that there is 95 percent confidence -- I think  
8 these are 95 percent confidence intervals, correct me if I  
9 am wrong -- that the true difference is going to fall within  
10 that range.

11           So part of the question is, is that range close  
12 enough. If we are to look at simply showing that the cells  
13 adequately engraft, is it good enough to know that they  
14 adequately engraft, that we are sure that they don't do two  
15 or three days longer on the median.

16           Of course, there is more of interest than the  
17 median, I should point out, because you can have very close  
18 medians and have tales of, you know, in 20 patients, you  
19 could have a 15 percent failure to engraft rate, and not  
20 observe it in 20 patients, you know, 5 percent of the time,  
21 and that won't show up in the medians or in a study of 20  
22 any way you look at it, potentially.

23           The other issue, are those really appropriate  
24 confidence intervals, and that gets to the discussion that  
25 you heard regarding the bootstrapping. Bootstrapping, which

1 is a resampling of data from the trial data itself, will  
2 give a good estimate, and one of the best ways, perhaps the  
3 only or the best way we know of really estimating confidence  
4 intervals in this setting, will give a good estimate if the  
5 distributions of data that were observed in their trial  
6 reflect the distribution in the actual population from which  
7 the patients were selected.

8 I think the concern expressed by small numbers is  
9 that if you do a trial with very small numbers and happen to  
10 get a very tight data range, you can resample that and  
11 bootstrap it, and no matter how many times you do it, it is  
12 going to show you always that there is very little  
13 difference because everything is tight, so the question is,  
14 is this artificially tight or are these fair distributions,  
15 but assuming that this represents a distribution of the  
16 population, these should be good estimates of the 95 percent  
17 confidence intervals.

18 Finally, I guess I would address that last  
19 comment, which I think was stated, the statement was there  
20 were consistent -- the wording might have been delays, but  
21 let me say there was consistently longer time to engraftment  
22 of a variety of different cutoffs of neutrophils and  
23 platelets, and I think that is a correct observation that  
24 should be considered, though, with the fact that none of  
25 those observations are statistically significant, and they

1 are all highly intercorrelated.

2           So if by chance one group takes a day longer to  
3 reach 20,000, it is not unlikely they are going to take a  
4 day longer to reach 50,000 or 100,000, so I am not sure of  
5 the extent to which that consistency strengthens.

6           I think what you have to look at is that your best  
7 estimate is a day longer and that it could be a day shorter,  
8 it could be three days longer if you accept the  
9 bootstrapping, that is really what you have to deal with.

10           DR. LACHENBRUCH: My name is Tony Lachenbruch. I  
11 am branch chief of Biostatistics at CBER.

12           One of the things that statisticians always revel  
13 in, and Jay almost said it, is that being a statistician  
14 means never having to say you are certain.

15           [Laughter.]

16           DR. LACHENBRUCH: It is getting late. I did want  
17 to comment on my reading of this question, which when I  
18 heard Dr. Auchincloss or Dr. Anderson I guess talk about it,  
19 I think I had a slightly different take on this because it  
20 says are these data adequate to establish that, et cetera,  
21 and it seems to me that is addressing actually two points,  
22 one of which is the quality of the data, and the other is  
23 given that the data are of sufficient quality, are you happy  
24 with the delays in engraftment that you observe.

25           DR. VOSE: I appreciate that. I agree that I

1 think you have to be concerned about the quality of the data  
2 that goes in, so that you can understand the information  
3 that comes out, and I think that that is a concern.

4 MS. MEYERS: I am trying to understand this from a  
5 layman's point of view. Having sat through all this  
6 discussion about statistics, and I can't even balance my  
7 checkbook, okay, I want to try to boil it down to the  
8 basics.

9 First, I heard the manufacturer explain that this  
10 device is still in development, they are still refining it.  
11 They recognize that it is not perfect, and they refined it  
12 several times since they collected this data, so they have  
13 come up with something better already.

14 I would think it would be smart to just wait for  
15 them to give the new data on the updated machine. Why would  
16 you want to approve an old machine? There is no emergency  
17 here.

18 Second, it seems that the data is saying there is  
19 no clinical benefit, and third, the data is also saying that  
20 there is a delay in engraftment from the control group --  
21 from the control group, not from some historical group that  
22 it is out there in the medical journals that everybody is  
23 comparing their statistics with, but the control group,  
24 people who didn't use this device engrafted faster.

25 So, it is illogical to me that we should still be

1 talking about the data and whether they are valid or not  
2 when the data is clearly showing that this device is really  
3 not terrific, and if you approve it, will the company have  
4 to put five cents more into research to develop it. It will  
5 be approved and on the market.

6 DR. VOSE: Dr. Anderson.

7 DR. ANDERSON: I will respond for you.

8 Abbey, anytime a company has a robust pipeline,  
9 there are going to be things in Phase I that are better than  
10 their Phase III products, but it is not appropriate to  
11 constantly judge a Phase III product based on what might be  
12 coming along.

13 The criteria is whether or not this device  
14 satisfies the requirements for this device, not if another  
15 device is better and it is going to come along next year or  
16 the year after.

17 Your second point is there isn't a clinical  
18 benefit, well, that is not what we are judging at this  
19 point. Now, as part of the overall package perhaps, but  
20 this is the device that concentrates CD34 cells. That is  
21 what it does. If it does that, then, that is what we have  
22 to decide.

23 Safety is obviously an issue, and if there are  
24 other problems, that gets taken into account, but I don't  
25 think that our mandate is, or that their mandate is, that

1 they have to show a clinical benefit.

2 MS. MEYERS: Well, how do you judge safety when it  
3 shows that more people who used this device died than the  
4 people in the control group?

5 DR. ANDERSON: Now, that was your point 3, and  
6 that is, does the device increase the time to engraftment or  
7 increase deaths, and this gets back to granted statisticians  
8 never have to say they are certain, but on the other hand,  
9 it isn't fair to any of us, as investigators, to say you  
10 have to have statistical significance for benefit, but we  
11 can get you from the back that it is not statistically  
12 significantly unsafe, but because there is a trend that way,  
13 you know, the answer is no.

14 This falls into a category where Jay and I talked  
15 at the last one about post-marketing studies. The last time  
16 we were talking about efficacy studies, and I was arguing  
17 companies shouldn't be required to do it.

18 Safety studies are quite another matter, and the  
19 last question comes to that, and if the conclusion of the  
20 committee is, and ultimately the FDA is, that there is a  
21 potential safety issue, whether it is deaths or whatever,  
22 but that the device does what it is supposed to do and  
23 therefore should be licensed, in this case, I could see a  
24 legitimate reason for requiring a post-marketing study to  
25 look at safety.

1 DR. SIEGEL: I feel compelled to interject here  
2 that regardless of whether it is considered fair, the Agency  
3 can and does routinely apply that exact difference in  
4 approach to efficacy and safety, and indeed, we see many  
5 products in which regardless of whether there is a  
6 statistically significant difference in efficacy, where  
7 there is no statistical significance in safety but there are  
8 inadequate safety data, we say that is unapprovable until  
9 there are adequate safety data.

10 Now, some safety data we might defer to post-  
11 marketing depending on how important they are, but I do want  
12 to make clear, you know, we have guidelines. There are  
13 certain diseases you want to treat, you know, it doesn't  
14 matter how significant the benefit is if you don't have so  
15 many hundred or so many thousand, or whatever it is,  
16 patients to ensure that you are not going to cause aplastic  
17 anemia in treating somebody's sniffles or something like  
18 that, then, it doesn't matter that there is no significant  
19 difference, we say that is not good enough, and so we do  
20 apply a different approach to safety and efficacy in that  
21 regard.

22 DR. BROUDY: But I think we would all agree that a  
23 better study could be done than the 20 or 21 we had in each  
24 arm, and I would like to read a couple of comments here from  
25 the FDA commentary, that the assay procedure for CD34

1 measurement was not standardized and varied by site, and  
2 varied a lot between the sites and the central review, and  
3 from Protocol 105, CD34 cells were transplant peripheral  
4 blood progenitor cells in non-Hodgkin's lymphoma,  
5 significant technical problems were observed during the  
6 processing of the cells, clumping in the device, recovery  
7 was 15 to 20 percent in two patients.

8 I mean I think there are enough problems with this  
9 study that I am just not excited about approving this device  
10 based on this small study. I think a better study certainly  
11 could be designed and carried out.

12 DR. O'FALLON: The study wouldn't be any better if  
13 it was 20 or 30 times this size if all of those same flaws  
14 were still here, so let's not keep focusing on 20 in each  
15 arm. That would have been perfectly adequate if there were  
16 no problems, if we were all completely satisfied that those  
17 20 represented the population of patients that they were  
18 supposed to represent, that there were 20 that were  
19 randomized to the other arm, represented that same  
20 population, et cetera, et cetera.

21 I have heard all sorts of comments around the  
22 table that challenged that, so it isn't the number 20 that  
23 is the problem here. It is whether or not those 20 are  
24 doing the job for us, i.e., representing the population of  
25 patients that we need them to represent, so that we can be

1 sure when this device is put out there that it is --

2 DR. VOSE: As we talked about in the last study,  
3 we have to judge this based on the information that we have  
4 available, and from the information we have available there  
5 are a number of different concerns that we have whether  
6 there is 20 patients or 200 patients. We need to take that  
7 into context.

8 Dr. Bensinger.

9 DR. BENSINGER: As a clinician who has  
10 transplanted hundreds of patients with stem cells, the  
11 majority of which have been unselected stem cells, I think  
12 it is worth pointing out that the ranges, the 95 percent  
13 confidence intervals for both the control group and the  
14 selected group in the pivotal study are well within the  
15 expected ranges that you would see, are that we have seen  
16 with unselected stem cells.

17 I do think it is a mistake to focus on the one or  
18 two outliers that have delays in engraftment because we see  
19 that with unselected cells, as well, and you have always got  
20 this biologic variability when you are doing clinical  
21 trials, and I think that would be a real mistake to focus on  
22 that.

23 The one-day difference that is seen -- which again  
24 is not statistically different, and I think not clinically  
25 different either, I think is probably related to the dose of

1 CD34 cells. There was a lower dose in the selected group,  
2 and that happened I think because they allowed all the cells  
3 that were collected unselected to be reinfused, and so there  
4 was more than double the number of CD34 cells.

5 But I think that if you look at those ranges, you  
6 will see they are well within what we see from a variety of  
7 other published studies.

8 DR. VOSE: I guess I would have to agree with you  
9 completely. As I said earlier, I don't think it is a  
10 clinically important difference. The concern is whether the  
11 data is adequate to be able to tell us if that really is the  
12 case or not.

13 Dr. Cornetta.

14 DR. CORNETTA: There was three points, then, in  
15 the discussion I think that were concerning to me. First,  
16 related to the indication and the relation to another device  
17 and its approval in marrow, and while it is being used in  
18 peripheral blood stem cells, I mean I think it is important  
19 to remember that is really not an indication, if I am  
20 correct, and so I think trying in that discussion, to say  
21 there is something out there that is being used off-label  
22 should be permissible in regards to that, I think that is  
23 sort of questionable.

24 Secondly, I think I have some concerns about  
25 saying that this hasn't necessarily been shown to be

1 efficacious, because the indication that is being asked for  
2 is the removal of non-target cells, and partly it is my  
3 bias, looking at gene therapy, where the target cells we are  
4 looking for are CD34+ cells, this does remove the non-target  
5 cells in that clinical situation, and again, there are  
6 patients who need to be treated with this, and the  
7 indication would apply to those patients that it is being  
8 asked for.

9 I think the third area where I am concerned as an  
10 investigator relates to breast cancer, and I have the same  
11 concerns, too, about where are relapses coming after breast  
12 cancer, but I feel like without this device, investigators  
13 may be put into a catch-22 situation.

14 Relapse after breast cancer is probably from two  
15 sources. It may well be coming from the transplanted  
16 marrow, and I think disease relapse from residual disease  
17 currently is probably our bigger problem, but I think these  
18 are two problems we need to face with.

19 This is a technology that at least allows us to  
20 deal with one problem as we try to deal with the other, but  
21 as you try to deal with efficacy, if you are giving back  
22 infusion of marrow and your outcome is relapse, again,  
23 trying to design more and innovative trials in there, we are  
24 limited.

25 So I think again, this is a very tough issue to

1 deal with, but I think just saying that we are going to  
2 remove the marrow, and that is going to affect relapse is  
3 probably not the case, because we are trying to deal with  
4 two problems here.

5 DR. VOSE: But, Dr. Cornetta, we are not talking  
6 about, and there was no data presented related to trying to  
7 get rid of the tumor cells today, so that is an implied  
8 benefit, not something that is asked for.

9 DR. KLEINERMAN: But what he is implying is that  
10 to do the study, to determine where the relapses are coming  
11 from, you have to have a device where you can select your  
12 target cells. Let's say you want to label your CD34 cells,  
13 the marrow cells, with some innocuous gene, so that you can  
14 determine whether the relapse is coming from the cells that  
15 you are reinfusing from the marrow, or whether they are  
16 cells that just weren't wiped out from your chemotherapy.

17 Well, the only way you can do that is to label  
18 your cells, and if you have only 0.1 percent of the cells in  
19 this 99 percent gamish, what is the efficiency of your being  
20 able to label the cells that are going to engraft.

21 So, if you concentrate your cells down to a small  
22 number of cells, where you can get a better uptake of the  
23 gene, you can infuse that and then you can determine where  
24 the relapses are coming from.

25 So what I think you are saying, and what I believe

1 to be true, is that this is a device which will allow  
2 investigators to create novel types of protocols to answer  
3 the questions that we need to get at.

4           Personally, as a clinical investigator, I think it  
5 is very helpful to have things that are commercially  
6 available which will allow you to do the type of questions  
7 that you want to ask without having to go to the company and  
8 say I want to do this trial, will you support it, but I also  
9 want to use this gene product, so you are working with two  
10 different companies, and you have got two sets of lawyers  
11 that are coming through, and nothing gets done.

12           If you have a commercially available product, you  
13 say I am going to use this to select my cells, I am working  
14 with this company with this gene, we will try to label these  
15 cells with the gene, and you are off and running. You are  
16 dealing with one company, not two, three, or four.

17           So, I think this may be a very valuable tool if it  
18 can concentrate CD34 cells, which I believe it can from the  
19 data that is presented.

20           DR. SIEGEL: Just one point of clarification.  
21 Excuse me for interrupting, but I do want to make clear -- I  
22 wasn't sure exactly what Dr. Cornetta said about this -- but  
23 I want to make clear that those potential uses of this  
24 product aside, whether as a tool for experiments to study  
25 tumor relapse or as an ancillary product with gene therapy,

1 those potentially are very important uses, those are not, in  
2 fact, related to the indication today.

3           The indication being sought is not one to purify  
4 CD34 cells generically. It is a clinical indication which  
5 is for use of the cell product of the device for autologous  
6 peripheral blood progenitor cell transplantation.

7           DR. VOSE: Dr. McCurdy, did you have a comment?

8           DR. MCCURDY: I think he just answered my  
9 question. I seem to believe that if we approve this, we are  
10 approving it for routine clinical use in any setting where  
11 peripheral blood stem cells are being collected and  
12 transplanted, and not as an investigative drug or a device.  
13 It is already that, so I think we should focus on whether  
14 the data support it being useful in the clinical setting.

15           DR. VOSE: I think some of the concern relates to  
16 issues, as Dr. Cornetta pointed out, that it would then be  
17 used for many of these other indications off-label, and that  
18 is a concern when there may not be indications to use it in  
19 the routine clinical situation, and then we continue to use  
20 it in an investigational situation.

21           Dr. Shpall.

22           DR. SHPALL: I wanted to address the concerns of  
23 the patient representative. First, by saying that there has  
24 been no delay in engraftment and no increased relapses if  
25 you really look carefully, so I don't think that is the

1 issue, and the confidence intervals, I think we have heard  
2 from a number of statisticians, granted it is a small study,  
3 all of us would like to see a bigger study, but I, as a  
4 clinician, am confident that the engraftment rates are  
5 comparable to the control.

6           The issues here are much more complicated in terms  
7 of clinical benefit because, number one, if you look at  
8 clinical benefits, such as a reduction in infusional  
9 toxicity, this study couldn't answer that.

10           Not having been involved in the study, but talking  
11 to the clinicians who were, they slowed the rate of infusion  
12 when any toxicity develops, so that you would never be able  
13 to see that benefit here, and, you know, yes, they could do  
14 another hundred patients and standardize the infusion, and  
15 show that with an infusion rate that was comparable, you  
16 could have a reduction in toxicity, and that is up to the  
17 committee to determine whether you want them to do that.

18           I think in terms of the tumor cell detection, yes,  
19 they should have had better assays or done more careful and  
20 more comprehensive tumor detection studies before and after,  
21 but, you know, none of our assays are very good, and I think  
22 we are highly underestimating the amount of breast cancer,  
23 for example, that you are finding in the marrow blood, and  
24 absent the clinical purging trial where, in the example, 10+  
25 node adjuvant breast cancer setting, we have designed such a

1 trial, and to detect an improvement in relapse rates of 10  
2 percent, it is going to be a 1,200-patient trial, it is  
3 going to take five years, it has to be done, but I think  
4 that that is not the question posed to the committee today.  
5 I think the real thing you have to look at is was  
6 engraftment comparable, and I would have to say yes, and our  
7 statisticians corroborate the fact that we don't see a  
8 problem there.

9 DR. VOSE: Dr. Anderson.

10 DR. ANDERSON: Anytime you have a complex issue  
11 which is not at all clear-cut, other factors go into the  
12 decisionmaking, and I intentionally had not brought up the  
13 gene therapy side, but since that has been brought up by  
14 others -- and I appreciate it has been -- the fact is that I  
15 am biased, because this is an important device for gene  
16 therapy, and so all of my statements have been trying to get  
17 at how good the study is, and so on, and so forth, because  
18 my bias is I want to approve this, and others -- I agree  
19 with Paul, who said that what we are supposed to be focusing  
20 on is this indication, and that is correct, but we are  
21 humans and other things influence us.

22 So I guess I am sort of putting it out on the  
23 table that just as I was influenced in the last vote by  
24 Abbey Meyers' statement that what things get reimbursed by  
25 insurance and what things don't, and that shouldn't play a

1 major role, but when you are absolutely on the fence, that  
2 can tilt you over.

3           So my point of this is that even though there does  
4 appear to be uncertainty as to the equality of the study, I  
5 don't see a problem in terms of this device, and because of  
6 other issues which in theory shouldn't be taken into  
7 account, but in reality are, my preference is to vote yes on  
8 this.

9           So the question is can we go through our  
10 questions, so that we come to a vote sometime before 6  
11 o'clock tonight.

12           DR. BROUDY: I would just like to say I don't  
13 think you can approve something on promise, I think you have  
14 to approve it on data, and that is where you and I take  
15 issue on this particular product.

16           DR. ANDERSON: I don't agree.

17           DR. VOSE: I think our charge is really to look at  
18 the data as presented, and that is what we are supposed to  
19 do, and we should be doing that.

20           DR. AUCHINCLOSS: I understand, but I don't think  
21 you are fair to yourself. This product has a benefit. It  
22 has got an enormous benefit. It enriches CD34+ cells, which  
23 you are going to find enormously useful, and lots of other  
24 people are going to find enormously useful, and that is all  
25 it says it does safely, and I think that is a very good

1 reason to approve it because it does have value and it is in  
2 the data that we have here.

3 DR. VOSE: Dr. Loken.

4 DR. LOKEN: I am Dr. Michael Loken from  
5 Hematologics in Seattle.

6 Dr. Broudy brought up a question with regard to  
7 the quality of the data, especially with regard to the CD34  
8 enumeration, and that is very crucial for this particular  
9 study, a multicenter study done, the enumerations were done  
10 at the sites using different instruments, different  
11 reagents, different protocols for data analysis.

12 In order to assess how that data was to be put  
13 together, the list mode data were all sent to me personally,  
14 and using a similar strategy of gating and being able to  
15 detect the CD34s as distinct from dead cells, distinct from  
16 other contaminating cells, I did the analysis blindly, so I  
17 did not know what their analysis was.

18 Having had close to 15 years of experience in  
19 enumerating CD34, the correlation between the data that I  
20 generated with regard to CD34 enumeration and the sites was  
21 essentially identical. Only one site had a minor variation,  
22 and that was a slight shift in where the gates were set and  
23 it was only a 10 percent difference, and we are talking  
24 about percentages of under 1 percent, and so when you are  
25 talking about quality of the data, the CD34 enumeration was

1 very, very good.

2 DR. VOSE: Thank you.

3 Dr. Goldsby.

4 DR. GOLDSBY: I think the question has been simply  
5 put, does the device separate CD4 cells and does it separate  
6 them safely, and I just had a question because statistics is  
7 for me a second language, and Dr. O'Fallon, I believe said  
8 it is not so much the size of the population, it is the  
9 quality of the population from which the data is being  
10 taken.

11 I just wonder if the company representatives and  
12 members of the committee could translate the quality of the  
13 population for me, that is to say, since the device is being  
14 approved for general clinical use, is this a population,  
15 small though it is, that is generally representative of the  
16 many different populations on whom it might be used. Are  
17 there pediatric representatives, men, women, and so forth,  
18 and so on?

19 DR. VOSE: There definitely aren't any pediatric  
20 patients in here, in that particular study. There were in  
21 other studies.

22 DR. LEITMAN: It wasn't so much, I think, the  
23 quality of the patients, it was the way the data was  
24 gathered that was flawed. Instead of insisting upon the  
25 same number of cells infused in each arm, which could have

1 been forced -- that wouldn't have been difficult -- there  
2 were different cells allowed.

3           When the dose is different, I don't think you can  
4 comment on any differences in time to engraftment. There  
5 don't seem to be any anyway, so it would make the small  
6 differences get even smaller, but it was a flawed study, not  
7 because of the quality of the patients or the accessioning  
8 of the patients, but the way the study was designed.

9           DR. GOLDSBY: So should I assume there is no  
10 concern about the kinds of patients that went into the  
11 population?

12           DR. CHABANNON: I am Dr. Christian Chabannon from  
13 Marseille, France, and Baxter supported the work, brought  
14 the patient and people to study. Other than that, I have no  
15 financial interest with the Baxter Company.

16           I would like to make comments on two points and  
17 maybe bring a European perspective in this question. The  
18 first point is that on several occasions, you have asked  
19 whether there is any clinical benefit for the use of this  
20 device.

21           I would think this is unfair to ask this  
22 particular study or more generally Baxter to demonstrate the  
23 clinical usefulness of tumor purging. Tumor purging is not  
24 new. It is a question that has been around for 15 years,  
25 and people will continue to purge marrow on blood products

1 whether or not this device is approved.

2 I think there is at least one benefit with this  
3 device, is that you process cells in well-defined conditions  
4 with clinical grade reagents, which was I believe not always  
5 the case with old methods.

6 The second point I would like to make is on  
7 several occasions, again, it was said that this was not a  
8 large study, that numbers were small. I agree that numbers  
9 are small, but this has to be compared with the actual size  
10 of most transplant programs for breast cancer even in the  
11 larger institutions.

12 Our center has the largest program for breast  
13 cancer transplantation in Europe. That means 75 patients  
14 per year. So it is very difficult to accrue more patients  
15 over a short period of time than what was accrued in this  
16 study, and extending the number of patients in future  
17 studies would also mean extending the length of the study in  
18 the rapidly evolving field which introduces other bias.

19 DR. VOSE: Can I just comment on that? The number  
20 of breast cancer patients that are transplanted in the U.S.  
21 is huge, and it wouldn't be a problem to get a large study  
22 done quickly.

23 Dr. Civin.

24 DR. CIVIN: Just to address Dr. Broudy's question,  
25 I have transplanted on a separate IND that is not part of

1 any of the studies presented here, but using the same  
2 device, children with pediatric solid tumors, boys and  
3 girls, age ranges from in the first years of life to above  
4 teenage, and consistently obtained high percent purity CD34+  
5 cells and acceptable yields with a similar mean to the  
6 published literature with this device and with other  
7 devices, and higher purities, and observed with other  
8 devices in the literature, something which I am concerned  
9 with, because purity correlates with tumor depletion in the  
10 measurements that we have made.

11 Each product has led to sustained and rapid  
12 engraftment whether it was bone marrow or whether it was  
13 mobilized peripheral blood progenitor cells.

14 Thank you.

15 DR. BROUDY: Could I clarify? Do you have data on  
16 tumor depletion with this device, because that is the thing  
17 that I think we are missing here?

18 DR. CIVIN: Yes, I do, and we submitted it to ASH  
19 and published and presented this last year, and found a 2 to  
20 4 log tumor depletion with a mean or median -- I can't  
21 remember -- of about 3 log tumor depletion.

22 This was in neuroblastomas and Ewing's tumor  
23 peripheral dermal tumors where we could do PCR, as well as  
24 immunocytochemistry, and it was done by two different labs.  
25 The results agreed and further correlated with the non-

1 target cell depletion calculations that you do in every  
2 case.

3 DR. VOSE: That is not information that we were  
4 given today or asked for.

5 DR. SIEGEL: There is actually a number of things  
6 I would like to comment on. First, I have never  
7 transplanted anyone, and I have no financial relationship  
8 with the Baxter.

9 [Laughter.]

10 DR. SIEGEL: A comment regarding Dr. Auchincloss'  
11 comment. I think it is important to retain a perspective.  
12 I personally believe very strongly in the importance of the  
13 type of research Dr. Anderson does, the type of experiment  
14 Dr. Kleinerman talked about, but we are really faced with  
15 decisions to make under a set of laws written by Congress  
16 and regulations promulgated by the FDA.

17 They call for us to assess the safety, purity, and  
18 potency of this product for the indicated use. It is the  
19 clinician and the patient that are going to be using this  
20 product, that are going to be either reaping its benefits or  
21 experiencing its adverse effects, or both, and it is really  
22 that has to be the principal focus of what we look at when  
23 we are talking about a marketing approval.

24 Again, its use for experimental therapy is allowed  
25 under IND, it is being used for many of the types of things

1 that were discussed. It, of course, will have secondary  
2 impact on those uses, what the approval decision is, but I  
3 caution you to keep that in its framework in terms of what  
4 we are here for and what we are asking you to do.

5           On the question of tumor purging, I guess a  
6 statement was made that it would be unfair to ask a company  
7 to demonstrate the benefits of tumor purging. We, as many  
8 of you will recall, discussed this issue with this advisory  
9 committee and with ODAC in 1984 -- in '85, was it -- '95,  
10 May and December, as I recall, and there was a diversity of  
11 opinion ranging from those who thought that survival data  
12 ought to be required, in fact, I would say the consensus was  
13 of this committee at least at that time that that was too  
14 much to ask of a device, and let me make this distinction  
15 here, because it may or may not be an important one when we  
16 -- I agree with French, it would be nice to address the  
17 questions, although I think this is a very productive  
18 discussion -- when we address the questions, how to make  
19 that distinction will come up, but for a device intended for  
20 tumor purging, there was a lot of discussion about what  
21 needed to be shown, and I think the consensus of this  
22 committee was that in those diseases in which tumor purging  
23 of the marrow itself was likely to provide benefit, and  
24 where there was substantial reduction in the amount of tumor  
25 cells, and preferably, but not necessarily to the extent of

1 below the limits of detectability, and that where there  
2 wasn't much concern about engraftment, that those tumor  
3 reduction data per se ought to be sufficient evidence of  
4 efficacy for licensing, notwithstanding the importance of  
5 ultimately knowing the impact on survival.

6 I should note, however, that this application does  
7 not contain the data that we just heard mentioned, that we  
8 have, in fact, asked this company to provide any and all  
9 data they have on tumor purging. I am not exactly familiar  
10 with those data, but I think you have heard from the company  
11 and the Agency what we have regarding the reduction of tumor  
12 cells, and I think those are the data that should be under  
13 consideration here.

14 DR. VOSE: Dr. Anderson, last comment.

15 DR. ANDERSON: Exactly. This is the last thing I  
16 am going to say.

17 DR. VOSE: Thank you.

18 DR. ANDERSON: In response to Jay, there is no  
19 question that just as our chairman has said, and as you have  
20 said, that one has to look at the data that exists for the  
21 indications that are called for, and that other issues  
22 should not come into play.

23 If the answer is a yes, that is fine; if the  
24 answer is no, that is fine. What I referred is when it is  
25 borderline, when it is clearly fuzzy, and each one of us

1 looks to come to a decision, and I was simply putting on the  
2 table where my bias is and where I am going to be coming  
3 down, so that the FDA can simply take that into account.

4 That is the last thing I am going to say.

5 DR. VOSE: I think we have had enough discussion.

6 We are going to vote on Question No. 1. Is everyone  
7 comfortable with voting?

8 Are these data as presented in this trial adequate  
9 to establish that, in patients with breast cancer who  
10 undergo peripheral blood progenitor transplantation, Isolex  
11 processing does not substantially impair the engraftability  
12 of a cell population, that it yields a cell population  
13 effective for transplantation and engraftment?

14 All that believe that this does show adequate  
15 information, that it is effective for transplantation and  
16 engraftment, please signify by raising your hand.

17 [Show of hands.]

18 DR. FREAS: Thirteen.

19 DR. VOSE: Any abstentions?

20 [One hand raised.]

21 DR. FREAS: One abstention.

22 DR. VOSE: Any no votes?

23 [Two hands raised.]

24 DR. FREAS: Two no votes.

25 DR. VOSE: We are going to move on to Question No.

1 2. For products seeking labeling for tumor cell purging or  
2 diminishment of graft versus host disease, CBER has viewed  
3 engraftment data as safety data and has sought patient  
4 benefit data as evidence of efficacy. In the randomized  
5 controlled trial for the Isolex device as presented, there  
6 was no evidence of patient benefit, either in incidence of  
7 adverse events or in engraftment.

8 An alternative approach for cell selection  
9 products not specifically seeking claims regarding tumor  
10 cell purging or graft versus host disease would be to  
11 consider evidence of ability of the cells to engraft as  
12 efficacy data.

13 Within this context, in this case of CD34+ cell  
14 selection device for peripheral blood progenitor cell  
15 transplantation, should failure to impair engraftment  
16 substantially per se be considered evidence of efficacy?

17 Any additional comments that people want to make  
18 regarding this?

19 DR. AUCHINCLOSS: I just don't understand the  
20 question.

21 DR. VOSE: A Dr. Siegel question.

22 DR. SIEGEL: This gets to the heart of what the  
23 committee has discussed. Having advised at this point that  
24 these data are sufficient to say that there is not a  
25 substantial impairment of engraftment, what we would like to

1 know from the committee is, is it reasonable that, as far as  
2 efficacy, that is all we need to know.

3           In other words, some have said already, well,  
4 where is the benefit to the patient, and others have said  
5 this effectively facilitates CD34 transplantation,  
6 therefore, that is efficacy.

7           I think that as I indicated before, we have some  
8 internal legal and policy discussions ongoing on that, but  
9 we are interested in terms of, you know, the expertise and  
10 experience of this committee as to whether that sort of data  
11 ought to be considered evidence of efficacy or whether the  
12 committee believes the burden for evidence of efficacy ought  
13 to be higher.

14           DR. AUCHINCLOSS: I guess I would say no, but that  
15 is because engraftment is the safety analysis, and the  
16 efficacy of the device is that it produces CD34+ cells.  
17 That is what the device says it is doing. It says it  
18 produces CD34+ cells. The safety feature is that they can  
19 engraft and do so safely.

20           DR. SIEGEL: We would normally look at efficacy in  
21 terms of some impact on patients.

22           DR. VOSE: Efficacy in the past has been needing  
23 to have some benefit for the patient.

24           DR. AUCHINCLOSS: I understand, and it is not  
25 here. There is no benefit for the patient we agreed. I

1 think almost everybody here agreed. The device does what it  
2 says it does, and does so safely.

3 DR. VOSE: But in the case of there has to be some  
4 benefit for the patient in some --

5 DR. SIEGEL: Well, doing what it says it does.

6 DR. AUCHINCLOSS: I think that is a mistake.

7 DR. SIEGEL: Meaning it produces CD34 cells which  
8 engraft.

9 DR. AUCHINCLOSS: CD34+ -- which engraft.

10 DR. SIEGEL: And you just said that is efficacy.

11 DR. AUCHINCLOSS: So the efficacy is producing  
12 CD34+ cells, the safety is that they engraft.

13 DR. VOSE: But is that really efficacy? That is  
14 not efficacy for the patient.

15 DR. AUCHINCLOSS: For a device, in my mind, yes.

16 DR. BROUDY: But you could reword it, is there any  
17 patient benefit that outweighs the risks.

18 DR. SIEGEL: Well, I prefer not to reword it that  
19 way. I think that the question as it stands is asking I  
20 think exactly what you are getting at. I would say if you  
21 say that it -- I am no sure I would say producing cells is  
22 efficacy, but I think -- and this may just be a semantic  
23 thing -- I think that one viewpoint that may reflect yours  
24 is that if this produces a product which engrafts  
25 effectively, that could be considered efficacy.

1 I can understand what I am hearing from this side  
2 of the table, but, you know, if all you have shown is that  
3 yes, they engraft, but as I point out in another question,  
4 you could also dump in 100 different chemicals, stir them up  
5 with a silver spoon, and they would still engraft, but do  
6 you then say, well, that spoon is effective.

7 So, really, this gets at where we do draw the line  
8 and how.

9 DR. VOSE: Dr. McCurdy.

10 DR. McCURDY: It seems to me that the issue here  
11 is one of labeling. If you are going to label it that it  
12 produces relatively pure CD34 cells, then, that is what it  
13 should do. That's an in vitro measurement. If you label it  
14 for tumor cell purging, then, you ought to demonstrate that  
15 it gets rid of tumor cells. We have heard how difficult  
16 that is to determine whether that does anything good for the  
17 patient.

18 The same thing is true of diminished graft versus  
19 host disease. If that is going to be part of the labeling,  
20 then, they should demonstrate that it does indeed reduce  
21 graft versus host disease.

22 DR. VOSE: And they are not asking for any of  
23 those labeling. That is not what they are asking for. This  
24 is more of a general question related to efficacy.

25 Dr. Hong.

1 DR. HONG: It is entirely semantic, and I think  
2 the problem with us as clinicians is that when we talk about  
3 efficacy, we always have in the back of our minds efficacy  
4 compared to, and I think where we are having trouble is, it  
5 is clear that treating these to get the CD34 cells doesn't  
6 give you a better CD34 if you didn't treat them at all, and  
7 that is why we are struggling.

8 So as far as we are concerned, it is efficacious,  
9 but is it worth it all, and so that is our problem, it is an  
10 emotional problem.

11 DR. VOSE: But not for something to be efficacious  
12 when it is I guess implied that there must be some benefit  
13 to the patient, to compare it to what, and that is what we  
14 are talking about.

15 DR. LEITMAN: It sounds like you need to have a  
16 different kind of question there. What you could say is  
17 this is a procedure whose direct clinical benefit is yet to  
18 be realized or has not been documented in the studies  
19 presented to us.

20 However, as a facilitating or enabling device, the  
21 benefits are obvious, although not presented here. So it is  
22 a step further that this produces a product which can be  
23 used in investigational of IND-mediated studies, and that is  
24 a direct clinical benefit, and that is the benefits that we  
25 have heard about.

1 But the question that is asked here is one for the  
2 FDA, it is not really one for this committee.

3 DR. SIEGEL: I think we frequently ask this  
4 committee what are appropriate standards for approval, and I  
5 would hope that members of this committee believe, as we do,  
6 that in fact do have appropriate expertise to rule on that  
7 question or to advise on that question.

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

9 DR. AUGUST: I think that getting involved with  
10 the questions of tumor reduction and graft versus host  
11 disease, and then the clinical outcomes of preventing graft  
12 versus host disease and in curing cancer, is sort of beyond  
13 the scope of this machine.

14 We are going to cure more cancer when the  
15 treatment for all the different varieties of cancer and  
16 leukemia are better, and we are going to cure or we are  
17 going to prevent more graft versus host disease when we are  
18 able to do something that is different for mismatch or  
19 alternative donor transplants as compared to HLA identical  
20 sibling transplants.

21 I would bet that this would do a very good job.  
22 We have seen depletions of 2 and 3 logs of T cells, and that  
23 probably would work fine for HLA identical sibling  
24 transplants. It probably wouldn't work very well at all,  
25 and actually we have seen some of that data, for alternative

1 donor transplants.

2           So I think that in a sense, these are issues that  
3 are beyond the scope of this machine to have any real impact  
4 in, and I would go along with a more narrow approach to  
5 making our decision, and I think personally that we have  
6 seen that it has done the job that it is intended to do,  
7 which is to isolate and concentrate CD34 cells which, in a  
8 sense, work in the human bioassay that they have been tested  
9 in, which is to say the engraftment that we have already  
10 seen, and I think that we could reasonably leave it at that.

11           DR. BROUDY: The other option would be to have the  
12 company come back with some of Dr. Civin's data that could  
13 be actually reviewed and shown, and it sounds like the data  
14 has already been collected, but weren't presented.

15           DR. VOSE: On the other hand, they are not really  
16 asking for that as an indication.

17           DR. BROUDY: But they are saying reduction of non-  
18 target cells, and that has an obvious implication.

19           DR. CIVIN: May I be clear that this was my own  
20 IND. This was not a company study.

21           DR. VOSE: So are we clear on what efficacious  
22 means?

23           [Laughter.]

24           DR. SIEGEL: If you are not adequately confused, I  
25 can help. One thing that might be worth thinking about is

1 were this device to have some benefit in terms of the  
2 outcome of transplantation, the question of whether there is  
3 benefit to the patient would also rest on the quality of the  
4 data showing that high-dose chemotherapy with  
5 transplantation is beneficial as compared to other  
6 approaches to managing various patient populations that this  
7 might be used in

8 DR. VOSE: That in itself has never been shown.

9 DR. SIEGEL: Right. What I am saying is that I  
10 should note that the approach of this committee and the  
11 Agency over the last few years in marrow transplantation has  
12 been to require benefit to the patient in terms of showing  
13 whether there is fewer infections or fewer bleeds or more  
14 neutrophils or platelets, and those are a benefit, but  
15 benefits with accepting as a given that the patient is  
16 getting marrow transplantation and that there is a reason  
17 why they are getting that, the point being -- and this is  
18 true in the way we regulate a number of devices.

19 If a device is effective in a certain procedure,  
20 and that procedure is in widespread use, we don't always  
21 require, you know, if a device facilitates appendectomy,  
22 hysterectomy, or whatever, the Agency hasn't always required  
23 that one prove that appendectomy or hysterectomy are worth  
24 doing in the first place.

25 I am not sure how relevant that is to this issue

1 and maybe I should stop there.

2 DR. VOSE: I have no idea what you just said.

3 [Laughter.]

4 DR. CHANG: I just want to ask a little broader  
5 question for the future. In terms of, firstly, defining  
6 what level of purity of CD34 cells you would be willing to  
7 accept for purity, and then way down the line, as technology  
8 improves, where you can purify to an even more primitive  
9 stem cell, you might get into a situation where you will  
10 delay engraftment because it takes more time for these cells  
11 to mature. So how are we going to address these issues?

12 DR. ANDERSON: Later.

13 DR. VOSE: Dr. Hong.

14 DR. HONG: I think the issue about efficacy hinges  
15 on this one. The CD34 cells are efficacious because they  
16 are CD34 cells. It has nothing to do with any treatment  
17 anywhere. So the question is really inappropriate.

18 What you really want to say here, I think you  
19 answered in the first question, is the treatment did not  
20 decrease the inherent efficacy of the cell, and therefore it  
21 is not a bad treatment per se, we do not pay that as a  
22 price, another price we pay for it should be addressed, so  
23 you get more into cost-benefit ratios if you want to talk  
24 about whether it is worth doing all the things you want, but  
25 I think that that is an inappropriate question.

1 DR. SIEGEL: I understand why you would say that  
2 from a scientific perspective. I think, nonetheless, we  
3 have to make a decision whether this is effective in order  
4 to approve it, and so I guess that means we need some  
5 guidance as to what is meant by that decision. Maybe it is  
6 a semantic one, but it is not a question we can avoid  
7 because we don't approve things without making that  
8 decision.

9 DR. VOSE: We also hardly ever approve anything  
10 without having some evidence of patient benefit in some  
11 perspective.

12 DR. SIEGEL: Right.

13 DR. BERMAN: Why can't you view engraftment, Jay,  
14 why you can't you view engraftment as efficacious? That  
15 shouldn't be a stumbling block. It is efficacious. It  
16 engrafts without difficulty, period. It seems simple to me.

17 DR. SIEGEL: But the question reads, although  
18 several other people said that that is the wrong question,  
19 but the question reads should that, should failure to impair  
20 engraftment substantially be considered evidence of  
21 efficacy.

22 DR. BERMAN: Well, by the general vote, we have  
23 decided to look at this in a narrow context, and that is,  
24 does this isolate CD34 cells, yes, does it engraft without  
25 substantial delay, yes, so this is kind of a corollary to

1 that is that, yes, it can be viewed as efficacy, and  
2 engraftment can be used as efficacy.

3 DR. VOSE: It is the efficacy of the CD34 cells.

4 DR. BERMAN: But the instrument has produced these  
5 cells which are, in fact, efficacious in engraftment.

6 DR. VOSE: The instrument didn't produce the  
7 cells, but the cells were there and they were concentrated.

8 DR. BERMAN: But they isolated the cells. I think  
9 it is a semantic issue.

10 DR. PRETI: Does it help to view the use of the  
11 cells as an issue of medical practice and the actual  
12 production of the cells in the laboratory by the device has  
13 something which is efficacious or not, so does the device  
14 select CD34 cells, and we have said that it does, we all  
15 feel that it does, and then whether the physician uses them  
16 or not clinically, an issue of medical practice, does that  
17 help tease it apart?

18 DR. CHABANNON: More than two years ago, both the  
19 Cell Pro device and the Baxter Isolex have been approved for  
20 sale, which means that clinical investigators have been able  
21 to buy this device for at least the last couple of years.

22 That doesn't mean that it is used in routine  
23 practice, but that means that it allows cooperative groups  
24 to conduct, for example, randomized studies to demonstrate  
25 that there is additional benefit associated with tumor

1 purging and there are several examples of such studies in  
2 Europe, for example, in multiple myeloma.

3 DR. VOSE: Do people feel comfortable enough with  
4 this question to vote on it or not?

5 DR. HARTIGAN: Can I ask a question? Jay, you are  
6 asking whether the engraftment is -- can we say that the  
7 product is efficacious. The rules for devices are different  
8 than the rules for other things.

9 The devices, when you approve devices, do they  
10 simply have to mechanically do the particular process that  
11 the sponsor suggests that they do, and that is good enough,  
12 if they do it well enough, or does it have to actually have  
13 a specific patient efficacy shown?

14 DR. SIEGEL: There are effectiveness standards and  
15 regulations for devices. How exactly that is applied  
16 depends greatly on the nature of the device. This is  
17 actually a biological device, right, so it would be subject  
18 I think to both biological and device regulations. Is that  
19 correct?

20 There are effectiveness standards for devices, and  
21 there are regs about how to determine effectiveness, which  
22 talk about type and nature of evidence for determining  
23 effectiveness. However, I think approaches are going to be  
24 different, obviously, for, say, a band-aid from an in vitro  
25 lab test, from the scalpel, from certain devices used

1 specifically to treat specific diseases.

2 DR. HARTIGAN: But does each one have to have  
3 patient efficacy associated with it? I mean can this device  
4 be approved as a device which concentrates CD4 cells and  
5 doesn't impair their effectiveness without actually showing  
6 the fact that it does that is of benefit specifically to the  
7 patient population in which it enriched cells or  
8 concentrated the cells?

9 DR. SIEGEL: First -- and I think this may be  
10 getting more at another comment than that comment -- but if  
11 its use is just to be for in vitro use, whether for  
12 experimental or whatever, and then to leave it as a clinical  
13 decision, then, you know, it is not at all clear that an  
14 approval for that sort of use is even appropriate to be  
15 considered.

16 This is being considered in the context of a  
17 clinical setting. I think the best way that can answer that  
18 question -- and we have had substantial discussions with our  
19 colleagues in the Center for Devices, obviously, my  
20 experience is much more limited than theirs -- is that for  
21 devices that are used as part of medical procedures, if you  
22 might consider this one, they would look to the use of that  
23 device in the procedure to ensure that it is safe and that  
24 it is effective in allowing that procedure to occur.

25 They will not necessarily -- and this gets to what

1 I was talking about before -- if a procedure is an  
2 experimental procedure, they would not consider that a  
3 device is effective if it is only useful for a highly  
4 experimental procedure, but if the procedure is in  
5 reasonably widespread use, and the device facilitates that  
6 procedure, then, it would generally be considered that that  
7 would provide sufficient evidence of what we would call  
8 efficacy without specifically having to address the issue of  
9 the impact of that procedure.

10 I hope that answers your question, but to the  
11 extent it doesn't, I don't think I am able to answer your  
12 question.

13 DR. HARTIGAN: So in that sense of concentrating  
14 the CD4 cells facilitate the transplant, is that a question  
15 that --

16 DR. SIEGEL: I think from that perspective -- one  
17 can take different perspectives here. Now, we are not  
18 asking the committee to tell us what is legally correct. We  
19 are asking the committee for input as to what they think  
20 makes the most sense in terms of public health policy  
21 basically.

22 I think one could look at it and say CD34  
23 transplants are being done, they are being done generally.  
24 This makes CD34 cells which, according to Question No. 1,  
25 implant, therefore, it is effective, I don't think that is

1 inconsistent with any of our regs, however, you would be  
2 left with the situation of not knowing if doing the CD34  
3 transplant as opposed to doing the non-CD34 transplant  
4 offers any benefit to the patient to compensate for the  
5 extra whatever, leukophereses or whatever, and I think an  
6 alternative and very reasonable proposal would be to say,  
7 no, really, marketing for this product should require more  
8 than just facilitating CD34 transplantation, it should  
9 require, whether it is diminished toxicity, whether it is  
10 some data regarding diminished tumor cells, or whether it is  
11 survival or some other sort, that is what this question is  
12 asking, and if you are asking me what do our regs and laws  
13 say to that question, I would simply say they don't provide  
14 a definitive answer.

15           That is why we are asking -- we believe that, as  
16 we have asked this committee many questions about what the  
17 standards for approval, I mean we could make the standard  
18 for approval that patients live longer -- we are asking  
19 largely, you know, is this where it ought to be as opposed  
20 to somewhere else.

21           DR. VOSE: I think we have discussed several times  
22 that not necessarily should we require that it provide  
23 survival benefit, but some sort of benefit to the patient, I  
24 think it is important to say, or we could, as you mentioned  
25 earlier, have some stir thing that gets a few extra CD34

1 cells, and that could be approved.

2           It doesn't make sense to me without having some  
3 benefit for the patient.

4           Dr. Hong.

5           DR. HONG: It seems to me that we could make  
6 everybody happy and end the discussion by coming to three  
7 decisions, because there are really three things that  
8 happen. You either lessen the efficacy, you either have no  
9 effect on the efficacy, or you promote the efficacy.

10           We make our decision which one of those three  
11 things have happened with the treatment with the isolation  
12 of CD34 cells, and then you can decide whether or not you  
13 want it to increase, have no effect, or decrease, because  
14 clearly, one of those three things is true.

15           So, we have an answer. Now, if you want us as a  
16 committee to tell you what we think should be a minimal  
17 requirement, I think we could come to a decision on that,  
18 that we either expect to keep it the same or improve it. It  
19 seems to me that that we don't have to keep beating this  
20 dead horse about what is efficacious and what isn't.

21           DR. VOSE: Dr. Auchincloss, last comment.

22           DR. AUCHINCLOSS: I think you have got to remember  
23 that you have already approved the CD34 enriching device,  
24 and the benefit to the patient that was cited in approving  
25 that device was decrease in infusional toxicity.

1           Now, I have got to say that is a pretty marginal  
2 benefit, and, of course, it didn't pop out in this study,  
3 because it is just not a very big problem, but there wasn't  
4 any efficacy of CD34+ cells that was demonstrated in that  
5 study, yet, the device for enriching CD34 cells is out  
6 there.

7           So you have already kind of walked yourself into  
8 the position of allowing this form of transplantation to go  
9 as if you thought it was a good thing, but you actually  
10 never really looked at whether 34+ transplantation is a good  
11 thing.

12           DR. SIEGEL: That may be true. The vote of this  
13 committee was specifically as to whether the benefits to the  
14 patient outweigh the potential adverse effects. Your  
15 perspective may be a correct one, I can't speak to that, but  
16 at this point we are not being asked the same question. We  
17 are not being asked are there benefits that outweigh it or  
18 benefits that outweigh -- the question, rather, is do we  
19 need to have those benefits.

20           If, in fact, those of you who voted the last time,  
21 I guess, are speculating if, in fact, the decision was,  
22 well, not so much that they outweigh the effects, but that  
23 the level of those benefits isn't that important, then,  
24 obviously, that would guide your answer to this question, I  
25 guess.

1 DR. BROUDY: I am going to make my last comment.  
2 That is a promise. That is, that I voted to approve that  
3 last device, and I agreed there was a demonstrated decrease  
4 in infusional toxicity -- which as we all know is not a  
5 major clinical problem -- but as I recall, there was also a  
6 demonstrated, carefully done documentation in decreased  
7 tumor cell contamination, and when we met I think three  
8 years ago in this committee to talk about what sort of  
9 benefits would we request for a depleting device or a CD34  
10 selection device, one of the things we wanted to request was  
11 a several log decrease in tumor cell contamination.

12 Those data just were not available today except  
13 for Dr. Civin's personal studies.

14 DR. KLEINERMAN: Except you don't know that  
15 decreasing by 2 or 3 logs will ultimately have any patient  
16 benefit.

17 DR. VOSE: No, I agree, I don't think that we know  
18 that for sure. It is barely supportive information. I  
19 think the concern is related to the other approval, that we  
20 did have something at least that showed some patient  
21 benefit. Here, we have nothing that shows patient benefit.

22 DR. BERMAN: If I recall, the survival in that  
23 discussion was not significant, but tended to show a shorter  
24 survival in the women who had had the selected.

25 DR. VOSE: But that was also the same issue that

1 we had earlier. It was not statistically significant, it  
2 was all different stages of breast cancer, and we decided  
3 that wasn't appropriate to look at that.

4 DR. BERMAN: Right. So if we thought the  
5 precedent was correct then, why should be changing now. We  
6 should just be very focused on the question and not look at  
7 either tumor cell or survival since those weren't questions  
8 addressed to the company.

9 DR. VOSE: I think the question really gets back  
10 to the big issue of what the regulations are and do we need  
11 to have to show some patient benefit, and we are not really  
12 getting a straight answer.

13 DR. BERMAN: Did we show a patient benefit then?

14 DR. VOSE: It showed patient benefit related to  
15 the infusional toxicities, which was some patient benefit.

16 DR. ROSENBERG: I am Amy Rosenberg. I am the  
17 chair of the Licensing Committee for this device and for the  
18 previous device. I just want to correct the record. There  
19 were no tumor depletion studies formally submitted for the  
20 previous device, so we really did not evaluate the ability  
21 of that device to deplete tumor cells.

22 DR. VOSE: There was some information that we  
23 received and presented at the meeting, however. It was not  
24 a claim in any way. It was just supportive information.

25 Dr. Kleinerman.

1 DR. KLEINERMAN: I think we all have to make our  
2 own decisions, you know, vote on our conscience our  
3 definition of efficacy, and let's vote, because I think we  
4 have all made up our minds right now.

5 DR. VOSE: All right. Let's vote.

6 In the case of CD34 cell selection device for  
7 autologous transplants, peripheral blood progenitors, should  
8 failure to impair engraftment per se be considered evidence  
9 of efficacy?

10 So, everyone please raise their hand if they think  
11 that failure to impair engraftment does show efficacy of  
12 this device.

13 [Show of hands.]

14 DR. FREAS: Six votes stating that --

15 DR. VOSE: Failure to impair engraftment does show  
16 efficacy.

17 Any abstentions?

18 [Show of hands.]

19 DR. FREAS: Five abstentions.

20 DR. VOSE: And no votes?

21 [Show of hands.]

22 DR. FREAS: Five no votes.

23 DR. AUCHINCLOSS: Regarding that vote, does that  
24 vote, the second vote constitute a recommendation to approve  
25 this product?

1 DR. SIEGEL: No. None of these votes per se  
2 constitute a recommendation. They are all factors that we  
3 are considering, that we need advice in making an  
4 appropriate decision regarding this.

5 DR. VOSE: I am sure we helped a lot.

6 [Laughter.]

7 DR. SIEGEL: I took a similar vote actually among  
8 the Review Committee. I won't speak to that.

9 DR. VOSE: Would you like me to move on the next  
10 question or not? It was kind of a split vote.

11 DR. SIEGEL: I think it would be worth having. I  
12 don't know that we will need detailed discussions. We have  
13 discussed it. But I think it is going to be very important  
14 depending on what we do with this product.

15 The next question gets into the issues if somebody  
16 were to come with -- this is a positive selection -- if  
17 somebody were to come with a negative selection device, say,  
18 that binds tumor cells or binds T cells with a rather  
19 implicit or even explicit claim, the purpose being to remove  
20 tumor cells or do we need data, for example, or should we  
21 only be asking for data like this, that the cells still  
22 engraft.

23 I think that is an important issue.

24 DR. VOSE: Just to go through this, then, rather  
25 quickly, for Question 3.

1           If failure to impair engraftment can be considered  
2 efficacious, should a device regarding tumor purging to  
3 claim of tumor purging and change in survival, would a tumor  
4 specific antibody need to provide data in support of the use  
5 or should data regarding adequacy of engraftment be  
6 considered evidence of efficacy for such a device?

7           So if they are making a claim regarding tumor cell  
8 purging, do they need adequate information.

9           DR. SIEGEL: The purpose we are saying if they are  
10 making that claim, obviously, they need the information.  
11 Now we are getting at the issue of when claims are implicit  
12 or not. If the device were an antibody to tumor cells, you  
13 know, normally, if there are strongly implied claims, we  
14 would want evidence of that, and if so, would one feel  
15 differently, for example, if this were negatively selecting  
16 out tumor cells. Those who think that there needn't be any  
17 more tumor purging data than we have now seen, I wonder  
18 would the feeling be different if it were an antibody  
19 against tumor cells, that you also didn't need to see  
20 whether it removed tumor cells.

21           So this is largely for those who voted yes.

22           DR. VOSE: Dr. Auchincloss.

23           DR. AUCHINCLOSS: I just wanted to explain my  
24 abstention there. To me, again, the question is worded  
25 wrong. The device is efficacious when it does what it says

1 it does. It is safe when it allows engraftment, and then  
2 whether it is worthwhile is a separate issue.

3 So the only way I could deal with these questions  
4 you have now brought up in a consistent fashion is to not g  
5 along with Question No. 2 the way it was phrased. Does that  
6 make sense? I think it is all internally consistent.

7 DR. VOSE: So if we have an implied concept based  
8 on the information they are implying that it gets rid of  
9 tumor cells, even though they are not claiming that on the  
10 label, do we need additional information?

11 DR. SIEGEL: To put it more pragmatically, if we  
12 were to go ahead and approve this device -- and I am by no  
13 means saying we will -- I am just saying that if we were to  
14 go ahead and do that, the companies out there making  
15 antibodies, say, an antibody to lymphoma cells or to breast  
16 cancer cells to run marrow over, should they take from that  
17 and from the advice of those who voted yes, that if they  
18 show that their device also doesn't impair engraftment by  
19 more than a couple of days, that that is really all they  
20 have to show, or do they have to show that it removes tumor  
21 cells, or if it is to deplete T cells, that it depletes T  
22 cells?

23 DR. VOSE: From my standpoint, it has to show that  
24 information, to imply or to say that in any manner that it  
25 is used, that it needs to have data that says that.

1 Dr. Berman, or, French, what do you think?

2 DR. BERMAN: I agree. I think that to set out to  
3 answer the question, you would need to show a depletion of  
4 tumor cells, and not just engraftment efficacy.

5 DR. VOSE: Dr. August.

6 DR. AUGUST: I think the device we just approved  
7 has anti-CD34 antibody implicit in it, embedded in it.  
8 Another antibody to replace that would be another device,  
9 which would be considered with different criteria, and if it  
10 was an antitumor antibody, then, we would focus on whether  
11 it removed tumor cells in the laboratory, and we would focus  
12 on whether the patient seemed to benefit from it. I think  
13 that goes without saying.

14 DR. VOSE: I think we should correct what you just  
15 said. We didn't vote to approve that. We had a split vote.  
16 It was very confusing about what you recommend actually.

17 DR. LEITMAN: I think to just backtrack, I have  
18 been trying to think of the benefit of this device, because  
19 I need a benefit or else I feel very uncomfortable leaving  
20 here.

21 When you look at the actual indications as listed  
22 in the packet for the device, it says it concentrates CD34  
23 cells, decreases the volume, decreases the storage space,  
24 and results in less DMSO infused.

25 Decreasing the storage space itself from a 50 mL

1 freezing bag to a 1 mL vial is a huge advantage for the  
2 entire process of manipulating cells during the infusion,  
3 and decreasing the amount of DMSO given has to result in  
4 less infusional toxicity even though the way the study was  
5 done didn't get at that, because they waited 60 minutes  
6 after any toxicity occurred, and they were never going to  
7 get that answer.

8 So it does have benefit, direct clinical benefit.

9 DR. VOSE: But again, you have to look at the  
10 information that is presented to us, and they did not  
11 present the information that there was a decrease in  
12 infusional toxicity. Granted, because of the way it was  
13 done, but I don't think we can say that from what  
14 information we have.

15 I think we discussed the concerns about the tumor  
16 and the T cell depletion. Are you satisfied with that  
17 discussion?

18 DR. SIEGEL: If there aren't any comments beyond  
19 that, generally, those should show that --

20 DR. BROUDY: One brief comment. If the Baxter  
21 application is approved, I would suggest a modification in  
22 the proposed indication to reduce the quantity of  
23 lymphocytes by 2 to 3 logs, because that is what they did  
24 show, that the number of lymphocytes went down by 2 to 3  
25 logs.

1           When they say non-target cells, that to me implies  
2 that it might contain breast cancer cells, and they haven't  
3 demonstrated that.

4           DR. VOSE: Any other comments regarding the tumor  
5 cells?

6           Just as a slight extension of that in Question 4,  
7 a discussion of the tumor cells, should it be required that  
8 there is information for each type of malignancy, and if so,  
9 for how many patients should that information be obtained if  
10 we are requiring information?

11           DR. SIEGEL: The sheet you got today has  
12 inadvertently left out a phrase or two from Question 4. I  
13 just wanted to clarify that. What you received in your  
14 briefing package, although slightly restructured, is the  
15 question we are interested in asking, so if I might, let me  
16 read that out loud. My apologies for our error there.

17           DR. VOSE: I have it here. If a CD45+ cell  
18 selection device can demonstrate efficacy other than through  
19 tumor cell purging, should the sponsor, nonetheless, be  
20 required to produce data either pre- or post-approval  
21 regarding tumor cell purging for the product labeling, and  
22 if so, for which malignancies and how many patients should  
23 the data be required?

24           DR. SIEGEL: So the question is, to put in the  
25 context of where we are now, if we were to make a

1 determination that engraftment is adequate evidence of  
2 efficacy or selection of CD34 cells, and that they engraft  
3 and that they are selected are adequate evidence to gather  
4 up safety and efficacy, the question might still remain  
5 should this device, which certainly has some significant  
6 level of implicit claim of tumor cell purging, should the  
7 sponsor be required to produce data on the labeling as to  
8 that, as to the extent to which it actually does remove or  
9 not tumor cells, and if so, what types of tumor cells ought  
10 that be done in, and importantly, would those sorts of data  
11 be important necessarily pre-marketing or post-marketing?

12 DR. VOSE: Dr. Swain or Dr. Dutcher, do you have  
13 any comments?

14 DR. DUTCHER: If they are not asking for it, and  
15 they are not going to implicitly say that that is what is  
16 happening, I mean if you say, as Dr. Broudy suggested, that  
17 it is a several log reduction in lymphocytes, then, I think  
18 you have defined what it is doing.

19 If the real issue is going to be, then, we are  
20 going to look at tumor cell purging, then, yes, you need  
21 data, but those are the three questions from 3, it seems to  
22 me, that if you are going to ask for those things, you have  
23 to have some information that says that that is what is  
24 happening.

25 If the implicit comments or studies are going to

1 be done, then, the data will be provided. I mean I think  
2 that we all know that one of the issues is going to be tumor  
3 cell depletion, well, then, look at the data.

4 DR. SIEGEL: There is a presumption that the  
5 reason many investigators use CD34 cells is because of that  
6 hope. I would assume that is why many people who would use  
7 this device or others would use them, so it is a pretty  
8 powerful implicit --

9 DR. DUTCHER: But the problem, as we said, is  
10 there is still no clinical efficacy data even if you do  
11 reduce the numbers of cells. You can show that the cells  
12 are reduced, but we all are still going to be looking for  
13 clinical trials that show that it clinically makes a  
14 difference.

15 DR. VOSE: The other part of that question relates  
16 to, if we are talking about different malignancies, do we  
17 need to have trials to look at different types of  
18 malignancies, breast cancer versus lymphoma, versus others  
19 that may be different.

20 I think that is a important benefit because they  
21 certainly may be very different in the different  
22 malignancies, and to look at that, it is going to be implied  
23 or a claim it would be important.

24 Dr. August.

25 DR. AUGUST: I think we are talking now about what

1 is going to be written in the label and what the company is  
2 going to be able to say in their advertising, and if the  
3 claim is for this or that tumor, that it reduces tumor  
4 cells, then, there has to be evidence brought to the FDA  
5 that that, in fact, is true.

6           You can divide that into sort of two parts. One  
7 is the number or the log reduction in tumor cells, and the  
8 second is that that log reduction produces some sort of  
9 clinical benefit, and I think that clearly, if those claims  
10 are going to be made anywhere, that it has to be documented.

11           DR. VOSE: I guess the concern is that if that  
12 isn't being asked for and isn't being claimed, if it is an  
13 implied benefit, what are the requirements for that.  
14 Obviously, since this information isn't available, it is  
15 going to be hard to have that available.

16           Other comments or questions?

17           The last question relates to the fact that there  
18 were only 20 patients, approximately 20 patients in each arm  
19 of the trial, and the mortality is slightly higher, but not  
20 significantly so in the control, are there additional tumor  
21 outcome or survival data needed prior to considering  
22 marketing approval of the Isolex device?

23           If this device is approved, should additional  
24 post-marketing survival data be required? If additional  
25 data are required, would followup of the limited number of

1 patients as presented to date be adequate or should  
2 additional studies be performed?

3 Dr. Broudy.

4 DR. BROUDY: I think I have said enough. I will  
5 pass on this one.

6 DR. KLEINERMAN: I think post-marketing studies  
7 should be tied to the approval like we talked about earlier,  
8 like Dr. Anderson stated. I would think that more than the  
9 20 patients should be followed in terms of tumor outcome.

10 DR. SIEGEL: Are you suggesting that we ask for a  
11 commitment to do a control trial, a larger control trial in  
12 the post-marketing, or are you talking about accruing data,  
13 or are you talking about accruing data in an open-label  
14 fashion, registry fashion, or observing trials that go on?

15 DR. KLEINERMAN: Well, certainly a single-arm,  
16 open-label -- I don't know how difficult it is going to be,  
17 not being a transplanter, I don't know how difficult it  
18 would be to do a randomized trial without CD34, using the  
19 CD34 concentrated device, I just don't know what the state  
20 of the art is.

21 DR. SIEGEL: It doesn't seem from the feeling of  
22 this committee --

23 DR. VOSE: I will answer that. I think that since  
24 it has never been shown to be a survival advantage as of yet  
25 in any study, and certainly in a 20 patient per arm trial,

1 that is going to be almost impossible to do, that if you are  
2 looking at survival benefit or outcome benefit, you have to  
3 do another large randomized trial, and I don't think that  
4 would be a problem.

5 DR. SIEGEL: This question is more at the safety  
6 side. I think at the heart of what we are asking here is  
7 this, you know, that given that there are 7 versus 4 deaths,  
8 no difference out one year, but it is such a small number  
9 that mortality could conceivably be much higher or much  
10 lower.

11 The question of whether one wants those data or  
12 not largely falls on expert opinion as to whether there is a  
13 reasonable safety concern that this therapy might have an  
14 adverse effect on survival. If there were a sufficient  
15 concern about that, you know there are different levels of  
16 concern. There might be one that you would want to know  
17 before you would consider licensing the product, you would  
18 want to know survival outcomes enough to exclude a  
19 significant impact on survival.

20 The committee has said more generically for this  
21 class of products in the past, they don't have that level of  
22 concern, but they have enough concern they want to see data  
23 accumulate. The question is do you want to see more data  
24 than will accumulate from these 40 people, do you need to  
25 see more data I should say. Obviously, you want to see

1 more, do you need to see more to satisfy safety concerns.

2           Putting aside whether, obviously, that, it would  
3 be nice to know what the impact this has on survival and  
4 ultimately to get an efficacy study, we all agree that would  
5 be nice. That is not -- getting back to the discussions we  
6 had earlier -- we are not likely to require they do a post-  
7 marketing study to establish survival benefit. The question  
8 is ought there be one to rule out a survival -- is there  
9 enough concern about a survival effect that there ought to  
10 be one required to be more sure that there isn't a major  
11 negative impact on survival.

12           DR. VOSE: Dr. Swain.

13           DR. SWAIN: I personally wouldn't want this  
14 company to be required to do it because as I think Dr. Hong  
15 mentioned, it is more a question of using CD34 cells in  
16 general, not just for this particular device, which it is  
17 answering a much larger question, which I think is extremely  
18 important.

19           I think E.J. mentioned that a trial -- I don't  
20 know if it is this device -- is being done, and I think that  
21 is very important, but I don't personally feel that it  
22 should be required, because I am not as concerned about  
23 that, and it would take a huge study to do that, as she  
24 said, 1,200, 2,000 patients.

25           DR. VOSE: Dr. McCurdy.

1 DR. McCURDY: If devices of this nature are likely  
2 to be used allogeneic transplants, and if indeed T cell  
3 depletion is likely to or is part of their claims, then, I  
4 think it may be important, at least in some diseases like  
5 CML, to be sure that you don't have a late penalty of  
6 disease relapse in it.

7 Now, this one is not being talked about today,  
8 although we did see some data on allogeneic which really  
9 didn't look very good to me, but if it is going to go into  
10 the allogeneic other than the autologous setting, then, I  
11 think you need more information, more late information.

12 DR. VOSE: Dr. Auchincloss.

13 DR. AUCHINCLOSS: I thought given the concerns we  
14 had about the original study, that I would actually feel  
15 pretty strongly that a second prospective randomized study,  
16 not large because what you are looking for is how  
17 sufficiently to detect bad outcomes both in failure to  
18 engraft and in cancer recurrence.

19 I think that is reasonable given that Phase II  
20 retrospective data or post-hoc data were used for this group  
21 at this point, if that is the case.

22 DR. SWAIN: It is really hard in breast cancer to  
23 find a survival benefit in general, so are you saying you  
24 would --

25 DR. AUCHINCLOSS: I am not looking for benefit, I

1 am looking for the possibility of an important disadvantage.

2 DR. SWAIN: Right, so you want equivalent or not  
3 to be worse than. It would still be a large study.

4 DR. AUCHINCLOSS: No, it is going to be exactly  
5 the same kind of study we just had here. It probably could  
6 be done with the same 20 or 25 patients.

7 DR. SWAIN: I wouldn't be convinced by survival  
8 data on 40 patients.

9 DR. O'FALLON: The difference in survival is going  
10 to be spread all over the place. What we were told earlier  
11 was that the measurements that they made for us to evaluate  
12 the data had a very narrow range, and that was why we had  
13 such a tight confidence interval.

14 DR. VOSE: Right.

15 DR. AUCHINCLOSS: So you can get safety about  
16 engraftment, but you are saying you can't get safety about  
17 more than a dramatic worsening of survival.

18 DR. MILLS: Just for informational purposes, we in  
19 fact have a table that summarizes the kinds of numbers that  
20 might be required to show various differences in survival in  
21 the different groups, and this would be to show  
22 statistically meaningful differences in a time to an event,  
23 such as death or relapse, and if I can just share that data  
24 with you

25 [Slide.]

1           In fact, there is a lot of information on the  
2 slide. What you see is an analysis in the two left panels  
3 and the top right panel that the sample size per arm were,  
4 in fact, 25, 50, or 100, with 25 or 50 patients per arm,  
5 that is a total of 50 or 100 patients in a study, one would  
6 never have better than 43 percent power to show a 30 percent  
7 difference in a time to event.

8           In fact, with 100 patients, one would only have  
9 better than an 80 percent power to show a difference of  
10 greater than 33 percent. If, in fact, you would want to  
11 show a difference, for instance, of 20 percent in a time to  
12 event analysis at an 80 percent power, this would require  
13 greater than 600 patients or 316 per treatment arm.

14           This just gives you a feel for the kinds of  
15 numbers that would be required to show a meaningful  
16 difference in one of these kinds of parameters.

17           DR. VOSE: Thank you.

18           Dr. Siegel, Dr. Weiss, any additional questions or  
19 things we can clarify for you?

20           DR. SIEGEL: Yes, you can clarify what that vote  
21 meant.

22           [Laughter.]

23           DR. SIEGEL: Just one question. Bill, do we have  
24 a record of who voted which way, do you have that recorded?

25           DR. FREAS: No, we do not. We only have the

1 total.

2 DR. SIEGEL: It went by very fast. I usually try  
3 to write it down.

4 DR. FREAS: Would you like me to poll the  
5 committee members/

6 DR. SIEGEL: I wonder if we could go back over  
7 that original 6-5-5.

8 DR. O'FALLON: I think we are about to do a  
9 statistical test that we will not be interested in.

10 [Laughter.]

11 DR. O'FALLON: Plus the confidence interval that  
12 the totals will be the same as we had before. Are you sure  
13 you want to know the answer to that question?

14 DR. SIEGEL: The question is not how you vote on  
15 the question, but how you voted on the question 20 minutes  
16 ago. I would like to have that information in the record.  
17 Obviously, we have to do some more thought and consideration  
18 about what to make of all of this, and I think that would be  
19 helpful.

20 DR. FREAS: I would like to go around the table  
21 and read off your name, and if you would say yes, no, or  
22 abstain on the efficacy question. You have already voted on  
23 it.

24 DR. SIEGEL: The No. 2 question.

25 DR. FREAS: The No. 2 question.

1 [The committee members were polled.]

2 DR. SIEGEL: Did you get that, Dr. Freas?

3 DR. FREAS: I did, yes.

4 DR. SIEGEL: Thank you. I didn't really want to  
5 put you through another vote, but that is very helpful.

6 DR. VOSE: I think we are done for today.

7 See you tomorrow at 8 o'clock.

8 [Whereupon, at 5:30 p.m., the proceedings were  
9 recessed, to be resumed at 8:00 a.m., Friday, July 25,  
10 1997.]

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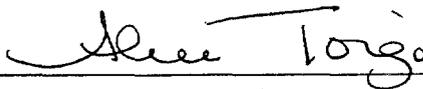
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**C E R T I F I C A T E**

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written above a horizontal line.

**ALICE TOIGO**