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BLOOD PRODUCTS ADVISORY COMMITTEE

Twenty-Fifth Meeting

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Conference Rooms D&E
Parklawn Building
Rockville, Maryland

P A R T I C I P A N T SCommittee Members:

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P R O C E E D I N G S

1
2 DR. KEATING: Good morning. We have two items on
3 our agenda this morning. First we will be discussing
4 erythropoietin and then we will be dealing with a medical
5 device classification for cell separators. First we will
6 hear from Dr. Smallwood, then from Dr. Solomon, and then we
7 will get on with the meat of the discussion. Dr. Smallwood?

8 DR. SMALLWOOD: Good morning. I am Dr. Linda
9 Smallwood, Executive Secretary of the Blood Products Advisory
10 Committee. I would like to make just a few announcements so
11 that we can facilitate our meeting this morning.

12 First of all, I would like for all FDA personnel to
13 sit in the reserved seating so that we may allow enough
14 seating for all interested parties. Secondly, there is
15 reserved seating for sponsors. Would all manufacturers that
16 are participating in the meeting this morning, please sit in
17 the appropriate seating. If the room becomes very crowded,
18 we have available cards so that you may gain reentry if you
19 have to leave the room. Lastly, please do not bring any
20 drinks or anything to eat into the room while the meeting is
21 going on. Thank you. I will turn the meeting back over to
22 the Chairman.

23 DR. KEATING: Dr. Solomon has some remarks that he
24 would like to make before we hear from Dr. Fratantoni.

25 DR. SOLOMON: Thank you, Dr. Keating. These are

1 remarks that were made at the opening of the session yester-
2 day. Looking around the audience and the profusion of the
3 business sections of The Wall Street Journal, it is apparent
4 we have a somewhat different audience than we had yesterday
5 and it might be worthwhile, therefore, to repeat them.

6 I wish to open with a brief explanation of the
7 purposes of this Committee. The Blood Products Advisory
8 Committee is unique within the Center because of its dual
9 function. First, the Committee is constituted under provi-
10 sions of Section 601.25 of the Code of Federal Regulations to
11 evaluate and provide advice on the safety and effectiveness
12 of biological products and review the labeling of such
13 products. The views of the Committee, which may represent
14 unanimous or majority opinions, a consensus or a series of
15 individual judgments are, indeed, advisory and final decisions
16 and recommendations rest with the Agency.

17 It is necessary to stress this point to forestall
18 any precocious conclusions based on suggestions emanating from
19 the Committee. A recognition of the advisory nature of the
20 opinion of the Committee members is essential to permit the
21 members' free expression of ideas.

22 In addition, the Committee will today also fulfill
23 its responsibility as a classification panel, operating under
24 provisions of the 1976 Device Amendments to the Federal Food,
25 Drug and Cosmetic Act, under Section 860.125 of the Code of

1 Federal Regulations, which requires referral of a classifi-
2 cation petition to a classification panel for recommendation.
3 The Committee will operate as a classification panel in
4 considering the reclassification of blood cell separators
5 from Class III to Class II.

6 I have two other comments. One, with respect to
7 the discussion of erythropoietin, first on our agenda this
8 morning, the Committee will hear and consider issues related
9 only to safety and efficacy. Issues that may be related to
10 legalities or to complications that may or may not arise with
11 respect to the Orphan Drug Act will be issues that will be
12 dealt with by the Agency at a later time but will not form
13 the substance of any discussion today.

14 Finally, we have been asked to provide time at the
15 end of the agenda discussion on erythropoietin to have
16 statements made by individuals in the audience with respect
17 to the use of erythropoietin in the treatment of anemia from
18 treatment with AZT. We will make such time available if
19 those statements are brief, with the recognition that there
20 will be no response from the Agency and no response from the
21 Panel. At this point, let me turn it back to Dr. Keating.

22 DR. KEATING: Thank you very much, Dr. Solomon.
23 Now we will hear from Dr. Fratantoni, who will introduce this
24 subject.

1 remarks before the manufacturers present their clinical data.
2 The FDA has reviewed, and will continue to review each
3 submitted erythropoietin product and review them as separate
4 entities. Today, however, we will present you with some
5 issues that apply to the therapeutic use of erythropoietin in
6 a general way.

7 (Slide)

8 We will be talking about recombinant human erythro-
9 poietin. This has been assigned an official name of Epoetin,
10 intended to be used with a suffix that will be specific for
11 each manufacturer.

12 (Slide)

13 In the course of the review, the FDA has evaluated
14 efficacy and safety and has defined efficacy of erythropoietin
15 given to patients with chronic renal failure as an increase
16 in the red blood cell level in these patients and efficacy in
17 that it obviates the need for transfusion in these patients.

18 (Slide)

19 As a result of the FDA review, we believe that
20 there is a favorable benefit-risk ratio for erythropoietin
21 products that have been reviewed. We are not asking the
22 Blood Products Advisory Committee for a specific recom-
23 mendation on approval of any specific product but we are
24 asking for input and advice on specific issues.

25 (Slide)

1 The issues to the Blood Product Advisory Committee
2 relate to dosing and to the scope of indication of these
3 products.

4 (Slide)

5 I said I am going to present very little data and
6 there will be very little. You will be hearing the bulk of
7 this from the manufacturers. One bit of information that you
8 may well hear again, but I will point out now, is that from
9 the data that we have reviewed -- and what I am presenting to
10 you here is an amalgamation of two or more separate data
11 bases -- there is a dose-response relationship between the
12 initial dose of erythropoietin. In these patients it is
13 administered intravenously three times per week.

14 As one increases the initial dose from 25-150 U/kg
15 3 times per week, there is an increase in the response of the
16 hematocrit. This is expressed in hematocrit points per day.

17 (Slide)

18 Just to get a different perspective on those
19 numbers, this is the same slide but with 3 different sets of
20 units in hematocrit points per week on grams of hemoglobin
21 per week. They are obviously just arithmetic manipulations
22 in the columns.

23 There is considerable data regarding what serious
24 adverse effects were seen. As the manufacturers will tell
25 you, there does not appear to be any intrinsic serious

1 adverse effect to erythropoietin, rather, the effects that
2 are seen appear to be the result of increasing the hematocrit
3 in this patient population, effects which could be observed
4 also if these patients were transfused, especially if they
5 were transfused rapidly or to too high a level.

6 One adverse reaction that is seen with particular
7 frequency is either an increase in existing hypertension or
8 at times the development of de novo hypertension that is
9 difficult to control.

10 (Slide)

11 I hope that even the Committee can see this slide
12 because the operative part of it is the numbers rather than
13 the bars. Very quickly, the bargraph part is the number of
14 patients at each level, stratified by rate of rise of
15 hematocrit in the first 30 days of the study. It goes from 0
16 up to 0.5 hematocrit U/day. The important part of the slide
17 is the percentage of patients with episodes of hypertension,
18 which increases with the increasing dose.

19 Because of the size of the data base, which is
20 small, and the size of each patient stratification, which is
21 small, we do not have really firm statistical evidence to
22 support the correlation between the rate of rise between
23 hematocrit and the adverse effects. However, there is a
24 trend. There is a strong indication.

25 (Slide)

1 On the basis of that, the FDA recommends that the
2 initial dose of erythropoietin in these patients be 50 U/kg 3
3 times per week and that the target hematocrit be in the range
4 of 30-33 percent, with the clinician stopping treatment at a
5 maximum of 36 percent. We believe that this is the prudent
6 path, given the fact that the data do not permit a firm
7 conclusion and since this is a new experience in therapy.

8 (Slide)

9 The second issue relates to the scope of indication.
10 I will begin by first giving a definition which has been the
11 source of some confusion. The definition given here for the
12 term end stage renal disease is that stage of renal impairment
13 that appears irreversible and permanent and requires a
14 regular course of dialysis or kidney transplant to maintain
15 life. This is quoted from -- I was going to say the Scrip-
16 tures but it is about the same thing -- this is quoted from
17 the CFR, in proposals and regulations that came in force in
18 1976-78.

19 Our discussions with the nephrology community have
20 led us to believe that this term is used by nephrologists in
21 that way. It is used by the NIH in their chronic renal
22 failure program and we believe it is an established part of
23 the lexicon so that end stage renal disease is a patient with
24 chronic renal failure undergoing dialysis or waiting for a
25 transplant.

1 Chronic renal failure is, therefore, a more global
2 term, encompassing a serious position in the spectrum of renal
3 insufficiency. Patients who are being dialyzed or patients
4 who are not being dialyzed may both be anemic and may require
5 transfusion and, with the advent of erythropoietin, may be
6 candidates for treatment with erythropoietin.

7 We have received proposed labeling that would
8 restrict the use of erythropoietin, that is, would restrict
9 the approval to end stage renal disease, even though that it
10 is likely that, regardless of the wording in the label,
11 erythropoietin will be used off label for all chronic renal
12 failure patients.

13 There are some safety data available for review
14 that have suggested that the adverse reaction profiles for
15 dialysis and non-dialysis patients may be different. This
16 may be related to differences in the patient populations that
17 have been used as a basis for these studies and the diffe-
18 rences may also be dependent upon the varying ages of these
19 patients, or perhaps the difference in underlying diseases in
20 non-dialysis patients versus the diseases in dialysis
21 patients.

22 (Slide)

23 The FDA recommends regarding label indication that
24 erythropoietin be labeled for all chronic renal failure
25 patients, that this is preferable to a restricted label

1 indication.

2 Does the Committee have any questions before we
3 introduce the manufacturers?

4 DR. KEATING: Are there questions of Dr. Fratantoni?

5 DR. ALVING: Can you tell me why you recommend for
6 all chronic renal failure? Do you feel you have enough data
7 the FDA would be comfortable with that? Are there enough
8 studies in these patients?

9 DR. FRATANTONI: Yes. Again, I am not speaking for
10 any particular product but trying to speak in general terms.
11 Yes. Perhaps to take the other side of that question, an
12 approval for, let's say, end stage renal disease patients on
13 dialysis only -- we are well aware that once the drug is
14 licensed and available it will be used off label and, in that
15 case, we will have clinicians using it for non-dialysis
16 patients, without any awareness that there may be some other
17 things they should consider. For example, a patient not on
18 dialysis, not being seen three times per week, may not get
19 monitored as frequently. A patient not on dialysis may not
20 be on dialysis because there is not a commitment by the
21 physician, the patient or the family to embark on dialysis
22 and there may be a very tenuous clinical risk.

23 So these indications need to be in the label and
24 the clinician, looking at the label for guidance, should
25 realize that people have thought about using it both for

1 dialysis and non-dialysis patients.

2 DR. ALVING; That is a sort of two-edged sword.

3 You are assuming clinicians read package inserts.

4 DR. FRATANTONI: If I do not assume that, I cannot
5 function.

6 DR. SOLOMON: Dr. Fratantoni, your slide only spoke
7 to one half of the recommendation that is in our position
8 statement.

9 DR. FRATANTONI: The statement on the slide was
10 that the FDA prefers the global indication. The position
11 statement, I believe, goes on to state that they would
12 consider doing it other ways.

13 DR. KEATING: Dr. Fratantoni, when I read that I
14 wondered what exactly you meant by that. Could you elaborate
15 a little more on what you mean by "other ways?" You would be
16 open to other considerations like what?

17 DR. FRATANTONI: If there were data to support
18 label warnings and if it were decided by the Agency to label
19 with some restrictions, then the label warnings would cover
20 the areas of renal disease that were not included in the
21 restricted indication.

22 DR. KEATING: That is not really clear either. Such
23 as?

24 DR. FRATANTONI: Let's say, for example, that we do
get in a situation where there is a decision made to approve

1 for end stage renal disease only and a manufacturer has no
2 specific data on one segment of the renal failure population
3 but there are data in the literature that could be used,
4 those data could be quoted in the label.

5 DR. KEATING: Okay. Any other questions? Any
6 questions from anyone in the audience for Dr. Fratantoni?

7 MR. COURIN: John Courin, Courin Capital Management.
8 How quickly to you expect to approve EPO?

9 DR. FRATANTONI: As soon as we can finish reviewing
10 all the data at hand.

11 The first on the agenda for the manufacturers is
12 listed as Amgen. They have arranged with Ortho to present
13 some data. So Ortho will be making a brief presentation.

14 DR. ABELS: Good morning. My name is Dr. Robert
15 Abels. I am the medical monitor for erythropoietin for Ortho
16 Pharmaceutical Corporation.

17 (Slide)

18 This morning I would like to very briefly discuss
19 the use of erythropoietin, or EPO, to treat anemia in
20 predialysis patients. As you know, both significant and
21 symptomatic anemia may occur in predialysis patients, as well
22 as in dialysis patients. The major cause of anemia in
23 predialysis patients and dialysis patients is a reduced
24 production of erythropoietin by the damaged kidneys and, of
25 interest, a recombinant human erythropoietin has similar IV

1 pharmacokinetics in anemic dialysis patients and predialysis
2 patients, with the half-life being approximately eight hours.

3 (Slide)

4 Accordingly, several studies were presented in the
5 PLA describing the treatment of anemic predialysis patients
6 with EPO. There were four studies reported, as listed.
7 Three of these were acute studies, as listed. There were two
8 placebo-controlled, double-blind studies and one long-term
9 maintenance study.

10 (Slide)

11 Overall, 234 patients were enrolled in these
12 studies and 181 of them were treated with recombinant human
13 erythropoietin, 79 were treated with placebo and 26 were
14 initially treated with placebo and then were switched over to
15 EPO. The mean exposure to EPO was 19 weeks; 76 patients were
16 treated for 12 weeks; 28 for 12-24 weeks; and 77 for 24-44
17 weeks.

18 (Slide)

19 I would like to first discuss the results from one
20 of our major pairs of placebo-controlled studies, G86-
21 011/053. In the initial acute 011 studies patients were
22 randomized to EPO 50, 100 or 150 U/kg or placebo intravenously
23 3 times per week for 8 weeks. They were subsequently treated
24 in a follow-up study, 053, with EPO on an open-label basis
25 for 6 additional months to maintain their hematocrit at

1 approximately 38 percent.

2 (Slide)

3 This slide shows the baseline characteristics for
4 these patients and 117 patients were entered on the study,
5 with the numbers in treatment group indicated. The patients
6 were mainly in their late 50s. Sex distribution is as shown.
7 Of significance, these patients were significantly anemic
8 and, as you can see, their mean hematocrits were mainly in
9 the high 20s and they also had very significant renal
10 insufficiency, as indicated by their serum creatinine levels,
11 ranging from 5.75 mg/dl to 6.94 mg/dl. Also of interest,
12 their serum erythropoietin levels were extremely low for
13 their degree of anemia, suggesting that anemia in predialysis
14 patients is caused by reduced production of erythropoietin,
15 just as it is in dialysis patients.

16 (Slide)

17 This slide shows the median hematocrit over the
18 cause of the acute 011 study. As you can see, there was no
19 increase in hematocrit in the placebo-treated group, whereas,
20 there was a dose-related rate of increase of hematocrit in
21 the various erythropoietin-treated groups, with the greatest
22 response being in the 150 U/kg group, followed by the 100
23 U/kg group and the 50 U/kg group.

24 Of interest, the rate of rise of hematocrit in the
25 150 U/kg group was 0.26 hematocrit points per day; in the 100

1 U/kg group, 0.20 hematocrit points per day; and in the 50
2 U/kg group, 0.12 hematocrit points per day.

3 (Slide)

4 In addition to trying to determine the effect of
5 EPO on strictly hematologic parameters, we also tried to
6 determine whether EPO has an effect on a patient's overall
7 quality of life. Accordingly, they were asked to rate their
8 energy level and ability to do work on a 5-point scale prior
9 to therapy and also after therapy.

10 Of significance, correction of anemia was associated
11 with a statistically significant improvement in energy level
12 and ability to do work where correction of anemia was defined
13 as attainment of a hematocrit of 40 percent in males or 35
14 percent in females. EPO 150 U/kg also was associated with a
15 statistically significant improvement in ability to do work
16 compared to placebo. So we have improvement both in hemato-
17 logic and overall quality of life parameters here.

18 (Slide)

19 This slide shows the median hematocrit and median
20 EPO dose over the entire course of studies G86-011 and 053.
21 As you can see, over the early phase of the therapy the
22 hematocrit peaked out at about 8 weeks and then we were able
23 to maintain it at the target level of more or less about 38
24 percent over the entire course of study.

1 can see that during the maintenance phase of the study the
2 dose of erythropoietin remained constant at approximately 150
3 U/kg every 2 weeks.

4 (Slide)

5 In addition to studying the erythropoietin intra-
6 venously, we also studied it subcutaneously in study H87-054,
7 in which patients were given EPO 100 U/kg subcutaneously or
8 placebo 3 times per week for 12 weeks. In this study 93
9 patients were enrolled. Again the age was mainly in the late
10 50s. Sex distribution is shown. These patients had signi-
11 ficant anemia, as indicated by their baseline hematocrit, and
12 they had significant renal insufficiency, as indicated by
13 their baseline serum creatinines.

14 (Slide)

15 This slide is just a brief summary of the effect.
16 Again you can see that subcutaneously administered EPO caused
17 a significant increase in median hematocrit over the course
18 of the study, whereas, in placebo-treated patients there was
19 no increase in hematocrit. These data indicate that sub-
20 cutaneous EPO is effective in treating the anemia of pre-
21 dialysis patients.

22 Of significance, the rate of increase of hematocrit
23 after administrating of EPO 100 U/kg subcutaneously 3 times
24 per week was 0.24 percentage points per day. When EPO was
25 given 100 U/kg intravenously 3 times per week in the previous

1 011 study the rate of rise of hematocrit was 0.20 percentage
2 points per day. These data would suggest that EPO can be
3 given by the intravenous or subcutaneous routes with equal
4 effectiveness.

5 (Slide)

6 In study 054 we also asked patients to rate their
7 quality of life before and after therapy. Patients were
8 asked to rate their energy level, ability to do work and
9 overall quality of life on a 100 mm visual analogue scale
10 prior to therapy and after therapy. Therapy with recombinant
11 human erythropoietin was associated with a statistically
12 significant improvement in energy level, ability to do work
13 and overall quality of life compared to placebo.

14 (Slide)

15 I would like to just summarize the efficacy of EPO
16 in predialysis patients. It can increase hemoglobin and
17 hematocrit, as we have seen. It can correct anemia. It can
18 increase exercise capacity. It can improve the overall
19 quality of life; maintain a corrected hematocrit over
20 prolonged periods of time and can be administered by intra-
21 venous or subcutaneous routes with equal effectiveness.

22 (Slide)

23 The safety profile of recombinant human erythro-
24 poietin will be discussed at greater length later this
25 morning. I would just like to summarize by saying that the

1 safety profile in predialysis patients is essentially similar
2 to the safety profile seen in dialysis patients, except that
3 it is important to determine the effect of EPO on the
4 progression of residual renal failure in predialysis patients.

5 (Slide)

6 I would just like to show some data on that.
7 Overall, we found no evidence of acceleration in the rate of
8 progression of renal failure based on the following: The
9 change in serum creatinine and creatinine clearance in the
10 EPO-treated groups were not significantly different from the
11 change in the corresponding placebo-treated group and there
12 was no increase in the slope of the reciprocal of serum
13 creatinine time plot after institution of EPO therapy
14 compared to the slope before institution of EPO therapy. I
15 would like to illustrate these points on the next two slides.

16 (Slide)

17 This slide shows the mean changes in serum creatin-
18 ine and creatinine clearance from baseline to the last
19 available laboratory analysis in study H87-054. In the two
20 left-hand columns we have serum creatinine in the EPO group
21 and the placebo group from beginning to end. In the right-
22 hand two columns we have the creatinine clearance from
23 baseline to end in the EPO-treated and placebo-treated
24 groups. I think you can see that there is no change in the
25 serum creatinine and creatinine clearance in the EPO-treatment

1 group compared to the change in the corresponding placebo-
2 treated group.

3 (Slide)

4 This slide is the reciprocal of serum creatinine
5 time plot before and after institution of EPO therapy for
6 patients who participated in studies G86-011 and 053. Again,
7 I think you can see that there is no increase in the slope of
8 the reciprocal of serum creatinine time plot after institution
9 of EPO therapy compared to the slope before institution of
10 EPO therapy. Taken together, these data would indicate that
11 EPO probably does not have a significant effect in hastening
12 the progression of renal insufficiency in predialysis
13 patients.

14 (Slide)

15 Finally, just to sum up, we feel that EPO therapy
16 is beneficial when used to treat the anemia of chronic renal
17 failure in predialysis patients and we believe that EPO has a
18 satisfactory safety profile when used to treat the anemia of
19 chronic renal failure in predialysis patients. Thank you.

20 DR. KEATING: Questions for Dr. Abels?

21 DR. SHERWOOD: Dr. Abels, the FDA has recommended
22 that the initial starting dose be limited to 50 ug. That is
23 the basis of one question. They also recommended that the
24 target level of 30-33 percent as a hematocrit and stopping
25 the dose at 36 percent, and have suggested that perhaps the

1 drug ought to be licensed in the global sense that the
2 universe of patients with chronic renal disease, be they
3 predialysis or end stage renal disease as dialysis. Those
4 are basically three questions and I am interested in your
5 position on them.

6 DR. ABELS: We clearly have data in the predialysis
7 population showing that 50 is an efficacious dose. It
8 increases hematocrit. There is also European data in the
9 dialysis population indicating that 50 is an efficacious dose
10 and increases hematocrit, and also from Canadian dialysis
11 studies. So I would agree that there probably are sufficient
12 data available to recommend a dose of 50 U/kg as an initial
13 dose 3 times per week. The second question?

14 DR. SHERWOOD: The target of stopping the drug at
15 36?

16 DR. ABELS: Yes, it would appear that the risk of
17 hypertension increases, both with the rate of rise of
18 hematocrit and with the absolute hematocrit attained. If you
19 drive the hematocrit too high, the blood viscosity will
20 obviously go up and peripheral vascular resistance may go up
21 and that may predispose to hypertension. I would agree that
22 a hematocrit in the 30 range is a prudent recommendation.

23 DR. SHERWOOD: And the third element? The global
24 use of EPO?

1 is a significant problem in predialysis patients. Many
2 patients have rather low hematocrits and they do appear to be
3 benefitted by treatment with recombinant human erythropoietin.
4 Clearly, I do not think I would recommend treating somebody
5 who had a creatinine of 2.1 and a hematocrit of 39. I think
6 this is only for the more severe predialysis patients who
7 have significant anemia, not the ones with just slight renal
8 insufficiency and maybe just slight anemia.

9 DR. SHERWOOD: And you have no problem with its use
10 in patients on dialysis and end stage renal disease?

11 DR. ABELS: None whatever.

12 DR. WEISKOPF: The data you presented to us showed
13 patients' hematocrits starting out about 29.

14 DR. ABELS: Yes.

15 DR. WEISKOPF: I assume the centers where you
16 studied it transfused their patients to maintain that level
17 of hematocrit. There are some centers that allow their
18 patients to be maintained at somewhat lower hematocrits and I
19 wonder if you have dose-response data for erythropoietin in
20 patients who were starting out with lower hematocrits than
21 the data you showed us.

22 DR. ABELS: We have not specifically pulled that
23 out but patients at all starting hematocrit levels do
24 respond, from the best of my recollection.

DR. WEISKOPF: Do they respond in a similar way?

1 DR. ABELS: Yes, I believe so. Of interest, the
2 rate of increase of hematocrit in dialysis and predialysis
3 patients to a given dose is essentially the same.

4 DR. ALVING: One concern with people receiving
5 erythropoietin who have chronic renal failure is that, for
6 example, some of them may be very old. Are you going to put
7 any age range on this? For example, your studies were done
8 in primarily 50-year olds, a mean age of 50. Predialysis and
9 dialysis patients are generally in their mid-40s. You can
10 have a sort of risk-benefit and the benefit will be a higher
11 hematocrit; the risk is that they are going to go into
12 congestive heart failure or have exacerbation of hypertension
13 which might not be noted because the clinician may not be
14 following this group of patients as closely. In what way can
15 you address these concerns?

16 DR. ABELS: Well, we entered patients, I believe,
17 up to age 70 or 75 and what we showed was just the mean age.
18 I do not remember the breakdown but there were clearly some
19 older patients. I think you would probably have to just use
20 the same general precautions about treating older patients
21 with potent medications that you would in general. I am not
22 really clear on just how I would address that right now.

23 DR. ALVING: What about patients with hypertension
24 in the predialysis population? Was there any problem with
25 this?

1 DR. ABELS: Hypertension seems to be a problem in
2 the predialysis patients, as well as in the dialysis popu-
3 lation. Although the statistics were not ironclad, for sure,
4 there was a tendency toward an increased number of hyper-
5 tensive events when the hematocrit was rising more than 0.2
6 percentage points per day and also when there was an excessive
7 hematocrit response. So I think that the same questions
8 related to hypertension apply to predialysis patients that
9 apply to the dialysis patients. Certainly, you would not
10 want to treat anyone with EPO who has uncontrolled hyper-
11 tension until the hypertension is brought under control. I
12 think most draft labels do incorporate that.

13 DR. MOSESSON: The predialysis patients had a mean
14 hematocrit of 28, 29 --

15 DR. ABELS: In that range.

16 DR. MOSESSON: And one of your global conclusions
17 is that the quality of life improved.

18 DR. ABELS: Yes.

19 DR. MOSESSON: How do you evaluate the assessment
20 when hematocrit is 28 versus when it is over 30? Most people
21 would not treat a patient who has a hematocrit over 28. I
22 know you did this for purposes of the study because it was
23 important to evaluate this in predialysis patients but do
24 these patients really get a significant improvement when
25 their crit goes from 28 to, say, 33 in any parameter that you

1 would judge quality of life or increased exercise tolerance?

2 DR. ABELS: Our overall impression was that
3 patients did feel better. We did, in one center, measure
4 oxygen uptake before and after therapy and there was a
5 significant improvement in both maximal oxygen uptake and
6 oxygen uptake at anaerobic threshold.

7 DR. MOSESSON: But in terms of the patient's
8 response in your questionnaire? I mean I can understand an
9 end stage renal disease patient with a crit of less than 25
10 going to 33. That is a clear improvement. But going from 28
11 to, say, 33 -- I mean do you have statistical evidence that
12 the placebo patients responded in a different way from the
13 patients whose crit was, say, 33?

14 DR. ABELS: These were somewhat crude tools but we
15 did try to measure the patients' overall functioning before
16 and after treatment with EPO. Basically, their hematocrits
17 went from 28-29 to about 36-37. They did, somewhat to our
18 surprise, note a significant improvement in their ability to
19 work, their energy level and their overall quality of life, as
20 we described it, because we did initially have some questions
21 about the benefit to be derived. But we did find statisti-
22 cally significant improvement in their overall functioning.

23 DR. EYSTER: You mentioned that the half-life was
24 eight hours.

25 DR. ABELS: Yes.

1 DR. EYSTER: Do you have any more pharmacokinetic
2 data about what the curves look like? Are the same for IV
3 and subcutaneous? What about renal excretion?

4 DR. ABELS: That is a very interesting point. I
5 did mention that the rate of rise of hematocrit after equal
6 doses IV and subcutaneous are the same. They essentially
7 are. But what is very interesting is that the pharmaco-
8 kinetics IV and subcutaneously are enormously different.
9 When you give a bolus dose of IV of EPO you get very high
10 levels. If you give, say, 100 U/kg you get a maximum level
11 of about 2000 mU/ml and it drops down rapidly. When you give
12 subcutaneous erythropoietin you find a maximum serum level at
13 about 5-12 hours after injection and then a very slow rate of
14 decline afterwards. There seems to be a repository effect.
15 The maximum serum level after you give it subcutaneously is
16 only about 5 percent of the maximum after a comparable
17 intravenous dose. But despite these enormous pharmacokinetic
18 differences, you seem to find pharmacodynamic equivalence.
19 It is hard to explain that but it may be related to the
20 prolonged elevation of EPO levels that you find after
21 subcutaneous administration.

22 DR. EYSTER: And renal excretion?

23 DR. ABELS: Renal excretion does not really seem to
24 be terribly appreciable as far as we can tell. Most excretion
25 is probably by other routes, I suspect hepatic. The excretion

1 rate in normal volunteers -- the half-life is about 5 hours
2 or so. It goes up in renal patients to maybe 6, 7 or 8.
3 There is a little increase in the half-life in renal patients
4 when you give the dose intravenously compared to the excretion
5 in normal volunteers but it does not make an enormous
6 difference; it makes a small difference.

7 DR. EYSTER: One final question, what is the
8 longest period of time that you had either end stage renal or
9 chronic renal failure patients on treatment and have you
10 noticed any evidence of antibody formation?

11 DR. ABELS: We have had no evidence of antibody
12 formation at all. Actually, we have had patients on treatment
13 for excess of two years now. There was a data cut-off for
14 the data I presented but many of these patients have continued
15 to be treated and we have had no evidence of development of
16 antibodies to EPO at all.

17 DR. BOVE: Are there oxygen uptake data in the
18 submission?

19 DR. ABELS: Yes, there is a special report.

20 DR. BOVE: I did not see that in the part that we
21 got. Could you just tell us a little about that?

22 DR. ABELS: I think there was a subgroup of 7
23 patients whose hematocrit prior to therapy was about 27
24 percent mean and after therapy I think it went up to about
25 37. Their oxygen uptake was determined at anaerobic threshold

1 and their maximum oxygen uptake determined prior to therapy.
2 Then, in a similar fashion, those parameters were determined
3 after therapy. There was a statistically significant
4 increase in both oxygen uptake at anaerobic threshold and
5 maximum oxygen uptake reported. I think these data are
6 reported in The Annals of Internal Medicine, in January of
7 this year.

8 DR. SHERWOOD: The Committee received a good deal
9 of data on the adverse effects, Dr. Abels. I was impressed
10 by the way that you were able to show that seemingly the
11 adverse effects, those which one might see in this population
12 of effects, the events of hypertension, the neurologic
13 disease perhaps associated with disequilibrium syndrome, and
14 the suggestion was that these adverse effects are either from
15 the rise of hematocrit, on the one hand, or secondarily, are
16 the background of adverse effects one would see in the
17 disease in general. We did not see much in the use of this
18 drug in patients who did not have renal disease, or normals,
19 and any adverse effects associated with those. Can you give
20 us a capsule of that?

21 DR. ABELS: Yes. In the filing there is a number
22 of clinical pharmacology studies in normals. I think there
23 are six. Included are studies of the effect on hematologic
24 parameters, showing that there is an effect as far as adverse
25 experiences. There was no hypertension. We also studied

1 electroencephalograms before and after EPO treatment and we
2 found no effect on electroencephalogram function.

3 DR. SHERWOOD: How many patients are we talking
4 about?

5 DR. ABELS: I think we have a total of 108 normals.
6 Also we have large programs ongoing in other disease states,
7 such as AIDS. We have studied rheumatoid arthritis patients,
8 perisurgical patients. In general, I think I can sum up by
9 saying that the problems of hypertension and seizure that you
10 see in the renal population are not found in the other
11 populations. We do see some seizures in AIDS patients but
12 they always seem to be related to CNS pathology, things such
13 as cerebral lymphoma, meningitis, etc. But they do not occur
14 in the context of hypertension which often occurs in the
15 renal patients.

16 DR. WEISKOPF: Are the rates of rise of hemoglobin
17 concentrations in normals or in anemic patients, with diseases
18 other than renal disease, similar to renal disease patients
19 for a given dose?

20 DR. ABELS: We have not directly compared that but
21 I think that the answer to that is yes.

22 DR. MARTENS: I suppose it would not make any
23 difference as long as you have substitution therapy but I
24 wondered if any of these studies showed any depletion in the
patients' own production of erythropoietin after the exogenous

1 use of this drug.

2 DR. ABELS: We have not directly studied that but I
3 think I can say from the normal studies that the patients, as
4 I remember, continued to have reticulocytes in their blood
5 after therapy was stopped, which would suggest that erythro-
6 poiesis was continuing. But I cannot answer that any more
7 than that.

8 DR. DOUGLAS: In the normals or the non-renal
9 disease group did you see antibodies or anaphylactic or
10 allergic reactions?

11 DR. ABELS: We have seen no IgG antibodies against
12 EPO in any population we have studied. The only thing I can
13 tell you is that in two of the normal volunteers, after a
14 second and third exposure to EPO, they did have some rash.
15 We did extensive immunological evaluation and could find no
16 objective evidence of immunological sensitivity. In addition,
17 two AIDS patients had hives after their first dose -- no
18 systemic symptoms but hives after their first dose of EPO.
19 One received the placebo, which did not contain EPO. The
20 other received EPO. Both had positive skin tests against the
21 material they received. I presume they had some sort of
22 preexisting hypersensitivity based on prior transfusions and
23 immunosuppression. But that is the sum total of the signifi-
24 cant allergic reactivity that I can think of.

DR. DOUGLAS: What is the length of treatment in

1 the non-renal groups?

2 DR. ABELS: In the non-renal groups, I think we
3 have treated some of the AIDS patients in excess of a year.

4 DR. KEATING: Thank you, Dr. Abels.

5 DR. ABELS: Thank you.

6 DR. KEATING: All right, one more question and then
7 we will get on.

8 DR. VYAS: What is the rationale for treating the
9 AIDS patients with erythropoietin? Is there any rationale
10 because they have no compromise in their renal function --

11 DR. KEATING: I do not think we want to get into
12 that particular rationale. We are dealing today with just
13 end stage renal disease and chronic renal failure. Thank
14 you, Dr. Abels.

15 DR. ABELS: Thank you.

16 DR. KEATING: Our next speaker is Dr. Rathmann,
17 from Amgen.

18 DR. RATHMANN: I would like to thank you for the
19 invitation to present an update on clinical studies with, as
20 Dr. Fratantoni had mentioned, Epoetin, or Epoetin-alfa in
21 the case of the product you have just heard about and the
22 product that I will describe, which is a generic name for
23 Amgen's recombinant human erythropoietin.

24 I would like to begin by giving an overview of the
25 patient population and the clinical studies and then tell you

1 about the results of those studies, discussing first efficacy
2 of the product and then its safety profile, and then close
3 with some of our responses to the issues being discussed
4 today -- dose and indication.

5 (Slide)

6 As Dr. Fratantoni mentioned, the end stage renal
7 disease population is at that stage of chronic renal failure
8 where it is necessary to sustain life either by transplant or
9 by dialysis. The anemia of end stage renal disease represents
10 virtually all patients, approximately 95 percent, and 75
11 percent have hematocrits below 30 and 25 percent are trans-
12 fusion dependent.

13 Transfusion dependence here is defined as requiring
14 at least six transfusions per year. Major factors limiting
15 rehabilitation are, of course, the symptoms of anemia,
16 fatigue, decreased energy, activity levels, shortness of
17 breath and exercise tolerance.

18 (Slide)

19 This is an overall summary of all the data you will
20 be hearing about, including that which was presented by Dr.
21 Abels. You will see that in ESRD there are 1000 patients and
22 the patient years experience is 986 years. The U.S. ESRD
23 represents about two-thirds of that and the non-U.S. ESRD is
24 about one-third. Then you see the work that has just been
25 presented, CRF non-dialysis, 66 patient years with 181

1 patients, averaging approximately 4 months duration. In the
2 other studies over 100 patients have been treated for more
3 than 2 years and quite a number have been treated up to 3
4 years.

5 (Slide)

6 So I will limit the remarks in this portion of the
7 discussion to the ESRD population. In a double-blind,
8 placebo control it is quite clear that we can see a trend
9 upwards with the administration of EPO and, of course, with
10 the placebo and then when they are transferred over to
11 erythropoietin, there is an immediate rise following the same
12 curve shape and the same response. In all cases in this
13 study the Epoetin-alfa level was 150 U/kg.

14 (Slide)

15 Here we see the sustained response to Epoetin-alfa
16 therapy. On the left side is the multiphase study in the
17 U.S. On the right side is the European study. The left side
18 actually represents two years of experience and the right one
19 represents one year.

20 More than 95 percent of all patients responded.
21 The response was sustained through 2 years of therapy. The
22 median maintenance dose was about 75 U/kg; 65 percent of
23 patients required 100 U/kg or less. So the maintenance dose
24 ranges between 75-100 3 times a week. The maintenance dose
25 is stable and, therefore, there is no resistance to therapy.

1 That is a partial answer to the question on whether you are
2 diminishing the patient's background erythropoietin level,
3 although it is probably a clear indication of just the
4 possibility of building up either an antibody or some type of
5 refractory response. So there is no reduction in the level
6 required to maintain over 2 years and substantially longer.

7 (Slide)

8 The key benefit for patients that are receiving
9 transfusions is an immediate and rapid reduction in that
10 transfusion rate. As you can see here, after 8 weeks of
11 therapy virtually all patients, including transfusion-
12 dependent patients, were transfusion independent and the
13 occasional units of blood required in the early stages and
14 possibly later were actually where a patient auto-donated his
15 own blood because he had adequate amounts of red cells
16 because of the erythropoietin administration.

17 (Slide)

18 The dosing response shows clearly that there is a
19 good dose response right up to 500 U/kg. The slope here is
20 approximately the same at 1500 U/kg and there is an excellent
21 dose response. Perhaps the conclusions are clear. There is
22 a dose-dependent increase in hematocrit. The therapeutic
23 range probably should be viewed as 50-500 because it does not
24 go up any more with the excess amount of material. There was
25 no direct toxicity seen in any dose level, even the maximum.

1 (Slide)

2 This is another way of charting it. Recognizing
3 that there is a very substantial variability from patient to
4 patient, a very substantial overlap between many of the
5 patients receiving 50, those receiving 100 and those receiving
6 150 and seeing the knee in the curve it would, of course, be
7 inadvisable to go beyond the knee. There is an excess amount
8 of material clearly being administered, although it has not
9 shown any adverse effects. Doses from 300-1500 U/kg result
10 in equivalent rates of hematocrit increase, as shown here.
11 Again, there is variability from patient to patient and these
12 conclusions are statistically significant.

13 (Slide)

14 The adverse events experience -- quite a long list.
15 These ESRD patients have multiple medical problems. The
16 adverse events experience in the course of the studies were
17 those generally experienced by ESRD patients. They are
18 listed here: Hypertension, headache, tachycardia, nausea,
19 clotted access, shortness of breath, hyperkalemia, diarrhea,
20 lethargy, dizziness.

21 In the non-U.S. studies there have been somewhat
22 different characterizations and we tried to match them up as
23 well as we could. Actually, all of the conclusions we are
24 presenting today validate the conclusions of the U.S. studies
25 alone. There are no statistically significant results that

1 we are describing today that were not already significant in
2 the U.S. studies. So it is supportive. The placebo patients
3 reported the same pattern and frequency of events as did the
4 Epoetin-alfa treated patients.

5 (Slide)

6 These are the key adverse events that are of concern
7 to ESRD patients and, obviously, of concern to us and of
8 concern to the FDA: Hypertension, seizures, the thrombotic
9 events and the deaths. I will take them up in that order.

10 (Slide)

11 First, hypertension. This
12 chart clearly shows over the course of 32 weeks a hypertensive
13 event average of the entire population moving up from 80 to
14 approximately 82 mmHg. We have called this statistically
15 significant and, in fact, it is. The change is from 80 and
16 82 and then after the first 90 days there is resumption back
17 to normal diastolic pressure. Approximately 25 percent of
18 the patients required intensification or initiation of anti-
19 hypertensive medication. But blood pressure control was
20 readily managed with changes in diet, dialysis prescription
21 and anti-hypertensive medication. Over the long period, as
22 you can see, it was possible to restore the average and be
23 statistically indistinguishable from the initial blood
24 pressure.

25 (Slide)

1 It is important to understand whether there are any
2 trend lines. Here we see breaking down these events in 90-
3 day periods, the number of patients. Obviously, there are
4 not quite as many at the longer periods. The percent of
5 patients reporting events ranged from 7.9-9.7 percent of the
6 events. But the highest number is within the first 90 days,
7 although it is not statistically distinguishable from the
8 other numbers throughout the entire period. So there is no
9 statistically significant difference in the number of
10 patients reporting episodes of hypertension in any 90-day
11 period.

12 (Slide)

13 If we look at more analyses of the hypertension
14 episodes, on the right-hand chart are the placebo. There is
15 a little rise there. There is 0 percent placebo in the
16 Canadian study. There obviously was some type of bias in how
17 hypertension was measured among those dialysis patients.
18 They were looking for exceptions apparently. So that does
19 bias the placebo number down. However, as can be seen here,
20 looking across from right to left, in the U.S. double-blind,
21 placebo-controlled study we have 8 percent and 8 percent. In
22 the next there was no placebo but 0, 11 and 20 where there
23 does seem to be a dose response and there is no significant
24 dose response. So there is no apparent correlation between
the episodes with hypertension with starting dose during

1 first 90 days of treatment.

2 (Slide)

3 The rate of hematocrit rise, in the U.S. Phase III
4 study in this case, the patients experienced episodes of
5 hypertension during the first 90 days of therapy. Again, we
6 see the number of patients and we look at the rate of
7 hematocrit rise. This is the type of information that
8 suggests that the more rapid rate of rise does seem to
9 produce larger numbers in the percent of patients with
10 hypertensive events but, in actual fact, they are not
11 statistically significant. This is despite the fact that it
12 is a large patient population, not a trivial one, and, yet,
13 obviously broken down in this way there are relatively small
14 populations, as low as 11 in the control group here. But the
15 trend is not statistically significant.

16 (Slide)

17 The comparison of incidence of seizures, moving
18 from hypertension to seizures -- the annualized rate of
19 seizures is shown here. If we look at the U.S. studies, it
20 is 0.099. That is the number of events per patient year,
21 approximately 10 percent during the first 90 days, dropping
22 to 30 percent after 90 days and during the entire time of
23 the study, about 43 percent. The Canadian study shows 55
24 percent; the European study, 57, again reaching approximately
25 the same conclusion. All 3 seem to be consistent. All the

1 ESRD studies with placebo have an average of about 3.7
2 percent versus the other figures. But the untreated cohorts
3 show somewhat larger numbers. So it appears that there is a
4 higher rate of seizures in the first 90 days but the overall
5 average is indistinguishable from either the placebo or the
6 untreated cohorts. On the average, 2.5 percent of patients
7 experienced a seizure during the first 90 days.

8 (Slide)

9 The starting dose level for patients experiencing
10 seizure during the first 90 days of study -- here we see a
11 scatter diagram with approximately 1.3, then down to 0, then
12 4.22, and it is not at all clear that there is any dependency
13 on the dose level. That was not apparent sometime ago. It
14 is only with exhaustive data that it is pretty clear that
15 there is not a strong trend and there is no apparent dose-
16 related effect on the percent of patients experiencing a
17 seizure.

18 (Slide)

19 The rate of hematocrit rise in the U.S. Phase III
20 study with patients experiencing seizure in the first 90 days
21 -- here we see again with the rate of hematocrit going up the
22 numbers of patients. The percent of the patients experiencing
23 seizure appears to show no correlation with the rate of
24 hematocrit increase.

1 was appropriate from 50-150 in the submission that we made,
2 however, I will have a comment about the recommendation by
3 the FDA at the end of this discussion.

4 (Slide)

5 Turning to thrombotic events, we have the myocardial
6 infarcts, TIA and CVA, the clotting of the fistulas in the
7 transient ischemic events, the clotted access and the cerebral
8 vascular -- I am sorry, I use the initials so often and I
9 cannot think of it now -- cerebral vascular and the transient
10 ischemic. Okay.

11 Actually, the numbers should be read vertically in
12 this chart, 0.022 and 0.013 in the U.S. studies and the non-
13 U.S. studies; in all ESRD studies, 0.037; for the combination,
14 which would be the sum of the MIs and the CVAs and TIAs,
15 there is no distinguishable difference there. The untreated
16 cohort actually shows somewhat larger numbers. That may be
17 selection criteria. The clotted access numbers are also
18 larger in both the placebo-treated and the untreated cohort.

19 I guess the reasonable conclusion is that there is
20 no evidence of an increase in the incidence of thrombotic
21 events in Epoetin-alfa treated ESRD patients.

22 (Slide)

23 Mortality rates for ESRD patients -- if we look at
24 the major ones, cardiac represents about 50 percent of the
mortality figures. If we look at the figures in the U.S.

1 studies and the non-U.S. studies, we see a significant
2 difference between the two, largely related to the demo-
3 graphics and the differences in the patient populations.
4 Cardiac is 0.045 in the U.S. studies, in the left column.
5 Added on to all the others, it leads to 0.092 rate of
6 mortality, which is roughly equivalent to an untreated
7 population, showing about 14 percent deaths a year as
8 compared to 9.2, and somewhat higher than the placebo. In
9 the non-U.S. studies it is close to that placebo.

10 In actual fact, in the placebo control study in the
11 United States, over a limited period of time there were no
12 fatalities at all. There was no mortality and the placebo
13 numbers were relatively low. That study was relatively short
14 compared to the long study, the U.S. study with 567 patients,
15 which was quite long. When placing the patients into the
16 study, both the placebos and in the placebo-controlled study,
17 the patients were generally in better health.

18 So again the conclusions -- the annualized death
19 rate in the U.S. ESRD patients is 16.5 percent and approxi-
20 mately 50 percent of all ESRD patients die of cardiac-related
21 events. In the European and Canadian data base the annualized
22 death rate is up to about 15 percent. So there is no
23 evidence of increased mortality by any of the studies
24 involving Epoetin-alfa treated patients under all conditions.

(Slide)

1 Summarizing -- Epoetin-alfa is well tolerated.
2 There is no evidence of antibody formation or increased
3 morbidity or mortality. We are looking at 150,000 doses that
4 have been administered in the studies involved and the
5 adverse events reported were those commonly experienced by
6 this patient population.

7 Because blood pressure control may increase and the
8 incidence of seizures may increase during the early phases of
9 therapy, blood pressure and neurological symptoms should be
10 monitored carefully in treated patients.

11 At initiating doses of 50-150 U/kg 3 times per
12 week, Epoetin-alfa is safe and effective in correcting
13 symptomatic anemias, sustaining elevated hematocrit levels
14 and eliminating transfusion requirements in over 95 percent
15 of the ESRD patients.

16 (Slide)

17 I would like to make a few additional comments.
18 First of all, with respect to dose, we find that the sugges-
19 tion of the FDA that the dose be limited to 50 -- we had
20 originally suggested 50-150 because we were well aware of the
21 major variability from patient to patient but it is certainly
22 an acceptable and conservative position to suggest a dose of
23 50 initially.

24 The end point is certainly an acceptable and
conservative end point to accept 30-33 as the target range.

1 It does raise perhaps the first issue with respect to the
2 data available on the predialysis population, as was discussed
3 by the Panel. With an average hematocrit of 28.5 and a
4 target of 30-33, it would seem rather difficult to define
5 significant benefit for that patient population.

6 The overall clinical experience with Epoetin-alfa
7 patients with end stage renal disease has established a
8 compelling benefit for this significant and needy patient
9 population. Indeed, the initial approval for Epoetin-alfa
10 in Europe was for dialysis patients. Well over 90 percent of
11 all blood transfusions performed in patients with chronic
12 renal failure are received by dialysis patients -- 90 percent
13 of all blood transfusions go to the dialysis patients.
14 Almost 95 percent of the data filed to date with the FDA is
15 from dialysis ESRD patients.

16 We have recently reviewed integrated data from all
17 of the available Amgen and Ortho-sponsored dialysis studies
18 and we believe the data submitted conclusively demonstrate the
19 safety and efficacy of Epoetin-alfa in patients with end
20 stage renal disease. We are happy to work with the FDA to
21 revise as promptly as possible the package insert to include
22 the appropriate dosage recommendations and any additional
23 precautionary statements that may be required for patients
24 with end stage renal disease maintained on dialysis.

1 appropriate and prudent initial indication for FDA approval is
2 the correction of anemia and elimination of transfusion
3 dependency in the end stage renal disease patient population.
4 These are the patients for whom we have complete and convin-
5 cing data. These are the patients for whom there is the most
6 compelling and urgent need and these are the patients who
7 will most immediately and demonstrably benefit from prompt
8 approval of Epoetin-alfa.

9 (Slide)

10 I would just like to show you a couple of slides in
11 support of that. These are the percent of patients who have
12 received at least transfusion in the last 12 months. For the
13 ESRD patients the number is over 50 percent; for patients
14 with chronic renal failure, not on dialysis, it is a little
15 under 10 percent.

16 (Slide)

17 The percent of patients receiving 6 or more
18 transfusions in the last 12 months is approximately 22
19 percent, as compared to 2.6 percent of those not on dialysis.

20 We certainly support an indication for non-dialysis
21 chronic renal failure patients as soon as the FDA finds the
22 data to be complete and compelling.

23 It may seem unusual for a conservative position on
24 such a wonderful drug, and that is precisely why we have
25 been, and we would prefer to continue to be extremely

1 conservative because it is our feeling that there is nothing
2 that should raise the risk of something happening with this
3 drug that would destroy its credibility before it has an
4 opportunity to be used extensively by a very important
5 patient population.

6 It may seem practical and attractive to physicians
7 or the National Kidney Foundation and certain patient
8 populations to have the product immediately available for
9 chronic renal failure broadly based on the data to date, some
10 possible publications and reasonable probability that it will
11 all work out. That, however, is a standard of safety and
12 efficacy that is far below that which we have adhered to for
13 the past three years. We should adhere, we believe, to the
14 same high standards that have been applied in bringing
15 Epoetin-alfa to this point.

16 It may seem reasonable that dialysis data alone has
17 proved the case for the less sick patients not on dialysis.
18 In fact, higher safety standards are required if less well-
19 defined benefits are available or if the potential treatable
20 population is diverse, subjectively defined and less well
21 controlled.

22 We have one last comment partially addressing the
23 question of what the indication or precautions might be on
24 the labeling. So Amgen recommends the approval of Epoetin-
25 alfa with a label indication restricted to end stage renal

1 disease patients and with the label precaution that it is not
2 indicated for use in dialysis patients since the safety and
3 efficacy of Epoetin-alfa has not yet been established for
4 these patients. There are a number of other precautionary
5 notes that have already been included in the labeling. Thank
6 you.

7 DR. KEATING: Questions for Dr. Rathmann?

8 DR. RATHMANN: Some of the questions will have to
9 be fielded by some medical experts we have out there. Yes,
10 sir?

11 DR. SHERWOOD: I guess I have to agree that what
12 you have presented on end stage renal disease does indicate
13 that it is a remarkable drug and would have a remarkable use
14 for that indication. You commented that those patients in
15 the predialysis group that were described by Dr. Abels
16 earlier have an average hematocrit of perhaps 28 percent and
17 that the use of that drug in that group of patients, reaching
18 a target level of 33 might perhaps not be terribly ap-
19 propriate. I only wanted to point out that an average of 28
20 percent suggests that half of those patients are below 28
21 percent and half of them are above 28 percent and that there
22 are patients in that lower half who perhaps are reaching a
23 degree of anemia equivalent to those who have end stage renal
24 disease.

DR. RATHMANN: I understand.

1 DR. SHERWOOD: And there might be quite a few
2 people who might also equally benefit from the use of the
3 drug. Does that sound like a reasonable approach, assuming
4 that it is safe?

5 DR. RATHMANN: We certainly agree with what you
6 say. There are a lot of people who will benefit from
7 erythropoietin. There are probably a lot of people in this
8 room who will benefit some day too. But the thing is that if
9 you look at that half that is below, you are still looking at
10 a data base that represents six percent of all the data we
11 have reported, covering all of those, including the ones who
12 are above and below, and you start to limit it to the ones
13 below you are talking about a relatively small data base and
14 only about four months of average time, as compared to many
15 more years. But there would be expected to
16 be a benefit for those patients, yes.

17

18 DR. SHERWOOD: Assuming the safety can be assured.

19 DR. RATHMANN: Yes. We have certainly found in
20 dialysis patients that this drug can be administered and can
21 be operated safely. Those are very controlled populations.
22 They are very well controlled. As a matter of fact, in many
23 cases they are not as sick as some of the predialysis
24 patients who are not being benefitted by dialysis.

(Slide)

1 I have this slide, just dealing with that. One of
2 the reasons that we are anxious, obviously, for making sure
3 that is approved as soon as possible and then working very
4 rapidly to get it approved as broadly as possible for all the
5 indications, particularly chronic renal failure, is because
6 this is the estimated rate of transfusions for the population
7 that could be benefitted just within the end stage renal
8 disease population. It is not likely that we will be able to
9 cover all of them. We are prepared to cover all of them and
10 we are looking at 40,000 units of blood being transfused
11 every month. The percent that we could reach is relatively
12 high and it should be relatively fast. Delays of the nature
13 that we are participating in today could, in fact, mean
14 hundreds of thousands of units in a relatively short span of
15 time. These are real transfusions for people that we have
16 studied, very, very thoroughly. They really should have the
17 drug as soon as possible. Thank you.

18 DR. BOVE: I have a little trouble going between
19 the patients that you have studied so carefully and so
20 thoroughly and in whom you propose that the hematocrit rise
21 will result in a lowered transfusion need and the 50 dose.
22 Most of your studies were with doses between 150-300.

23 DR. RATHMANN: Most were 150 actually.

24 DR. BOVE: Yes. And now we are being told how this
25 drug will do all of these things but the data suggesting that

1 the dose of 50 will do this -- I do not find them in here.
2 The studies, long-term, many patients, six months, the
3 beautiful graphs on reduced transfusions -- all are at doses
4 we are not being asked to approve.

5 DR. RATHMANN: We have assumed that if you elect to
6 go with the 50, after an initial period you would adjust the
7 dose upwards and be able to get to the target hematocrit
8 levels. It is a question of which you move toward it.
9 Frankly, I think the dose of 50 is more conservative by sort
10 of fundamental logic. The less you give, the less risk. On
11 the other hand, there is risk to these patients as long as
12 they have very low hematocrits. It was our feeling that the
13 balancing risks, since we had no statistical difference in
14 the rate of hematocrit rise and a lot of the side effects of
15 adverse reactions, it was our feeling that probably 150 was
16 preferable. That is why most of the studies are there. But
17 there was enough data to suggest, and it is certainly
18 logical, that you can start for a period at 50-150 and then
19 move to another number as required. You have an excellent
20 point.

21 DR. WEISKOPF: With respect to the risks relative
22 to dose, your blood pressure chart appeared to indicate that
23 the rate of hypertension looked as if it might well be dose
24 related. However, you indicated that statistically that was
25 not so. Do you know the statistical test that was applied?

1 DR. RATHMANN: No, I do not know. The data have
2 been presented and statistically analyzed to the FDA. I am
3 sorry we do not have the statistician here.

4 DR. WEISKOPF: Does anyone from the FDA know?

5 DR. RATHMANN: It was looked at about four times.

6 DR. WEISKOPF: This sort of gets as to whether or
7 not the adverse responses are, in fact, dose related.

8 DR. FRATANTONI: A statistician on the review
9 committee felt that there were not adequate data to really
10 perform an analysis that he would consider sufficiently
11 rigid. There was a trend. He felt that in order to get the
12 sort of really rigid statistical answer that you are hinting
13 about, you would need to have a very uniform method of blood
14 pressure analysis, a method of reporting by a standard
15 interval of time and have these stratified by dose. This was
16 not done prospectively in that way. That is why the position
17 of the review committee has been that lacking that type of
18 very solid statistical evidence, the prudent move would be to
19 favor a lower starting dose until we have a chance to get
20 more experience with this agent.

21 DR. RATHMANN: And as I indicated, we concur with
22 that. Actually, it is certainly prudent in the sense of
23 reducing the probability that erythropoietin can cause a
24 problem just by the odds of it. On the other hand, there is
25 a certain probability that those patients benefit from

1 bringing their hematocrits up quicker. That was sort of in
2 the judgment of many physicians. It seemed better to get
3 them well as soon as possible. It turns out that if you look
4 at only serious hypertensive events, there is no trend line.
5 There are no trends with the serious hypertensive events,
6 defined as those that represent substantial changes in
7 hypertension. That was also reassuring to us in going with
8 150.

9 DR. SHERWOOD: I guess, Dr. Fratantoni or Dr.
10 Rathmann, you can answer, this initial dose recommended by
11 the FDA of 50 ug/kg twice a week --

12 DR. RATHMANN: No, that is three times a week.

13 DR. SHERWOOD: I am sorry, three times every week.
14 If that is the only limitation, conceivably, the physician
15 community that would be using this might just consider that
16 the first dose and on Monday give 50 and on Wednesday give
17 150, just to comply with the FDA restriction.

18 DR. FRATANTONI: The proposed label, the one I
19 imagine will eventually be the official label, has the schema
20 for administration spelled out and there is an interval of
21 time after which one then evaluates the response and then
22 goes to a higher or lower dose.

23 The kinetics of the effect of the hematocrit
24 increase are spelled out in the label and it is pointed out
25 the clinician should not change dose before a certain time.

1 It is also very clearly stated that this agent is not
2 intended for the emergency treatment of anemia. Emergency
3 treatment of anemia is still transfusion. This is for a more
4 gradual increase and a chronic treatment.

5 I might say that the average maintenance dose,
6 depending on the data base you look at, is about 75 units 3
7 times a week.

8 DR. KEATING: Are there any other questions or any
9 other comments?

10 DR. EYSTER: I have a question about the issue of
11 iron supplementation in patients in whom your treatment was
12 associated with the functional state of iron deficiency. You
13 did not mention that in your presentation.

14 DR. RATHMANN: No, we did not. We have quite a few
15 individual slides on that subject but we did not put them in.
16 What is your question specifically?

17 DR. EYSTER: Well, can you give us some idea about
18 at what dosage levels or perhaps over what period of time
19 this was experienced, and in what percentage of patients, and
20 how it affected the results that you presented?

21 DR. RATHMANN: Either Dr. Paganini or Joan might be
22 able to comment on the exact extent. It certainly was
23 observed very often that some sort of iron supplement was
24 needed, particularly because of the rate at which the iron
25 stores had to give up the iron. Dr. Brown?

1 DR. BROWN: Virtually all patients, irrespective of
2 the starting dose, will eventually need iron supplementation
3 unless they come in with preexisting hemosiderosis, either
4 orally or intravenous iron.

5 DR. EYSTER: Will the labeling indication include
6 some comment about that?

7 DR. RATHMANN: Yes.

8 DR. KEATING: Does the iron supplementation start
9 immediately?

10 DR. RATHMANN: Not usually. The current practice
11 has changed. In the studies we did not start necessarily
12 right off the bat. Jeff, could you comment?

13 DR. BROWNE: The label indicates an evaluation of
14 the iron status prior to initiation of therapy and frequent
15 monitoring of the iron status while on therapy.

16 DR. EYSTER: Could you give some idea of how many
17 patients required intravenous iron versus oral iron? Because
18 I am surprised at the low incidence of the side effects that
19 were noted in all of your slides if you have a large number
20 of patients getting IV iron.

21 DR. RATHMANN: Dr. Kunzelman, perhaps you would
22 like to comment on that since you have a special background
23 in this area.

24 DR. KUNZELMAN: I am sorry, I did not hear the
25 question clearly.

1 DR. RATHMANN: She is surprised we did not see more
2 side effects if there was a lot of IV iron being administered
3 and required in order to maintain the production of the red
4 cells. I thought you might give a word of your own history
5 as well.

6 DR. KUNZELMAN: Yes, a history of my reason for
7 being on erythropoietin. I am a nephrologist and also a
8 patient. I started on erythropoietin in April of 1987. My
9 primary reason for gaining access to one of the research
10 centers to begin the erythropoietin was because I had been
11 transfusion-dependent for many years. I had received in
12 excess of 150 units of blood. I had a tremendous iron
13 overload, probably as high as anyone in the study, with a
14 ferritin level either unmeasurable or 10,000-12,000. That
15 has significantly fallen. I have not needed supplemental
16 iron. My percentage saturation has fallen. I still have had
17 adequate iron mobilized, apparently correlating with the fall
18 in the serum ferritin, to around 3000 at present, 3000-4000
19 per month recently.

20 I am not involved in the treatment per se in the
21 center with which I am associated. Dr. Paganini can address
22 the question of using it in patients in the study. I have
23 seen some slides; I have seen presentations that have shown
24 the increases in hematocrit in patients initially started on
erythropoietin but at some stage reaching a levelling off.

1 For example, starting with a hematocrit such as I -- perhaps
2 I had not been transfusion-dependent but I still had a
3 hematocrit of 16 -- I mean that happens to a lot of our
4 patients. Some patients tolerate a hematocrit of 16 or 20
5 without going further downward and they exist at that level,
6 but that is about all they do, especially in the last 2-3
7 years with the fear of AIDS and even a more widespread fear
8 of iron overload.

9 We are living longer. I have had end stage disease
10 for 20 years and I have been on dialysis for 12. More and
11 more complications come along but then something like erythro-
12 poietin comes along and really improves our "quality of
13 life." Even though I have worked full-time all of these
14 years, it has been such a change -- everyone else has told
15 you the same thing -- in the last 2 years since I have been
16 on this study. My last 2 units of blood -- I got 2 units a
17 month for many years -- was on April 2, 1987. When I started
18 the study, on April 29, 1987, my hematocrit was down to 16, a
19 level at which I, living in Albuquerque, usually was trans-
20 fused because we are over a mile in elevation. Within 8
21 weeks I was up to 42.5 and EPO was stopped until I fell down,
22 per protocol, to 35.

23 I know it is long and drawn out but I went on it
24 because of the fear of iron overload. When you asked the
25 question about initiating therapy or starting people on iron

1 initially, we have to assess really what the iron stores are
2 and then treat accordingly if there is a drop in hematocrit
3 or levelling off at a lower level concomitant with a decrease
4 in the serum iron, or maybe a dropping off the reticulocyte
5 count, for example, again. But as far as specific therapy,
6 Dr. Paganini can address that.

7 DR. RATHMANN: Dr. Paganini, could you make a
8 comment on the specific question of the side effects as-
9 sociated why we were not seeing more side effects associated
10 with IV iron administration?

11 DR. PAGANINI: Paganini, Cleveland Clinic. I would
12 like to address that specific issue. We have had the
13 opportunity of treating over the last 2.5 years a total of 68
14 patients, all of who were dialysis dependent. In our
15 population we had about two-thirds of those who needed
16 supplemental iron. Of those who needed supplemental iron, we
17 were able to treat with IV iron supplement in about half of
18 those and we saw absolutely no problems with the use of IV
19 supplemental therapy in that one-half. When they then went
20 on to the maintenance protocol, in which they use an average
21 of around 78 U/kg of erythropoietin for maintenance of their
22 non-anemic state, we have been able to maintain their iron
23 levels with oral iron. In only 3 patients have we needed to
24 supplement IV therapy, and in those 3 at an average of about
25 3.5 months per infusion. We have not seen any adverse

1 effects of the iron supplement in any of that study popu-
2 lation.

3 DR. RATHMANN: Is that a satisfactory answer?

4 DR. SHERWOOD: While Dr. Paganini is there, was the
5 IV iron generally given while the patients were on dialysis,
6 which might have a tendency -- I not sure if this is still a
7 side effect of IV iron --to remove some ionized elemental
8 iron that was given?

9 DR. PAGANINI: The approach to giving IV iron was a
10 test dose initially to see if there was any allergic reaction,
11 as is required by the package insert, and then a dose that
12 would allow the patient to raise their percent saturation to
13 above 20. That was given in an IV fashion and it was given
14 near the end of dialysis.

15 DR. KEATING: Are there any other questions for Dr.
16 Rathmann?

17 DR. WEISKOPF: I have a question regarding Figure 5
18 in your submission which shows the dose of erythropoietin
19 versus the number of patients on the maintenance dose. What
20 were the criteria for the end point of the maintenance dose?

21 DR. RATHMANN: I am not sure I can identify Figure
22 5. Oh, I see. Now, what is the issue?

23 DR. WEISKOPF: Is the end point of that to maintain
24 hematocrit 36 or 33?

25 DR. RATHMANN: Yes, probably closer to 36 than

1 anything else, right. It shows the peak and it also shows an
2 average just below that. The peak is occurring there close
3 to 100 and the average is about 75, something like that, yes.

4 DR. KEATING: Thank you, Dr. Rathmann. Next we
5 will hear from Dr. Sobota, from Chugai-Upjohn.

6 DR. SOBOTA: Dr. Keating, Advisory Committee
7 members, FDA officials, ladies and gentlemen, it is a
8 privilege for Chugai and Chugai-Upjohn to present our safety
9 and efficacy data on our unique version of recombinant human
10 erythropoietin. We call this compound Marogen.

11 The specific difference of our preparation,
12 however, is not the primary mission of this particular
13 Committee meeting. The assignment the Agency has given us is
14 focused on our safety and efficacy data from our application
15 for the treatment of anemia secondary to end stage renal
16 disease and the elimination of transfusions associated with
17 that condition. Those data, in turn, will help the Committee
18 deliberate on the Agency's questions related to dose and
19 scope of indications. We also have some information on
20 predialysis, which may be helpful to you if necessary.

21 We approach this presentation with some degree of
22 humility but are confident of the quality and the extent of
23 our data to support our claim.

24 Major placebo-controlled, double-blind studies form
the foundation of our program. This group of studies will

1 show that hemoglobin and hematocrit, quality of life and
2 transfusion elimination are supportable indications for this
3 particular compound. We will also go into a detailed
4 assessment of side effects -- I mean detailed.

5 (Slide)

6 Now I would just like to go into a little bit of
7 thanks. May people have contributed to bringing Marogen to
8 this stage of development. The complex discovery, development
9 and eventual commercialization process began with compound
10 isolation and the generic engineering genius of Genetics
11 Institute molecular biology scientists, followed by prelini-
12 cal studies by Chugai.

13 Medical development was coordinated by Chugai-
14 Upjohn and executed through Bessler Associates. Dr. Jack
15 Whalen, from Bessler, who has monitored our studies from
16 their very inception, will present the safety and efficacy
17 data infrastructure after my remarks. Marketing and distri-
18 bution for Chugai-Upjohn will be through the Upjohn Company.

19 This litany of collaboration and team work repre-
20 sents efforts spanning half the globe of scientists and
21 physicians dedicated to bringing erythropoietin protein
22 treatment for kidney disease patients and their physicians.
23 We also recognize the efforts of the Advisory Committee and
24 the importance of your review of our application.

1 of the FDA's Center for Biologics Evaluation and Research and
2 the speed and thoroughness of their review. You have already
3 received our summary data and four-month safety update. I
4 realize you are in a state of a great deal of data overflow
5 but, hopefully, that material will be helpful in this review.

6 We have 30 minutes to give our data. So we will
7 get on with it. I just want to make two other statements.
8 One, we have studied 985 patients with anemia secondary to
9 end stage renal disease for primary efficacy. Our safety
10 data are derived from 1219 individuals who have received
11 Marogen, of whom 183 are healthy male subjects. We hope this
12 presentation will elucidate and help your evaluation of the
13 FDA's recommendations. I would like to turn the podium over
14 now to Dr. Jack Whalen.

15 DR. WHALEN: Thank you. Dr. Keating, members of
16 the Committee, ladies and gentlemen, I am going to review the
17 major aspects of the clinical development program that was
18 conducted with Marogen, the erythropoietin preparation
19 developed by Genetics Institute, Chugai, Upjohn and G.H.
20 Bessler Associates.

21 (Slide)

22 My talk will consist of three major parts. I am
23 going to review the scope of the program, the clinical
24 development plan, study designs, numbers of patients, the

1 participated in the studies. Then I am going to review the
2 major efficacy parameters, hemoglobin, transfusion require-
3 ments and quality of life. Finally, I am going to look at
4 the safety results, common adverse events that occurred,
5 serious adverse events, blood pressure changes and changes in
6 laboratory parameters.

7 (Slide)

8 First, I would just like to review the nature of
9 the planned studies. There were 4 studies conducted in the
10 United States, a Phase I study to evaluate safety in pharmaco-
11 kinetics in healthy subjects; an open-label dose-response
12 study in end stage renal disease patients, with 131 patients
13 participating; and 2 placebo-controlled, double-blind
14 studies, 140 and 141, conducted in 115 patients and 131
15 patients with end stage renal disease.

16 (Slide)

17 In Japan there were also 4 major studies which
18 contributed to the program, a single-dose study in 24 healthy
19 subjects; a multiple dose study in 12 healthy subjects; then
20 a titrated dose study in 162 patients with end stage renal
21 disease; and a double-blind, parallel placebo-controlled study
22 in 176 patients with end stage renal disease.

23 As Dr. Sobota mentioned, overall 985 patients with
24 end stage renal disease were evaluated with treatment with
25 Marogen. Of those, 427 patients have now completed more than

1 6 months of treatment and 200 patients have completed a full
2 year of treatment.

3 (Slide)

4 This is the study design diagram for the open-
5 label, dose-response study, 125, that was conducted in the
6 United States. In this study patients were evaluated during
7 a screening period and those patients who met entrance
8 criteria were randomized to receive either 25, 100 or 200
9 U/kg 3 times weekly. They received this during a 26-day
10 fixed dose period. At the end of the 26-day fixed dose
11 period patients whose hemoglobin had increased above 12.5
12 g/dl could have the dose down-titrated. Patients were
13 followed for a 140-day or 20-week treatment period.

14 (Slide)

15 The 2 placebo-controlled, double-blind studies or
16 pivotal studies which we conducted, numbers 140 and 141, had
17 the same design. Patients who met entrance criteria were
18 randomized in a 2:1 ratio to either 100 U/kg 3 times weekly
19 of Marogen or placebo. After a 40-day, or approximately 6-
20 week, fixed dose period, patients who had not responded to
21 the initial dose by an increase in hemoglobin to at least 9.5
22 g/dl or 1.5 g increase from baseline could have the dose
23 increased to 150 units 3 times weekly. Patients were then
24 followed for an additional 6 weeks, for a total of 82 days of
25 treatment in the double-blind study.

1 During the course of this study, patients were seen
2 at each dialysis visit and study visits were conducted
3 periodically for the measurement of laboratory safety tests
4 during the course of the study.

5 (Slide)

6 Here we see the eligibility criteria for patients
7 who participated in the U.S. studies of Marogen. Patients
8 had to be on dialysis 3 times weekly for at least 3 months.
9 They had to have a hemoglobin of 8.5 g/dl or less. They had
10 to be 16 years of age or older. They had to be males or a
11 female patient who was postmenopausal or receiving an oral
12 contraceptive. If the patients were hypertensive, their
13 regimen for treatment of hypertension had to be stable for at
14 least 3 months.

15 (Slide)

16 This slide summarizes the demographics of the end
17 stage renal disease patients entered in the 3 studies
18 conducted in the United States. There was a slight predomi-
19 nance of males over females in both the patients receiving
20 placebo and receiving EPO. Caucasians made up the largest
21 racial group, with blacks being the next largest. There was
22 a small number of patients of other races. The average age
23 was approximately 50, with a range from as low as 17 to as
24 high as 90. The average weight was approximately 70 kg. The
25 average duration of end stage renal disease was 4 years.

1 That concludes the scope of the program we conducted.

2 (Slide)

3 Now I would like to review the efficacy results.

4 As I said, that consists of information on hemoglobin,
5 transfusion requirements and quality of life.

6 (Slide)

7 Here we see the group mean hemoglobin for patients
8 who participated in study 125. That is the open-label, dose-
9 response study. There were 3 dose units given in that study,
10 25, 100 or 200. During the course of the first 54 days, or
11 approximately 8 weeks, of the study hemoglobin increased in a
12 dose-related fashion. At baseline all groups had a mean
13 hemoglobin of just over 7. In the 25 unit group it increased
14 to just over 8; in the 100, to just over 10; and in the 200,
15 to just over 11.

16 After the completion of the first 8 weeks of the
17 study, patients continued on to complete the 20 weeks of the
18 dose adjustment period. During that time, patients in the 25
19 unit group continued to have a progressive increase in their
20 hemoglobin and the patients in the 200 and 100 unit groups
21 stabilized at approximately 11 g because of the requirement
22 to down titrate if the hemoglobin went above 12.5.

23 (Slide)

24 Here we see the final 32 weeks of the study.

25 Beginning with week 22, where the 25 unit group had increased

1 to 9 g, the 100 and 200 were between 10 and 11 g. During the
2 course of the final 32 weeks of the study, hemoglobin
3 remained within the 10-11 g range in the 2 highest dose
4 groups and increased into that range slowly in the 25 unit
5 group.

6 (Slide)

7 Here we see the group mean hemoglobin in the first
8 double-blind, placebo-controlled study. At baseline both
9 groups had hemoglobins of just over 7 g/dl. In the placebo
10 group there was little change during the course of the 12-
11 week treatment period. In the EPO group hemoglobin increased
12 to 10 g by day 40 and to 11 g by day 82, or approximately 12
13 weeks of treatment.

14 A statistically significant difference in hemoglobin
15 was noted as soon as day 5 and by the end of the study there
16 is an obvious highly statistically significant difference
17 between the 2 groups.

18 The second study, 145, which followed the same
19 design showed essentially identical findings, with the
20 placebo group showing no change and the Marogen group showing
21 increases to the 11 g range over the 12 weeks of treatment.

22 (Slide)

23 At the end of the 2 double-blind studies all
24 patients were converted to a 50 U/kg dose 3 times a week.

25 Here we see the group mean hemoglobin values in the patients

1 in study 141. Their initial baseline hemoglobins when they
2 started the study was approximately 7. In the group initially
3 randomized to placebo (the solid line), at the end of 12 weeks
4 they were still very close to 7. Then during the course of
5 the extension period where they received a 50 U/kg dose, they
6 showed a gradual increase in hemoglobin up to approximately
7 11 g over 12 weeks of treatment.

8 The group that was originally randomized to
9 erythropoietin 100 units, started down at 7. When they
10 entered the extension period they had already increased to 11
11 and during the course of the 24-week extension period on a
12 dose beginning at 50 U/kg they remained in the 10-11 g range.

13 (Slide)

14 Next I would like to look at the effects of Marogen
15 on transfusion requirements. Here we see the results from
16 the double-blind, placebo-controlled study 140, the results
17 for the placebo group and the erythropoietin group. During
18 the 12 weeks prior to study entry, the 40 patients who were
19 randomized to placebo had received 93 units of blood, for a
20 mean transfusion rate of 0.19 units per patient per week.
21 During the first 6 weeks of the double-blind period, the rate
22 was unchanged, again 0.19. During the second 6 weeks of the
23 study, it actually increased to 0.41 units per patient per
24 week.

In the EPO group there were 73 patients randomized.

1 They had received 146 units of blood during the 12 weeks
2 prior to study entry, for a transfusion rate of 0.17. During
3 the first 6 weeks of the study the transfusion rate was
4 approximately cut in half, to 0.09. During the last 6 weeks
5 of the study only 5 units of packed red blood cells had to be
6 transfused. All of these 5 units were administered to 2
7 patients who had required surgical procedures that required
8 replacement of blood loss.

9 In the second double-blind study which was con-
10 ducted, 141, there were essentially the same findings, with
11 no units of blood required during the last 6 weeks of the
12 study.

13 (Slide)

14 We also looked at global assessments of quality of
15 life in the double-blind, placebo-controlled studies. We
16 asked patients to evaluate their overall quality of health,
17 using a 10-point scale, with 0 defined as poor and 10 being
18 terrific. This was a digital ladder scale and patients were
19 asked to pick a number at the start of the study. This test
20 was repeated at baseline, day 40 and again at day 82.

21 On day 40 there were 37 patients randomized to
22 placebo and 67 patients randomized to erythropoietin who
23 answered the questionnaire. The average score at baseline
24 for these patients had been 5.22 in the placebo group and it
25 increased 0.35 units. In the group that received erythro-

1 poietin it was 5.61 and it increased by 0.66 units. There
2 was no statistical difference between these 2 increases.

3 At day 82 the score for the group on placebo was
4 only 0.03 units greater than baseline, whereas, the group on
5 erythropoietin had increased by 0.95 units. This difference
6 was statistically significant.

7 There was a question earlier about what is the
8 clinical importance of these various questionnaires and
9 asking patients to rate their quality of life. I think that
10 is very difficult to answer and very difficult to assess.
11 This is the basic question: "How do you think your health
12 status is?" They give a rating and all that can be said is
13 that it increases substantially in patients who are receiving
14 erythropoietin and it does not change very much on placebo.

15 (Slide)

16 Patients were also asked to rate their overall
17 satisfaction with life in the double-blind studies. At day
18 82 there was actually a deterioration in patients' satis-
19 faction with life in those randomized to placebo and a 0.41
20 unit increase in patients randomized to erythropoietin.
21 These findings were again statistically significant. We
22 performed these questionnaires in the other double-blind
23 study, 141, and received similar results.

24 (Slide)

25 That was the efficacy data. Now I would like to

1 look at the safety data. I am going to review the common
2 adverse experiences that were noted; serious adverse events;
3 changes in blood pressure, as well as changes in laboratory
4 tests.

5 (Slide)

6 Because end stage renal disease patients have so
7 many adverse events taking place in them because of the
8 seriousness of their illness, we thought that it was essential
9 to conduct placebo-controlled studies in which patients were
10 asked to record all adverse events, described as any un-
11 intended change in either signs or symptoms, whether or not
12 they were considered drug related. In this way we could make
13 a comparison between the incidence of these events in
14 patients receiving the drug and those receiving placebo and
15 make an assessment of which adverse events appeared to occur
16 more frequently.

17 (Slide)

18 Here we see a summary of the most commonly reported
19 adverse events in the 3 studies conducted in the United
20 States during the first 12 weeks of treatment. They are
21 listed in order of frequency of occurrence in patients
22 randomized to receive Marogen. As noted, for most of these
23 commonly reported adverse events, the frequency seen with
24 placebo is very similar to the frequency seen with Marogen.

25 However, there are some exceptions. Headache occurred more

1 frequently in patients receiving Marogen, as did nausea,
2 hypertension and clotted A-V grafts. In all of these there
3 was a substantially greater frequency of occurrence in
4 patients receiving Marogen than in those receiving placebo.

5 The reverse was true for 2 adverse experiences,
6 dyspnea, which occurred more frequently in patients receiving
7 placebo, as did peripheral edema.

8 We think that this substantial difference in
9 frequency does suggest a causal relationship between these
10 adverse events and the treatment with erythropoietin.

11 (Slide)

12 Another way to look at the likelihood of a causal
13 relationship between an adverse event and treatment with a
14 particular drug is to look at the relationship between dose
15 of drug and frequency of event. For all of those commonly
16 reported adverse events, when we looked at the frequency
17 versus dose we saw no consistent pattern. There were
18 increases and decreases as the dose was increased.

19 There were 2 exceptions. Headache showed a
20 consistent increase from the initial randomized dose,
21 occurring in 14 percent of patients initially receiving the
22 25 unit dose; 20 in the group receiving 100; and 37 percent
23 of patients initially receiving 200.

24 Likewise, clotted A-V grafts occurred in just 5
percent of patients receiving the lowest dose; 13 percent in

1 the mid-dose; and 26 percent in the 200 unit dose during the
2 first 12 weeks of treatment. We think this also suggests the
3 likelihood of a causal relationship between these adverse
4 events and treatment with this preparation.

5 (Slide)

6 We also looked at the relationship between rise of
7 hemoglobin and the frequency of side effects or adverse
8 events. All of the patients who participated in the studies
9 conducted in the United States were segregated into rate of
10 rise groups, less than 0.02 g/dl/week, up to a maximum of
11 greater than 0.6 g/dl/week. Looking at the overall frequency
12 of side effects or the overall percentage of patients
13 reporting one or more side effects, there was no consistent
14 relationship between rate of rise of hemoglobin and frequency
15 of adverse events. Adverse events were reported very
16 commonly in all rate of rise groups.

17 For the commonly reported adverse events, only
18 headache again showed a consistent relationship, increasing
19 from 12.1 up to 34.1 across the rate of rise groups.
20 Hypertension showed a suggestion of an increased relationship
21 with rate of rise of hemoglobin, going from 4.5 to 8, to 11
22 and 27 but then dropping off in the highest rate of rise
23 group. All of the other commonly reported adverse events
24 showed no relationship to rate of rise of hemoglobin.

25 (Slide)

1 We also looked at serious adverse events, those
2 occurring in the first 12 weeks of treatment in these 4
3 studies. We looked at 12 weeks because we had a 12-week
4 placebo period in studies 140 and 141.

5 As noted, the frequency of these serious adverse
6 events was relatively low in both groups, between 1-2 percent
7 for most adverse events in both the placebo group and the
8 EPO-treated group. Death occurred more frequently in
9 patients receiving placebo, 4 percent versus 1 percent.
10 Again, clotted A-V grafts, 6 percent versus 14 percent.
11 There was a marked preponderance of those events in patients
12 treated with EPO.

13 (Slide)

14 Here we see adverse events affecting the neurologic
15 system, the GI system and the pulmonary system. Again, there
16 were infrequent reports of most of these adverse events,
17 occurring in 1 percent or less in both placebo and the
18 erythropoietin group.

19 Convulsion was reported by 1/82 patients on
20 placebo, for an incidence of just over 1 percent during 12
21 weeks of treatment. In the erythropoietin there were a total
22 of 3, 1 classified as a seizure or convulsion, 2 as grand mal
23 seizures, giving a similar incidence of just 1 percent during
24 12 weeks of treatment. This is somewhat less than the
25 information we saw earlier today.

1 Nausea had been reported commonly and more frequent-
2 ly with erythropoietin than with placebo. But when nausea
3 with vomiting and vomiting alone are combined, we see 15
4 percent compared to just 13 percent with erythropoietin. So
5 whether serious nausea and vomiting are increased is unclear.

6 (Slide)

7 Blood pressure was, of course, measured in each
8 patient during their dialysis sessions and was recorded for
9 patients at each study visit. In study 141, one of the two
10 placebo-controlled studies, at baseline patients had a
11 diastolic blood pressure of approximately 80 mmHg. By the
12 end of 82 days of treatment, approximately 3 months, the mean
13 blood pressure had increased by 5 mmHg in the erythropoietin
14 group and had fallen less than 1 mmHg in the placebo group.

15 These findings were not statistically significant
16 in this study. But we did see a consistent small increase in
17 blood pressure in all of the studies that we conducted.
18 These findings of increase are probably less than what
19 actually occurs because, as was mentioned previously,
20 investigators treating dialysis patients can remove more
21 fluid in patients if they see the blood pressure rising or
22 they can adjust the anti-hypertensive drug regimen.

23 (Slide)

24 In study 141, either the addition of an anti-
25 hypertensive drug or an increase in dose was required by 11

1 percent of the 90 patients on erythropoietin and 7 percent of
2 patients receiving placebo. So there was a small excess need
3 to increase blood pressure medication in the EPO group.

4 (Slide)

5 Finally, I would like to look at selected laboratory
6 variables. When we began this program there was some concern
7 that in patients who had their hematocrit or hemoglobin
8 elevated there could be a decreased efficiency of dialysis
9 and an elevation of solutes, which are typically elevated in
10 dialysis patients. This did not occur for BUN, creatinine or
11 potassium. They remained virtually unchanged in the patients
12 on erythropoietin. Two solutes which did increase slightly
13 in each of the studies that we did were phosphorus. In this
14 study, 140, it increased from 6 to 6.7; uric acid, from 6.9
15 to 7.3. It is not a very great increase but it was seen
16 consistently in all the studies.

17 Platelets also increased consistently in each of
18 the studies that we did. In this study, baseline platelet
19 count was 232. It increased to 278 and 264 on day 40 and day
20 82. There was virtually no change in platelet count in
21 patients treated with placebo.

22 The other standard parameters of clotting function,
23 prothrombin time and partial thromboplastin time were looked
24 at carefully because of the increased incidence of clotted A-
25 V grafts and a decrease would be of concern. There was

1 actually a small increase by the end of the study in PT, as
2 well as PTT. So there was no evidence that those clotting
3 functions are increased.

4 (Slide)

5 That concludes the data that I wanted to present.
6 I think these data support the following conclusions: As a
7 result of these studies, which have been conducted with
8 Marogen, I think there is no doubt that in administered doses
9 of either 25, 50, 100 or 200 units 3 times weekly it is
10 effective in raising hemoglobin. The rate of increase of
11 hemoglobin is generally proportional to the dose or related
12 to the dose. It can be effective at a maintenance dose of as
13 low as 25-100 U/kg 3 times weekly.

14 In that 1-year study that I showed you, approxi-
15 mately 50 percent of patients receiving a dose of 50 units 3
16 times weekly or less, it eliminated the need for packed red
17 blood cell transfusion. In the 2 double-blind studies, the
18 requirement for transfusions was virtually eliminated. It
19 improves global assessments of the quality of life.

20 (Slide)

21 Finally, it was generally well tolerated. Adverse
22 events seemed to occur similarly in groups receiving Marogen
23 and in those receiving placebo. The only clinical adverse
24 events that do appear possibly causally related to the use of
25 this product are clotted A-V grafts, hypertension and

1 headache.

2 We cannot conclude that there is any relationship
3 between use of Marogen and seizures because the frequency
4 that we noted was essentially the same in both the placebo
5 group and the group receiving this preparation. It has no
6 consistent effect on laboratory parameters, with the exception
7 of small increases in platelet count, uric acid and phos-
8 phorus.

9 As was mentioned by the other speakers, we have not
10 seen any evidence of the formation of antibodies. They have
11 been looked for during as long as 6 months of continuous
12 treatment and no antibodies have been identified. Thank you
13 very much.

14 DR. KEATING: Thank you very much, Dr. Whalen.
15 Questions for Dr. Whalen? You are not planning to present
16 any data on chronic renal failure?

17 DR. WHALEN: On predialysis patients?

18 DR. KEATING: Predialysis patients.

19 (Slide)

20 DR. WHALEN: There is just a single study that has
21 been conducted on predialysis patients with Marogen. This
22 study was conducted in Japan. It was performed in predialysis
23 patients who had to have a creatinine of at least 3 g/dl and
24 a hemoglobin of 10 g/dl or less -- that is milligrams percent
25 creatinine.

1 Here we see increases of hemoglobin given as a
2 percent of baseline hemoglobin during the course of 8 weeks of
3 treatment. Patients in this study were randomized to receive
4 either a total dose of 3000 2 times a week or 6000 units 2
5 times a week. As noted, hemoglobin increased in both groups
6 by about 10 percent from baseline in the group that received
7 3000 units and approximately 30 percent from baseline in the
8 group that had received the 6000 unit dose.

9 (Slide)

10 There was also concern for worsening of renal
11 function in this study and BUN, creatinine, uric acid and
12 creatinine clearance were all measured. There was virtually
13 no change in any of these measurements during the 8-week
14 treatment period.

15 At least during short-term treatment, this study
16 would seem to support the earlier studies that were shown,
17 showing no significant problems with renal function up to 8
18 weeks of treatment.

19 DR. KEATING: Thank you.

20 DR. WEISKOPF: What was the number of patients
21 treated?

22 DR. WHALEN: There were 33 patients.

23 DR. ALVING: Any problems with hypertension or any
24 adverse effects along that line?

1 increase in their blood pressure. Three or four patients
2 required changes in their anti-hypertensive medications.
3 There was no hypertensive crisis or serious problems with
4 hypertension.

5 DR. ALVING: Any changes in potassium in these
6 patients? Does that seem to be any type of a problem,
7 something again that could be taken care of in a dialysis
8 patient but might have to be more carefully monitored in a
9 predialysis patient?

10 DR. WHALEN: No clinically important increases in
11 potassium.

12 DR. EYSTER: Your studies were limited to patients
13 18 years of age and above. Do you have any data at all in
14 children? And is there any reason to think that any of these
15 things should be any different in children?

16 The second question relates to the platelet
17 increases. Do you have any idea why they occurred? One
18 would not expect to stimulate platelet production with
19 erythropoietin. In the situations where that did occur, did
20 it appear in any way either to be beneficial in that these
21 patients perhaps bled less, or was it perhaps associated with
22 an increased tendency to clot their shunts?

23 DR. WHALEN: There have been no studies conducted
24 in the United States in pediatric patients. In Japan, a
25 study is currently ongoing in pediatric dialysis patients, as

1 well as a predialysis study in pediatric patients. Thus far,
2 there are no problems that have been noted that appear to be
3 unique to that population.

4 The increase in platelet count, which we have noted
5 in all of the studies or virtually all of the studies that we
6 have done, suggests to me that there is some cross-reactivity
7 between the receptors on the platelet stem cells and the red
8 blood stem cells. I am not a hematologist so I do not know
9 the precise details but when we look at all of our data, it
10 seems that there is a consistent effect on platelets.

11 We have not done any systematic analysis to attempt
12 to determine whether patients who have an increase in their
13 platelet count are more likely to experience a clotted A-V
14 graft or not. I might just add that the increase in platelet
15 count is in the 10-20 percent range and mean numbers typically
16 still remain within the normal range. It is an unusual
17 patient who would start with a normal platelet count and have
18 an increase to above the normal range.

19 DR. WEISKOPF: I have a couple of questions. The
20 first is related to exacerbation of hypertension in these
21 patients. Looking at mean blood pressure may not be the most
22 useful way of doing that. I wonder if you have information
23 that you can give us regarding the number of patients who
24 needed a change in their drug therapy versus the dose of EPO
25 that they were given?

1 DR. WHALEN: No. I have the overall number. In
2 the double-blind study 11 percent of patients required an
3 increase in anti-hypertensive drugs. Most of those patients
4 were receiving 100 U/kg. Similar findings occurred in the
5 other double-blind study. But we have not done an analysis in
6 the dose-response study.

7 DR. WEISKOPF: So you cannot say if less or more
8 numbers of patients receiving 50 U/kg required a change in
9 their anti-hypertensive therapy?

10 DR. WHALEN: Not right now. But I am sure it is
11 something that is easily obtainable.

12 DR. WEISKOPF: I have one other question and it is
13 related again to adverse experiences. The period of analysis
14 was 12 weeks, as I understand it.

15 DR. WHALEN: Yes.

16 DR. WEISKOPF: And you related that to rate of rise
17 of hemoglobin. Yet, we are really looking at two different
18 issues at that time because the lower doses do not achieve
19 stable hemoglobin or hematocrit during that period of time,
20 as I understood an earlier slide. How well do we know that
21 the symptoms that you do relate to rate of rise really are
22 related to that and not to eventual hemoglobin level? Is
23 there an analysis later on during therapy when hemoglobin
24 levels are stable relating to symptoms?

DR. WHALEN: No, we have not conducted an analysis

1 looking at eventual hemoglobin. We thought about that but it
2 was difficult for us to devise that analysis because virtually
3 all patients do get up to the same stable level if treated
4 long enough.

5 DR. WEISKOPF: I understand. Do you have data
6 regarding their symptom development at a time after they have
7 achieved the stable hemoglobin level?

8 DR. WHALEN: Not really.

9 DR. KEATING: Let's take one more question and then
10 we will break.

11 DR. VYAS: In the slide here phosphorus is absent
12 and, although clinically not significant, could you tell us
13 what values you have for phosphorus?

14 DR. WHALEN: I think I mentioned potassium. I have
15 not seen the phosphorus data. Up to 5.7, 5.9 for potassium.

16 DR. KEATING: Thank you very much, Dr. Whalen.

17 DR. WHALEN: You are welcome.

18 DR. KEATING: Now we will take a 25-minute break.

19 It is now 10:20 and we will be back at 10:45.

20 (Brief recess)

21 DR. KEATING: We are going to have a 5-10 minute
22 opportunity for people in the audience to ask questions. We
23 would like those questions to be limited to the scope of the
24 discussion which we are involved with, namely, dosage and
25 scope of indications. Anyone who would like to question the

1 speakers may do so at this time. Do we have some questions
2 from the audience? We are pushed for time but we want to
3 give you an opportunity if you have a desire to speak. Do
4 you have a question, sir? Yes?

5 DR. PAGANINI: Emile Paganini, from Cleveland. I
6 have a statement, not on dose, but the patient population and
7 I appreciate what the Advisory Committee is attempting to do
8 with the rapid release of this drug.

9 As a clinical investigator, I am concerned over the
10 relative low numbers of patients and the long-term patient
11 data in the predialysis chronic renal failure studies. I am
12 also quite impressed with the end stage renal disease
13 dialysis-supported patient data, both as an observer of all
14 presentations this morning and as a participant in the study,
15 having studied 68 patients, many of them for as long as 2.5
16 years.

17 As a clinician, on the other hand, I am personally
18 concerned with being placed in the dubious position of not
19 being able to treat non-study patients with a drug that has
20 been universally effective in this well-studied patient
21 subgroup.

22 I would also like to echo my
23 colleagues' concerns over not being able to treat with this
24 drug their own dialysis-supported anemic patient population.

24

1 Advisory Committee recommend the immediate release of this
2 drug for its primary target patient population, the severely
3 anemic dialysis-supported patients while the other population
4 studies be continued, if, in fact, this is the only choice,
5 rather than holding up the drug release pending any further
6 studies. Thank you.

7 DR. KEATING: Thank you. Yes, Dr. Fratantoni?

8 DR. FRATANTONI: There may be some confusion here.
9 I can only speak for the technical review committee of the
10 Center for Biologics, the committee of which I am chairman.
11 But regarding the review of available data, as we mentioned
12 before, we will be reviewing individual submissions, indivi-
13 dual agents but we are presenting things to you in a more
14 general way.

15 But with regard to individual submissions, there
16 will really be no significant, perhaps no statistically
17 significant difference in time to review the data that
18 include predialysis patients and dialysis patients versus the
19 data that include dialysis patients alone. That is, from
20 this point. So the time to review is not an issue.

21 DR. KEATING: So what you are saying is that there
22 would not be a problem with regard to holding up the licensure
23 of this drug while waiting for additional data on chronic
24 renal disease patients.

DR. FRATANTONI: At this point, no. You are aware

1 that the FDA was delayed because additional data was provided
2 by a mechanism which had nothing to do with the usual
3 submission mechanism. Otherwise, there may well have been
4 approval by this point. But from this point, from now,
5 whether predialysis are included or not, there should be no
6 difference in time to final approval.

7 DR. KEATING: Does that satisfy your concern, Dr.
8 Paganini?

9 DR. PAGANINI: Yes, thank you.

10 DR. CORBITT: Steve Corbitt, Rush Presbyterian
11 Medical Center, in Chicago. If I understand correctly,
12 predialysis information should not hold up the chronic renal
13 failure dialysis patients with respect to approval for EPO?

14 DR. KEATING: That is right. That is my understand-
15 ing. I think that is what Dr. Fratantoni said.

16 Let us now discuss the two issues that we have been
17 asked to provide some advice on. The first is dosage. Most
18 of the data have dealt with patients who are on higher doses
19 than what is being recommended by the FDA.

20 Let me go back a step. Dr. Solomon started today
21 by telling us something of the ground rules concerning the
22 nature of our Committee and the fact that we are advisory and
23 that all decisions are made by the Agency.

24 By the same token, while we are always interested
25 in knowing the position of the FDA, the Committee feels no

1 great obligation to support those recommendations. We are
2 individually thinking and we will express ourselves in that
3 regard.

4 So to go on with the consideration of dosage, the
5 recommendation has been made by the FDA that it would be
6 prudent, inasmuch as there seem to be decided side effects
7 related to the increase in crit, to start out with 50 U/kg
8 and then to determine the additional dosage based on the
9 clinical condition of the patient.

10 Does anyone on the Committee want to make a
11 statement regarding this? Does anyone have a problem with
12 this particular recommendation?

13 DR. SHERWOOD: The recommendation is merely as an
14 initial dose of 50 ug/kg 3 times a week. That is not
15 withstanding that we understand there will be an algorithm in
16 the package insert which allows an escalation of that over a
17 period of time.

18 I think it is appropriate that the FDA and the
19 Committee be very conservative on this point since it is a
20 brand-new drug. But it is my understanding that that
21 conservatism is for those physicians who really have not had
22 experience with the drug yet but will be using it for the
23 first time, as opposed to those clinicians who have already
24 been using it for over two years and who probably would not
25 like to be held to that particular scheme.

1 I was just hoping that there could be some facile
2 way, some easy way that once this conservatism is found to be
3 too conservative perhaps to change the package insert so that
4 clinicians can escalate the usage of the drug and dosage over
5 a period of time as more experience is gained with it,
6 without being burdened perhaps by regulatory issues.

7 DR. KEATING: Dr. Fratantoni, do you want to
8 comment on that?

9 DR. FRATANTONI: I would anticipate an enormous
10 amount of experience is going to be gained with the use of
11 this agent in the next period of months and years. With that
12 in hand, companies could, of course, always petition for a
13 change in labeling. With the data in hand, that should be no
14 great problem.

15 DR. EYSTER: I just have a point of clarification.
16 If you recommend starting at this dose, would that include
17 all patients who are already being maintained at a higher
18 dose perhaps? Would you have to go back and start at a lower
19 dose? Or are you just talking about newly treated patients?

20 DR. FRATANTONI: Starting.

21 DR. KEATING: Does anyone have a problem with this?
22 Are we all in favor of recommending the FDA's guideline?

23 DR. WEISKOPF: I have a question for Dr. Fratantoni.
24 Should this eventually be in the package insert, if data are
25 gathered in the succeeding months or years which indicate

1 that perhaps an adjustment to the package insert is necessary,
2 how big a process is that? How difficult is it to change the
3 package insert?

4 DR. FRATANTONI: I do not think it is very dif-
5 ficult. But I will defer to Joel on that.

6 DR. SOLOMON: The problem with changing the package
7 insert is a relatively trivial one. The problem comes in the
8 review of the data. But when the data are approved, it is
9 simply a matter of reprinting. How long it would take to get
10 the data and get the data reviewed is subject to the review of
11 the data itself.

12 DR. BOVE: Would people be comfortable with a range
13 rather than an absolute number, like 50-75 or something like
14 that?

15 DR. KEATING: I would certainly be comfortable with
16 a range. Does anyone have an objection to a range on the
17 Committee? Does this seem reasonable? Just on principle, I
18 prefer ranges to one number. Joe, what do you think? Would
19 this make you unhappy?

20 DR. FRATANTONI: I would be very happy with a
21 range. The range that was proposed recently was 50-150 and
22 we thought --

23 DR. KEATING: A little high.

24 DR. FRATANTONI: -- that with a new agent perhaps an
inexperienced clinician deserves a little more guidance. But

1 if you are talking about a narrower range, I am sure that
2 would be agreeable.

3 DR. KEATING: What do I hear for 100?

4 (Laughter)

5 DR. MOSESSON: It seems to me the data are rather
6 substantial from both applications that the mean dose is in
7 the range of 100. So if you start out at 50 you are simply
8 delaying the time when you are going to be raising the dose.
9 Because the patients are followed so carefully and because I
10 cannot see any evidence that a dose of 150 carries any more
11 toxicity than a dose of 50, but only gets you to the endpoint
12 faster, why play this waiting game when the patients could
13 get relief faster? As soon as you reach the point where you
14 realize the crit is at an acceptable level, you can cut back
15 any time you want. That is exactly what is done. So why
16 start low and go high instead of starting in the average and
17 moving in the direction that you need to go?

18 DR. KEATING: Well, I think their only point is
19 that there are people who are going to use this who are not
20 as experienced as the ones who are using it now. It is in
21 the interest of prudence that they are recommending a lower
22 dosage. I would certainly support 50-100 to start and go on
23 from there. Is this acceptable to the Committee? Do you
24 like 50-100?

(Several Committee members nod in agreement)

1 Everybody is in favor. Anybody not in favor? We
2 have one abstention. So that makes it nine for and one
3 abstention.

4 Now let's consider the somewhat more complex issue
5 of labeling and of indications. There certainly have been
6 adequate data to support its use in end stage renal disease.
7 The concept of supporting its use for the more global
8 concerns of chronic renal failure, as well as end stage renal
9 disease, make a considerable amount of sense.

10 There probably are not as many data available to us
11 concerning the use in chronic renal disease. That information
12 could be included in the label perhaps so that people using
13 it who are not as familiar with the drug would recognize that
14 chronic renal disease patients may present somewhat different
15 concerns. They are not as commonly monitored or as frequently
16 monitored as end stage renal disease and sometimes are even
17 harder to control. As more and more data are presented, that
18 certainly could be included.

19 But I think we have all decided that we are not
20 going to hold up on licensing the drug for end stage renal
21 disease because there are not as much data available for
22 chronic renal failure.

23 Is there any interest on the part of the Committee
24 to limit the recommendation for this drug to end stage renal
25 disease as opposed to chronic renal failure? Barbara, you

1 had some concerns in that regard. Do you want to voice them?

2 DR. ALVING: I feel very comfortable with the end
3 stage renal disease and the data that have been acquired. I
4 still have a lot of concerns that perhaps we do not adequately
5 know the side effects -- you know, chronic renal failure
6 encompasses a tremendous range of patients who are in renal
7 failure for all sorts of reasons and we have data on 181
8 patients. I do not really feel comfortable with the adverse
9 reactions in these patients. For example, what happens to
10 the potassium in a non-dialyzed patient who receives this?
11 Should we be advocating this for transfusion-dependent
12 patients in chronic renal failure?

13 DR. KEATING: Yes.

14 DR. ALVING: There are all sorts of things that I
15 really do not know. Now, if you want to include three
16 paragraphs of what you do not know in a package insert, that
17 is another option.

18 That is not to say that I feel that it should not
19 be used in chronic renal failure patients. What I am afraid
20 of is that physicians will see that the FDA has said it is
21 also indicated in patients with chronic renal failure and,
22 therefore, it must be okay. Maybe I am underestimating the
23 intelligence and savvy of the average nephrologist or
24 physician who is treating these patients. I am just not
25 sure. But these patients also are not followed that careful-

1 ly. They are not on dialysis. They are not followed as
2 carefully as the patients who are on dialysis.

3 DR. KEATING: My own sense about that though is
4 that I would not feel any more comfortable limiting use of
5 this drug to just end stage renal disease any more than I
6 would be limiting the use of transfusion to end stage renal
7 disease. There certainly are people who have chronic renal
8 failure who could benefit from this. That depends on the
9 clinical condition and what their hemoglobin is and what
10 their quality of life is.

11 DR. VYAS: I think in chronic renal disease we can
12 certainly suggest that it is only for patients in whom
13 transfusion become necessary and if there are hematologic
14 conditions or values that dictate that this patient really
15 needs EPO.

16 DR. EYSTER: And would you consider a baseline
17 creatinine in that equation also?

18 DR. KEATING: There are lots of possibilities.
19 What we can do is simply recommend that if chronic renal
20 disease is included, that there be some additional guidance
21 in the label to make it known that these are difficult people
22 to deal with; that they certainly deserve to be considered
23 for this treatment, but that there is not the same degree of
24 data available for them and that we are concerned about some
25 of those data at this point. And that may disappear as more

1 data are accumulated.

2 DR. WEISKOPF: I am persuaded that Girish's point
3 is a good one, that if it be extended to patients with
4 chronic renal failure, that it only be recommended for those
5 who would otherwise require transfusion. In the other
6 patients I fail to see that the risk-benefit ratio is
7 appropriate.

8 DR. SHERWOOD: I would be inclined not to be so
9 restrictive. I have the feeling that there are sufficient
10 chronic renal disease patients that poop along at a low
11 hemoglobin level, who are not getting transfused because of
12 the risks of transfusion, who would really benefit from EPO
13 if it were used wisely. I think most patients with chronic
14 renal disease are being cared for by physicians who understand
15 the issues and their complications and circumstances.

16 The medication has to be given correctly. It will
17 not be given in the home. It is not a bottle of pills they
18 take. They will have to visit the physician's office to
19 begin on the drug. And I feel very comfortable with the data
20 so far and I think I can translate some of that data to the
21 chronic renal disease patient and I would like to see a more
22 global licensing of it without significant restrictions.

23 DR. EYSTER: That is a good point. I would support
24 that because you get around this problem of requiring a
25 minimum hematocrit or hemoglobin and a minimum creatinine

1 value.

2 DR. BOVE: A lot really depends on how the package
3 insert is worded. I think that the concern of the Committee
4 is being expressed so that the people who will be reviewing
5 and helping with the writing will understand that we do not
6 think it is necessarily bad to use this drug in chronic renal
7 failure provided -- X, Y and Z.

8 DR. KEATING: I think that would probably be enough
9 guidance for the package insert writers. I think you have
10 gotten the flavor of our concerns. I would agree with Dr.
11 Sherwood that I would hope, let's say, that there are people
12 who are not being transfused who could benefit from this
13 drug; that transfusion would have greater restrictions placed
14 upon it than would erythropoietin.

15 As a blood banker, I am very excited about this
16 drug. I think I would like to congratulate the people who
17 worked on it. Anything that will take people off constant
18 transfusion is great.

19 DR. MASOUREDIS: Did you want to say anything about
20 the maximum hematocrit being 30-33, not exceeding 36?

21 DR. KEATING: Yes. Yes, I think that sounds to me
22 like an excellent recommendation. Is there anyone who does
23 not feel that that is reasonable? To strive for 30-33, with
24 a maximum of 36? Thank you, Sam.

1 Fratantoni, on this subject?

2 DR. FRATANTONI: Yes, thank you very much.

3 DR. KEATING: Good. Before we leave the subject of
4 erythropoietin, there are two people who would like some time
5 to speak to us about the use of erythropoietin in AIDS. We
6 are not primarily interested in that here but we are more
7 than happy to hear from them. Their names are Mark Harrington
8 and Peter Staley.

9 MR. HARRINGTON: Dr. Keating and members of the
10 Committee, thank you for the opportunity to make a statement
11 today. As everyone in the room is well aware, when a new
12 drug is approved for a given indication, doctors are free to
13 use it for other indications. It is a rather exciting and
14 rare opportunity when a drug becomes available that will have
15 such wide applications as EPO has.

16 I belong to the organization known as ACT/UP, which
17 is the AIDS Coalition to Unleash Power. For two years we
18 have been striving to expedite the development and availa-
19 bility of drugs for AIDS and for AIDS-related infections.
20 Last week we had two major successes with recommendations by
21 FDA's Anti-Infective Drugs Advisory Committee to recommend
22 NDA approval for aerosolized pentamidine for prophylaxis of
23 Pneumocystis carinii pneumonia, the leading killer of people
24 with AIDS, and of DHPG, also known as ganciclovir, for
25 treatment of cytomegalovirus retinitis.

1 Like those other two drugs, EPO will be a crucial
2 element in the chemotherapeutic armamentarium for AIDS. Many
3 people with HIV infection suffer from chronic anemia and
4 treatment with AZT, the only approved treatment for HIV
5 infection which sometimes makes that anemia acute. In fact,
6 anemia is one of the most common dose-limiting toxicities in
7 AZT treatment.

8 The New York City trial of EPO for AZT-related
9 anemia was sponsored by Ortho Pharmaceuticals and conducted
10 by the Community Research Initiative, which was the same
11 consortium of community-based physicians involved in the
12 recent aerosolized pentamidine trial which led to approval of
13 that drug. Ortho is to be commended for conducting clinical
14 trials in the innovative community-based clinical trials
15 program.

16 People with AIDS on AZT and EPO needed statistically
17 significantly fewer transfusions than those on AZT without
18 EPO and toxicity was relatively minimal. We do not really
19 know how many Americans are using AZT but at least 37,000 are
20 getting it from the government, either through Medicaid or
21 through the Patient Assistance Program. We know that half
22 the people with AIDS who use AZT need transfusions. So EPO
23 would be useful, at a minimum, to about 25,000 Americans
24 today. As the numbers of the epidemic continue to climb, more
25 and more people will need the drug.

1 EPO's use in people with AIDS could significantly
2 diminish the frequency of transfusions and raise the quality
3 of life for people infected with HIV. Also, as you are
4 probably well aware, people with HIV have depressed immune
5 systems which means that blood transfusions are quite
6 dangerous for them.

7 Yet something else has been obstructing EPO's
8 availability and this time it is not the FDA or the regulatory
9 process. It is the orphan drug status and the sort of
10 unintended adverse effect or side effect of the orphan drug
11 law, which was initially intended to speed delivery of
12 innovative treatments to people who need them. Because of
13 legal skirmishes between competing sponsors, the Orphan Drug
14 Act has actually impeded the availability of EPO, not only
15 for people with AIDS but for people with kidney disease.

16 The Orphan Drug Act is being abused in two different
17 ways. First of all, EPO's various sponsors define very
18 narrow indications for the drug's use, knowing that its
19 application would be far wider. A narrow indication rendered
20 it eligible for orphan drug status with the exclusivity
21 rights that confers while the true, wider use assures the
22 sponsor of seven years of an unjustified monopoly on that
23 indication.

24 Industry analysts estimate EPO's market to be
25 between 350 million and 1 billion within 5 years, far, far

1 larger than anything contemplated for protection under the
2 orphan drug provisions.

3 The second way that the Orphan Drug Act is being
4 abused is that the sponsors are engaged in a messy battle for
5 NDA approval and market share. Never has such an ugly
6 custody battle developed for an orphan drug. Amgen, in
7 particular, is to be chastised for its litigious and obstruc-
8 tive actions, seeking unsuccessfully to block Genetics
9 Institute trials and, according to the Delaware Federal
10 Court, violating its licensing agreement with Ortho.

11 We condemn the delaying tactics of all the parties
12 involved in delaying EPO's NDA. While lawyers prepare suits
13 and counter-suits, people living with AIDS or with kidney
14 disease are suffering needlessly.

15 ACT/UP urges EPO sponsors to resolve their quarrels
16 and ensure that this drug is widely available to all Americans
17 who need it as soon as possible. If situations like this
18 continue, ACT/UP will urge Congress to amend the Orphan Drug
19 Act to end such abuses and we shall urge our ACT/UP affiliates
20 around the country to bring our case to the sponsor's
21 doorstep.

22 Thank you. I am going to be followed by Peter
23 Staley, also a member of ACT/UP.

24 MR. STALEY: I would just like to add to the
25 comments with some personal notes, again, kind of reluctantly

1 thanking you for letting us talk. We were not invited. In
2 fact, we were strongly urged not to come. It took a lot of
3 strong-arming from the PR division of the FDA to get this
4 mike.

5 I think one of the main reasons for that -- and we
6 have had the trouble with other advisory committees -- is that
7 these advisory committees very much want to keep all testimony
8 and all hearings strictly scientific. Unfortunately, we find
9 a problem with that, and that is that usually the results are
10 that the committees seek pure science and ignore the needs of
11 people with possibly fatal diseases. That is why we are
12 trying to muscle in on a lot of these advisory committees and
13 I think that is one of the main reasons we had two successes
14 last week.

15 I would like to speak personally about EPO. I was
16 diagnosed with AIDS-related complex in October, 1985 and have
17 been battling that condition ever since. I first tried AZT
18 in 1987. I tried it on full dose, like most people, and got
19 absolutely walloped, like 50 percent of the people who have
20 tried it. I became severely anemic and gave it up at that
21 time. Given that I was largely asymptomatic, I did not
22 choose to take transfusions.

23 Since then I have tried the drug again, starting on
24 one quarter-dose, which is 3 pills a day. I have had good
luck with that. I have only had about 34 percent hematocrit

1 levels and the T4 count rose substantially above 300 after
2 hitting a low of 100.

3 But -- and this is a big but, at only 3 pills a day
4 there is probably very little AZT getting to the brain, where
5 the virus is free to do whatever it wants right now. I would
6 like to get on half-dose AZT. I have tested the erythro-
7 poietin level. I have found out that it is low and, there-
8 fore, I am a prime candidate for this drug. I, like many,
9 have written letters to Ortho asking for this drug on
10 compassionate use and have been turned down. There does not
11 seem to be any effective compassionate use for this drug and
12 none of the companies have applied for treatment IND as well,
13 which could get an early release for thousands of people with
14 AIDS.

15 We are here basically because it was a prime
16 opportunity. All the companies involved with this drug are
17 in this room. Even more than talking to this Committee, we
18 wanted to tell you that we are watching this drug. It is at
19 the top of our list of what we want released, and we want it
20 now, either on compassionate use, treatment IND or final
21 marketing approval. The squabbles that are going on in the
22 courts are purely for market share and they are ignoring my
23 problem and the problems of thousands of people with AIDS, as
24 well as people with kidney problems.

So we are here to put you on warning that we are

1 watching and we are losing patience very quickly. ACT/UP New
2 York has 3000 members, very close to Ortho Pharmaceuticals.
3 There is an ACT/UP Los Angeles, ACT/UP San Francisco, there
4 are five ACT/UPS in California, very close to Amgen and we
5 really wish you would straighten this problem out fast.

6 Thank you.

7 DR. KEATING: Thank you, gentlemen.

8 For the last item on the agenda this Committee will
9 become a medical device panel, which is another part of our
10 responsibilities as the Blood Products Advisory Committee.

11 Maybe we will just wait for a few minutes until
12 everyone has had an opportunity to exit.

13 We are going to hear from Mary Gustafson, from
14 CBER, recommending a change in medical device classification
15 for cell separators.

16 MS. GUSTAFSON: I thought everyone was here today
17 to listen to this presentation on cell separators. I am
18 upset and deeply disappointed.

19 (Laughter)

20 Unlike the other issue that you have been asked to
21 review, I think you will find this one relatively straight-
22 forward and simple. This is not a new entity or a new
23 indication even for an old entity.

24 What we are asking you to do today is consider a
25 recommendation to reclassify centrifugal-based cell sepa-

1 rators, intended for production of blood and blood components,
2 from regulatory Class III to Class II.

3 For a little background, when the Medical Device
4 Amendments to the Food, Drug and Cosmetic Act were enacted,
5 in 1976, there were provisions for classifying all medical
6 devices into three classes, I, II and III, depending on the
7 degree of regulatory control necessary to regulate these
8 devices.

9 A Class I device is a device that can be regulated
10 by general controls. By general controls we mean the
11 prohibitions against adulteration and misbranding that are in
12 the FD&C Act. The regulations that interpret these statutory
13 provisions are the general GMPs and the labeling requirements.

14 A Class II device is when it is classified as II
15 because it is felt that more stringent controls are necessary
16 but these are devices about which enough is known that
17 performance standards can be written for the control of the
18 devices.

19 Class III devices are those devices which it is
20 felt cannot be controlled adequately through general controls
21 or performance standards and require premarket approval
22 applications and review prior to marketing.

23 One of the tasks that was before the Agency after
24 1976 was to classify the devices that were already on the
25 market. In the late '70s, the hematology and pathology

1 devices panel met and recommended that centrifugal-based cell
2 separators for the collection of blood and blood components
3 be classified as Class III. They also proposed that this
4 classification and the resulting PMA requirements be given a
5 high priority.

6 These devices were classified in Class III in 1980.
7 In September of 1983, the FDA published a notice of intent to
8 initiate proceedings to require PMAs of 13 pre-amendment
9 Class III devices that were assigned high priority by the
10 FDA. In this were included these cell separators.

11 In February of last year, we published a proposal
12 to require PMA submissions for centrifugal automated cell
13 separators, intended for routine collection of blood and
14 blood components. The proposed rule provided interested
15 persons an opportunity to petition for reclassification in 15
16 days and to comment within 60 days from the date of the
17 notice.

18 We were requested to extend both periods of time
19 but we were unable to extend the 15 days for petitions
20 because that is what is listed in the Statute. We were able
21 to extend the comment period by an additional 30 days. We
22 received 17 letters of comment from manufacturers and the
23 blood banking community.

24 The vast majority of comments were in favor of
25 reclassification of the devices from Class III to Class II.

1 These commentors included such organizations as the Health
2 Industry Manufacturers Association and the American Associ-
3 ation of Blood Banks.

4 FDA has considered these letters and comments and
5 other factors, including the three classes that I just
6 covered, and also the devices that would be excluded from
7 this classification, which include the filtration cell
8 processors which are post-amendment devices. None of these
9 devices for collecting blood and blood components were on the
10 market prior to 1976. They have been classified in Class III
11 and are being handled under the premarket approval application
12 process.

13 Also the centrifugal cell separators intended for
14 therapeutic purposes were classified by the Gastroenterology
15 and Neurology Device Panel, in 1983, as Class II devices
16 already. So they are not included in the reclassification
17 proposal.

18 In comparing the processes involved in reviewing
19 applications for the products, manufacturers of Class III
20 devices are required to submit premarket approval applications
21 that contain sufficient data to establish the safety and
22 effectiveness of the device.

23 The FDA has 180 days to review these applications
24 if there are no major amendments and each and every appli-
25 cation has to come to the Advisory Committee for recom-

1 mendation.

2 On the other hand, in order to introduce a Class II
3 device to the market, a manufacturer files a premarket
4 notification or a 510(k) filing with the Agency. The
5 manufacturer has to prove substantial equivalence to a pre-
6 amendment device or one that has been classified into Class I
7 or Class II since 1976. Then major modifications in the
8 device that affect the safety and effectiveness require a new
9 510(k) filing and the Agency has 90 days to act on these
10 notifications.

11 We also included the adverse reactions. In your
12 position paper, I listed that we had only found, in reviewing
13 the MDR reports, one significant reaction in the past three
14 years of a normal donor that required hospitalization. Since
15 last week we have learned that we did not have a complete
16 list and there were a couple of others during the three-year
17 period that were significant. One was an ETO-mediated
18 sensitivity reaction in a normal donor and another one
19 appeared to be a citrate toxicity reaction. But still the
20 rate of reactions are amazingly low for this period of time.

21 We also looked at our regulatory experience with
22 these devices. Since the Medical Device Amendments were
23 enacted, we have reviewed approximately 15 premarket notifi-
24 cation or 510(k) filings for centrifugal-based cell sepa-
25 rators. Most of these were not actually new devices by new

1 companies but they were actually modifications to existing
2 devices, modifications that actually improved the safety and
3 effectiveness of the device over the years. We know of no
4 health risks associated with the marketing of these devices
5 during this period of time.

6 Based on this information and the comments that we
7 received, we consider that the devices today are safe and
8 effective for their intended use. We feel that we have a
9 decade of experience and technological advancements since the
10 original Hematology and Pathology Device Panel met in the
11 1970s. We also agree that we are to the point now that
12 enough information is known about these devices that we can
13 develop suitable and acceptable performance standards for the
14 devices.

15 It is our position that these devices should be
16 reclassified into Class II and the FDA asks you to consider
17 making a recommendation to that effect.

18 DR. KEATING: Thank you, Mary. Are there any
19 questions? This seems like a straightforward request, with a
20 fair amount of information associated with it. Yes, Bill?

21 DR. SHERWOOD: There is at least one device now,
22 and maybe some devices of the future that might combine a
23 centrifugal component with a filtration component. As I
24 recall, there is a little cartridge that combines the
25 centrifugation force against the membrane. How would those

1 that have combined actions be treated in the future?

2 MS. GUSTAFSON: I may need some help with this, but
3 at the present time, if it has a filtration component I
4 believe it would be Class III until someone asks us to
5 reconsider reclassification of those.

6 DR. KEATING: So we are not actually talking about
7 that particular piece of equipment at this point.

8 MS. GUSTAFSON: Yes, we are talking about the
9 straight centrifugal-based cell separators.

10 DR. KEATING: Right. Does anyone have a problem
11 with reclassifying the centrifugal-based cell separator from
12 a Class III to a Class II?

13 All in favor?

14 (Show of hands)

15 I think you got a unanimous vote, Mary.

16 MS. GUSTAFSON: Thank you.

17 DR. KEATING: Are there any other issues to come
18 before this Committee? Hearing none, we will adjourn the
19 meeting. Thank you for your attendance.

20 (Whereupon, at 11:30 a.m., the Committee adjourned)

Certificate of Reporter, Transcriber and Proofreader

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We, the undersigned, do hereby certify that the foregoing pages, numbers 1 through 107, inclusive, are the true, accurate and complete transcript prepared from the reporting by Marika Baversheff in attendance at the above identified hearings, in accordance with the applicable provisions of the current GSA professional verbatim reporting and transcription contract, and have verified the accuracy of the transcript by (1) comparing the typewritten transcript against the reporting or recording accomplished at the hearings and (2) comparing final proofed typewritten transcript against the reporting or recording accomplished at the hearings.

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