

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

Friday,
October 17, 1997

Grand Ballroom
Holiday Inn Gaithersburg
2 Montgomery Village Avenue
Gaithersburg, Maryland

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P R O C E E D I N G S (8:00 a.m.)

1
2 MS. DAPOLITO: Good morning, members of the
3 committee, invited guests, and public participants. I
4 would like to welcome all of you to this, the 21st meeting
5 of the Biological Response Modifiers Advisory Committee. I
6 am Gail Dapolito, the designated federal official for this
7 meeting. Should anyone in the audience need to communicate
8 with the committee, please do not directly approach the
9 committee members. Please wait for a scheduled break in
10 the agenda and see me. I will relay your questions to the
11 committee.

12 Today's presentations and committee discussions
13 will be open to the public. At this time, I would like to
14 announce that in the absence of Dr. Julie Vose, Dr.
15 Virginia Broudy will be the acting chair of today's
16 meeting.

17 I would now like to ask that the members seated
18 at the head table please introduce themselves to the
19 audience by stating their name and affiliation. If we
20 could start on my left with you, Dr. Hunsicker.

21 DR. HUNSICKER: I'm Larry Hunsicker from the
22 University of Iowa Hospitals and Clinics.

23 DR. JONSSON: I'm Johann Jonsson. I'm a
24 ~~transplant surgeon in Northern Virginia, director of the~~

1 kidney and transplant program at the INOVA Fairfax
2 Hospital.

3 DR. BERMAN: I'm Ellin Berman from Memorial
4 Sloan-Kettering Cancer Center in New York.

5 DR. WOODLE: Steve Woodle from the University
6 of Chicago.

7 DR. ANDERSON: French Anderson, USC School of
8 Medicine.

9 DR. O'FALLON: Mike O'Fallon, Mayo Clinic.

10 DR. BROUDY: Virginia Broudy, University of
11 Washington.

12 DR. KLEINERMAN: Eugenie Kleinerman, M.D.
13 Anderson Cancer Center.

14 DR. GRIMM: Paul Grimm, University of Manitoba,
15 pediatric nephrologist.

16 MS. MEYERS: Abbey Meyers, National
17 Organization for Rare Disorders.

18 DR. SUTHANTHIRAN: Manikkam Suthanthiran from
19 New York Hospital-Cornell Medical Center.

20 DR. STEIN: Katie Stein, Division of Monoclonal
21 Antibodies, CBER.

22 DR. WEISS: Karen Weiss, Division of Clinical
23 Trials, Center for Biologics.

24 MS. DAPOLITO: We have a couple of members who

1 will be joining us late, Dr. Hugh Auchincloss and Dr.
2 Richard Goldsby. Dr. Carole Miller from Johns Hopkins has
3 just joined us. In addition, we have two members who won't
4 be here today, Dr. Hardigan and Dr. Hann.

5 I would now like to read into the public record
6 the conflict of interest statement for this meeting.

7 "Pursuant to the authority granted under the committee
8 charter, the commissioner of FDA has appointed Dr. Lawrence
9 Hunsicker and Dr. Manikkam Suthanthiran as temporary voting
10 members for Topic 1. In addition, the director, Center for
11 Biologics Evaluation and Research, has appointed Dr. Paul
12 Grimm and Dr. Johann Jonsson as temporary voting members
13 for Topic 1, and Dr. Janice Gabrilove as a temporary voting
14 member for Topic 2.

15 "Based on the agenda made available, it has
16 been determined that all financial interests in firms
17 regulated by the Center for Biologics Evaluation and
18 Research which have been reported by the participating
19 members and consultants as of this date present no
20 potential for an appearance of a conflict of interest at
21 this meeting, with the following notations to preclude even
22 the appearance of a conflict of interest:

23 "Dr. French Anderson, a waiver was approved by
24 the agency permitting his full participation in the

1 committee discussions and deliberations on Topic 1.

2 "Dr. Hugh Auchincloss, a waiver was approved by
3 the agency permitting limited participation in the
4 committee discussions and deliberations for Topic 2. Dr.
5 Auchincloss will not vote on Topic 2. Dr. Auchincloss has
6 disclosed he will receive compensation for attendance in
7 the future for seminars supported by a regulated firm.

8 "Dr. Virginia Broudy, the agency approved a
9 waiver on November 8, 1995, regarding stock holdings. The
10 holdings remain unchanged.

11 "Dr. Janice Gabrilove, the agency approved a
12 waiver permitting her full participation in the committee
13 discussions and deliberations on Topic 2.

14 "Dr. Paul Grimm, a waiver was approved by the
15 agency permitting his full participation in the discussions
16 and deliberations on Topic 1.

17 "Dr. Lawrence Hunsicker, a waiver was approved
18 by the agency permitting his full participation in the
19 discussions and deliberations on Topic 1.

20 "Dr. Eugenie Kleinerman, a waiver was approved
21 by the agency permitting her full participation in the
22 committee's discussions and deliberations on Topic 1. Dr.
23 Kleinerman is excluded from participating in Topic 2.

24 ~~"Ms. Abbey Meyers reported that her employer,~~

1 the National Organization for Rare Diseases, received
2 donations in 1997 from regulated firms that could be
3 affected by the committee discussions.

4 "Dr. Carole Miller disclosed participation in
5 two unrelated grants awarded by a regulated firm. Dr.
6 Miller has reported receiving compensation from a regulated
7 firm for speaking on a subject unrelated to the particular
8 matter that the committee is discussing.

9 "Dr. Steve Woodle, a waiver was approved by the
10 agency to permit his limited participation in the
11 discussions of Topic 1. Dr. Woodle will not vote on this
12 topic.

13 "The following members, temporary voting
14 members, and consultants have no interests to disclose:
15 Drs. Berman, Goldsby, Hardigan, Jonsson, O'Fallon,
16 Suthanthiran, and Ms. Heinemann. In the event that the
17 discussions involve other products or firms not already on
18 the agenda, for which FDA's participants have a financial
19 interest, the participants are aware of the need to exclude
20 themselves from such involvement, and their exclusion will
21 be noted for the public record.

22 "A copy of the waivers are available by written
23 request under the Freedom of Information Act.

24 ~~"With respect to all other meeting~~

1 participants, we ask in the interest of fairness that they
2 address any current or previous financial involvement with
3 any firm whose product they wish to comment upon."

4 I would now like to turn the microphone over to
5 our acting chair, Dr. Virginia Broudy.

6 DR. BROUDY: Good morning. Next on the agenda
7 is the open public hearing. Gail, please call to the
8 microphone any speakers who have made requests to address
9 the committee.

10 MS. DAPOLITO: As part of the FDA advisory
11 committee meeting procedure, we hold an open public hearing
12 for members of the public who are not on the agenda and
13 would like to make a statement concerning matters pending
14 before the committee. I have not received any requests to
15 speak. Is there anyone in the audience at this time who
16 would like to make a presentation or address the committee
17 in this open public hearing for this morning's topic?

18 (No response.)

19 MS. DAPOLITO: I see no response. Should
20 anyone decide that they would like to address the
21 committee, there will be another open public hearing at the
22 start of this afternoon's session.

23 Dr. Broudy, I turn the microphone over to you.

24 DR. BROUDY: Thank you, Gail.

1 It's now time to move on to Topic 1, and I
2 believe we will start with a brief introduction by the FDA.

3 DR. RELLAHAN: Good morning. I'm Barbara
4 Rellahan. I'm the product reviewer from the Division of
5 Monoclonal Antibodies at CBER. This morning we're going to
6 be discussing biological license application 97-0736, which
7 is for the monoclonal antibody Zenapax. This BLA was
8 submitted to the FDA on June 10, 1997, and the FDA review
9 committee is listed on this slide.

10 Zenapax is a recombinant humanized monoclonal
11 antibody that is specific for the alpha chain of the human
12 IL-2 receptor, and it is being manufactured by Hoffmann-La
13 Roche, Inc. The proposed indication for Zenapax is for the
14 prophylaxis of acute organ rejection in patients receiving
15 renal transplants, and it is to be used concomitantly with
16 immunosuppressive regimens, which would include
17 cyclosporine-A and corticosteroids.

18 What I'm going to do in the next 5 minutes or
19 so is give you a very brief introduction into the structure
20 of Zenapax -- David Smith from Hoffmann-La Roche will go
21 into more depth -- and then I'm going to go over what the
22 proposed mechanism of action of Zenapax is and compare it
23 to the mechanism of action of the other prevailing
24 immunosuppressive drugs.

1 Again, Zenapax is a recombinant humanized
2 monoclonal antibody. Approximately 90 percent of it is of
3 human origin. It's an IgG1 immunoglobulin with a kappa
4 light chain. About 10 percent is of murine origin, and
5 this 10 percent consists pretty much exclusively of the
6 complementarity determining region of the antibody,
7 although a couple residues outside these regions were
8 conserved to help maintain the structural integrity of the
9 CDRs. The affinity of Zenapax for the alpha chain is
10 approximately 3×10^9 molar.

11 Now, T lymphocytes are the primary regulators
12 of antigen-specific immune responses, and so most, if not
13 all, of the prevailing immunosuppressive drugs are actually
14 aimed at regulating the activity of T lymphocytes. During
15 an antigen-specific T cell response, you can split the
16 response into two primary phases. The first phase involves
17 cross-linking of the T cell receptor which generates
18 signals, which leads to T cell activation. T cell
19 activation induces alterations in gene transcription, which
20 results in alterations in the surface receptors which are
21 expressed by T cells, and it also results in the production
22 of lymphokines, such as IL-2 and IL-4, by the T cell.

23 These early activation events allow for and
24 induce the second phase of the T cell response, which is

1 the proliferative phase. One of the receptors which is
2 actually altered during these early activation events is
3 the IL-2 receptor. The high-affinity IL-2 receptor is
4 composed of three unique chains. The alpha chain and the
5 beta chain in the receptor are able to bind IL-2, but it is
6 the alpha chain that has the highest affinity and is
7 responsible for the generation of a high-affinity IL-2
8 receptor. The beta chain and the gamma chain are the
9 signal-transducing elements of this receptor. These two
10 chains are expressed both in resting T cells and in
11 activated T cells. The alpha chain is not expressed in
12 resting T cells, and it requires activation events for its
13 surface expression.

14 Studies that were done on the murine antibody
15 that was used to generate Zenapax have shown that this
16 antibody is capable of competitively inhibiting the ability
17 of IL-2 to bind to the high-affinity IL-2 receptor.

18 Now, keeping all this in mind, we can move on
19 and split the mechanism of action of different
20 immunosuppressive drugs into three categories. The first
21 category includes agents which simply result in a depletion
22 of T cells, and this is thought to be the mechanism of
23 action of the monoclonal anti-T cell receptor antibody
24 OKT3. The second group of agents results in an inhibition

1 of T cell receptor-mediated activation events. This group
2 includes the drugs cyclosporine-A and FK506, and these
3 drugs are thought to affect the activity of immunophilins,
4 which is required for T cell activation. The third group
5 of agents appears to inhibit the proliferative phase of the
6 T cell response, and this group includes steroids,
7 azathioprine, mycophenolate mofetil, and Zenapax.

8 Now, steroids, azathioprine, and mycophenolate
9 mofetil inhibit proliferation by inhibiting or altering
10 gene transcription events and metabolic events which are
11 required for cellular proliferation. Zenapax is unique
12 from these other agents by virtue of the fact that it is
13 specific for the alpha chain of the IL-2 receptor and,
14 therefore, only affects the activated T cells, and its
15 proposed mechanism of action is to inhibit the ability of
16 IL-2 to bind to the high-affinity IL-2 receptor and thereby
17 inhibit IL-2-dependent proliferation of activated T cells.

18 This proposed mechanism of action is actually
19 supported by data that was generated during the clinical
20 trials of Zenapax, which showed that after a single
21 infusion of Zenapax, there is saturation of the high-
22 affinity IL-2 receptors by 10 hours, and the IL-2 receptors
23 remain saturated for up to 64 days. With multiple
24 infusions of Zenapax, you can get saturation of the high

1 affinity IL-2 receptor for up to 120 days.

2 Clearance of the activated T cells doesn't
3 appear to be a major mechanism, because Zenapax is an IgG1
4 antibody, and it binds very poorly to FC receptors, plus,
5 during the clinical studies, there was not a significant
6 reduction in the number of CD25-positive cells. Therefore,
7 the proposed mechanism of action of Zenapax would be that
8 it interferes with the ability of IL-2 to bind to the high-
9 affinity IL-2 receptor and thereby inhibits the IL-2-
10 dependent proliferation and expansion of activated T cells.

11 That concludes my introduction into the
12 mechanism of action of Zenapax, and unless there are any
13 questions, we can move on to the introduction by David
14 Smith.

15 Thank you.

16 DR. SMITH: Barbara and I talked about -- well,
17 first of all, I'm David Smith from Hoffmann-La Roche, and
18 I'd like to thank the Division of Monoclonals for allowing
19 us to present Zenapax to the committee today.

20 Barbara and I talked about our presentations a
21 few weeks ago, and it turns out that we were so much on the
22 same wavelength, that I think we came up with very similar
23 introductions. So I think what I'd like to do is go
24 ~~through my introduction and just highlight a few points.~~

1 You've already seen the proposed indication,
2 the wording. I just want to point out that Zenapax is a
3 unique biologic product, and we're asking for an indication
4 in renal transplant patients at this time. Zenapax is part
5 of an immunosuppressive regimen, and that regimen should
6 contain cyclosporine and steroids.

7 I think you're aware that this is a product of
8 recombinant DNA technology, and we have reserved the
9 complimentarity determining region from a murine monoclonal
10 antibody and grafted that gene sequence onto a human IgG
11 sequence. The resulting product is what's referred to as a
12 humanized monoclonal antibody. The currently approved
13 generic name is dacliximab.

14 Just so we don't have anymore confusion, the
15 "xi" infix really refers to chimeric antibody. Since this
16 is a humanized antibody, the proposed generic name is
17 daclizumab, with a "zu" infix. Because of the development
18 history of this product, a number of people that you'll
19 hear from today will refer to this by a number of different
20 names: anti-CD25, HAT, or humanized anti-Tac.

21 The Zenapax clinical program began in 1992.
22 The first indication we pursued was for prevention of graft
23 versus host disease following bone marrow transplant. That
24 clinical program was discontinued, and we're here today to

1 talk about the renal transplant program. That program
2 began in 1994 and enrolled a total of 630 patients; 336 of
3 them received Zenapax. That number is important because,
4 as you'll see later on, Dr. Light's going to talk about
5 some of the safety data. We pooled data from a number of
6 our studies because of nearly identical study design.

7 There were four studies in the biologics
8 license application. We demonstrated efficacy in an
9 initial study that enrolled a total of 19 patients. We
10 also conducted a Phase I/II study in which Zenapax was
11 added to an immunosuppressive regimen that contained
12 CellCept, cyclosporine, and steroids. This was a
13 pharmacokinetics and safety study that enrolled 76
14 patients. There were two randomized Phase III double-
15 blind, placebo-controlled studies in our application. We
16 refer to these as the triple-therapy study and the double-
17 therapy study. The triple-therapy study added Zenapax to a
18 standard regimen of azathioprine, cyclosporine, and
19 steroids; the other study added Zenapax to a regimen of
20 cyclosporine and steroids.

21 In a minute, Dr. Flavio Vincenti from the
22 University of California will take the podium. Dr.
23 Vincenti is a nephrologist who has been active in
24 immunosuppressive research for 20 years. Dr. Vincenti

1 participated in three of the four studies in our license
2 application. Dr. Vincenti is going to tell you about the
3 state of the art in immunosuppression. He's going to go
4 through some of the currently available immunosuppressive
5 agents, and he's going to help define a role for Zenapax in
6 immunosuppressive regimens.

7 Following Dr. Vincenti, Dr. Susan Light will
8 present some specific elements of the mechanism of action,
9 and then go through the study design for our Phase III
10 study. Susan will then go into some detail on our efficacy
11 results that demonstrate a clinical benefit for Zenapax,
12 and she's also going to go into some detail on our
13 excellent safety profile.

14 Roche will conclude this morning with Dr.
15 Robert Kirkman. Dr. Kirkman is a transplant surgeon from
16 Brigham and Women's Hospital at Harvard University. Dr.
17 Kirkman will add some clinical perspective to our results
18 and in particular focus on a risk/benefit assessment.

19 Dr. Vincenti?

20 DR. VINCENTI: Good morning. My name is Flavio
21 Vincenti. I'm a transplant nephrologist at the University
22 of California, San Francisco. I have participated in
23 several trials with Zenapax, and I'm delighted to be here
24 as part of the team presenting the Zenapax Phase III trials

1 to you.

2 In the first slide, I'd like to summarize the
3 drug's development over the past 50 years, as well as look
4 at the drugs coming down through the pipeline as we reach
5 the millennium. Immunosuppression started in 1960, when
6 several pioneers combined azathioprine with cortisone to
7 initiate the first effective immunosuppression. Several
8 polyclonal anti-lymphocyte agents were introduced in the
9 1970s, although only ATGAM was approved in 1982 for
10 treatment of rejection.

11 The new era of immunosuppression can be traced
12 back to the introduction of cyclosporine in 1983 that
13 resulted in a significant reduction in rejection and
14 improved outcome. In 1986 OKT3 was introduced for the
15 therapy of rejection and provided us a powerful tool to
16 reverse rejection, especially steroid-resistant rejection,
17 as well as severe vascular rejection. In the 1980s we had
18 two exciting drugs, mycophenolate mofetil and tacrolimus,
19 and then today as we stand in front of you to present the
20 data on Zenapax, the humanized anti-CD25, I believe that
21 this drug will mark the renaissance of immunosuppressive
22 therapy which is protein-based, with selectivity and little
23 toxicity.

24 And, finally, as we approach the millennium, as

1 you can see, there is a slew of new drugs, small molecules,
2 several humanized antibodies, and then some very novel
3 peptides, like antisense oligonucleotides and MHT peptides.

4 Now, the thrust of most of the
5 immunosuppressive drug development had been to reduce acute
6 rejection. Increased morbidity is associated with
7 augmented anti-rejection therapy. Acute rejection is still
8 the best predictor for the development of chronic
9 rejection, and there are increased costs associated with
10 treatment of rejection.

11 I would like next to personalize the impact of
12 these drugs on transplantation over the past 20 years. I
13 joined the faculty at UCSF in 1976/1977 as a transplant
14 nephrologist on the transplant team. At that point, in
15 cadaver transplants, rejection rates were at 90 percent,
16 graft survival at 1 year was 50 percent, 20 percent of all
17 patients never left the hospital with a functioning kidney,
18 had a nephrectomy by the first month, and aseptic necrosis,
19 a hated and disabling complication for patients, occurred
20 in at least 12 percent of patients. Twenty years later,
21 rejection rates have dropped to 20 to 25 percent,
22 especially with the introduction of CellCept, graft
23 survival rate in cadaver transplants are 85 percent and
24 going north, graft loss at 1 month is a rare event these

1 days, and aseptic necrosis has really declined
2 tremendously, to 1 or less percent, meaning that the
3 orthopedic surgeon these days doesn't have to be part of
4 the transplant team.

5 Now, for all the improved outcomes that I have
6 described, the next slide shows that while patient survival
7 on a 1- to 2-year basis and the yearly graft survival rates
8 have improved over the past 20 years, and with a major
9 improvement with the introduction of cyclosporine, the
10 half-life of graft, which is a good measurement of long-
11 term function, has improved very slightly, from maybe 7.5
12 to 9.5 years, meaning these are the grafts that function at
13 1 year, and half of them will be functioning at 7.5 or 9.5
14 years.

15 The continuous loss of these kidneys is due to
16 a concentrate of graft loss secondary to chronic rejection,
17 or better yet calling chronic transplant nephropathy. Now,
18 the etiology of chronic transplant nephropathy is
19 multifactorial and includes both immunigated as well as
20 non-immuted mechanisms. Acute rejection is still a major
21 risk factor. This is data derived from UNOS, showing that
22 patients who have no rejection have the best long-term
23 survival, those who have rejection have the poorest long-
24 term survival, and those who have a rejection that is

1 reversed have an outcome which is somewhere in between.

2 Delayed graft function is also closely
3 associated with rejection. Patients who have no delayed
4 graft function have much better long-term survival than
5 those that have delayed graft function, defined here as the
6 need for dialysis in the immediate first week after
7 transplantation. Now, delayed graft function with a
8 perfusion injury leads to non-specific inflammation that
9 leads to renal injury that makes the graft more susceptible
10 to rejection.

11 A major problem with acute rejection is that
12 the recognition of the subclinical rejection is still a
13 problem. We have had patients that never had the clinical
14 episode of rejection, yet surfaced many years later with
15 chronic rejection. Other important mechanisms are chronic
16 activation of the immune system, whether with T cells,
17 antidonor antibodies, platelets, and growth factors.

18 Now, donor pathology is another important
19 contributing factor to the progression of disease in the
20 graft. Especially the presence of sclerosis or vascular
21 disease can only be aggravated, especially with the use of
22 some of the immunosuppressive agents, such as cyclosporine
23 and tacrolimus. Hyperlipidemia, obviously, can deteriorate
24 renal function because of the progression of the vascular

1 disease. Glomerular hypertension and hyperfiltration are
2 well known non-immune mechanisms that produce chronic renal
3 failure, and especially in the kidney, with some decreased
4 nephron mass and with the addition of some of the
5 immunosuppressive agents, this can be certainly
6 accelerated. And, finally, both cyclosporine and
7 tacrolimus can produce ischemia-related fibrosis, and
8 clearly this is another major factor in progression of the
9 disease.

10 So while we have a lot to celebrate in the past
11 25 years in terms of improved outcome, clearly there are
12 still many issues that need to be resolved, and the next
13 slide shows some of the unmet needs that are currently
14 present in transplantation. The first one is worsening
15 organ shortage. We have close to 40,000 patients awaiting
16 cadaver transplants, yet we only get about 10,000 cadaveric
17 kidneys every year, with another 2,500 donated from living
18 donors, and this has not changed much in the past few
19 years. So, clearly the need for Zenapax is there.

20 Highly sensitized patients, patients who have
21 high levels of reactive antibodies, still have a problem
22 finding cross-matched negative kidneys, so that these
23 antibodies are still a value for transplantation. Acute
24 rejection, as I said, is less threatening, but I think the

1 optimal regimen is still unclear. Optimal immunotherapy
2 for delayed graft function is still not there, and
3 hopefully with some of the monoclonal targeting adhesion
4 molecules, we may be better able to deal with this. Then
5 we have to deal with the chronic drug toxicity and the
6 long-term complications of these drugs, from nephrotoxicity
7 to cardiovascular events, malignancy, and hepatotoxicity.

8 I'd like to turn now to the various
9 immunosuppressive agents that are used in 1997 and maybe
10 give you a look to the future in terms of what their use
11 may be. The first two agents I will be discussing, both of
12 them are anti-T cell agents. ATGAM is a polyclonal anti-
13 lymphocyte agent. Its current use is primarily for
14 induction in harvest patients, as well as for delayed graft
15 function. There is some use also with ATGAM for rejection.
16 Its major drawback is that we have to give a lot of protein
17 with it, and patients get susceptible to serum sickness. I
18 believe that this drug will be phased out in the future.
19 Quite frankly, the time of polyclonal antibody has come and
20 is going.

21 The next drug is OKT3, the murine anti-CD3
22 monoclonal antibody. I think this drug is extremely
23 effective for induction therapy for high-risk patients or
24 patients with delayed graft function. It is, again, the

1 drug of choice for treating patients with severe rejection
2 or steroid-resistant rejection. The major drawback is the
3 cytokine release syndrome. I think we're all familiar with
4 this syndrome. Patients have severe chills and fever, they
5 can develop aseptic meningitis. Some of these patients
6 develop ARDS, require intubation, and spend time in the
7 intensive care unit. Future use of OKT3, I think the
8 humanized anti-CD25 will replace this drug for induction
9 therapy, and hopefully for the future for rejection
10 therapy, we will have a new generation of non-activating
11 humanized anti-CD3 antibodies.

12 Steroids. This is the type of drug that our
13 patients like the least or dislike the most. Currently
14 we're trying to accelerate the taper of steroids so that we
15 can minimize their major side effects, whether cosmetic,
16 bone, or metabolic. I think in the future we should have
17 immunosuppressive regimens that spare steroids completely.

18 Azathioprine, its current use has diminished
19 tremendously, being replaced with mycophenolate mofetil.
20 At our center, we use it only in patients who are
21 intolerant to mycophenolate mofetil. Again, its major
22 drawback has been somewhat decreased effectiveness, and I
23 think in the future it will be probably phased out.

24 ~~Mycophenolate mofetil, introduced in the early~~

1 1990s, has replaced azathioprine as part of the triple-
2 therapy regimen and is certainly quite effective. The
3 major drawback is the increase in CMV infection, and then
4 we have to remember it's a new drug, so we really don't
5 know what the long-term effects of this drug could be. The
6 future use, I think its role in maintenance
7 immunosuppression is still being defined. Do we need it
8 beyond the first 6 months? And I think a key to that is
9 whether it has the ability to prevent chronic rejection.

10 Cyclosporine, an immunosuppressant, certainly
11 is still the drug of choice for patients for primary
12 transplant. There has been a trend to shift to the
13 microemulsion preparation Neoral. The major drawback with
14 cyclosporine is, obviously, the nephrotoxicity. There are
15 many cosmetic problems, gingival hyperplasia, and there
16 seems to be some reduced effectiveness in the very high-
17 risk patients. In the future, there may be a shift to
18 generic cyclosporine. I think the transplant community has
19 to be convinced, one, that it is safe, and, secondly, there
20 has to be a certain amount of cost differential with a
21 brand name.

22 Tacrolimus was, again, introduced in the early
23 1990s. Its current use is in high-risk patients and also
24 some patients who are concerned about the cosmetic problems

1 with cyclosporine, again gingival hyperplasia. A major
2 drawback, again, is it shares the nephrotoxicity of
3 cyclosporine, and it can produce a significant incidence of
4 de novo insulin-dependent diabetes mellitus. Its future
5 use, I think tacrolimus would be an important player, but
6 it may be a niche player.

7 Now, a review of all these drugs, it's clear
8 that while effective, they have major drawbacks. So when
9 we look to the future, what are the desirable properties
10 that we would like to see in our immunosuppressive drugs?
11 A sort of wish list, and the desirable immunologic
12 properties I've really summarized into two concise wishes.
13 One is selectivity. I think we'd like to have our drugs in
14 the future to inhibit the immune reaction in the cells that
15 target the graft so that the patient may remain completely
16 immunocompetent. The second need is to have drugs that can
17 induce more tolerance, and I think this is going to be the
18 one way that we can improve our long-term graft survival.

19 My wish list for desirable non-
20 immunosuppressive properties is somewhat longer. I think
21 it's time that we use drugs and we put together
22 immunosuppressive protocols that lack nephrotoxicity. We
23 also would like to have drugs that do not add to the
24 cardiovascular risk of our patients. Half of our patients

1 die of cardiovascular disease. So we want drugs that do
2 not produce more hypertension or more hyperlipidemia. We
3 also would like to have drugs that do not produce diabetes.
4 We also would like to have drugs that are skeleton
5 friendly, don't produce osteoporosis, osteonecrosis. And
6 we also want to have drugs that will not adversely affect
7 the quality of life for our patients. We would like to
8 have our patients to be fully functional, but we also all
9 would like to have our patients, as much as possible, to be
10 happy.

11 I think that Zenapax is going to be a first
12 important step in achieving these goals.

13 Thank you.

14 DR. LIGHT: Good morning. My name is Susan
15 Light, and I've been the clinical leader on the Zenapax
16 development project since 1992. As Dr. Vincenti mentioned,
17 we've made significant progress in the last 20 years in the
18 prevention of acute rejection, but as he also mentioned,
19 there still is a need and desire on the part of the
20 transplant community to have additional therapies which are
21 safe and effective and can prevent acute rejection. The
22 goal is to have therapies which can reduce rejection
23 without adding to the toxicity or increasing the
24 complications from infection of the current regimens.

1 We've already seen a very lovely presentation
2 of the mechanism action of Zenapax, so I'm not sure I'm
3 going to spend much time on this slide. Just to point out
4 again the receptor where Zenapax is binding, blocking IL-2.

5 This is a graphic rendition of the IL-2
6 receptor showing the three polypeptide chains, the alpha,
7 beta, and gamma chains, in IL-2 binding. The epitope for
8 Zenapax is on the alpha chain, and when it binds, binding
9 from IL-2 is prevented.

10 If a picture is worth a thousand words, then
11 there's not much to say about this slide, because this
12 really shows what a humanized antibody is, that it has an
13 IgG1 framework that is the same as the parent human
14 antibody, retaining only about 10 percent murine sequences
15 from the complementarity determining region of the murine
16 monoclonal. This allows for the specificity of the
17 antibody while retaining the safety associated with the
18 human immunoglobulin.

19 We all know that there are many problems
20 associated with murine monoclonal antibodies. Some include
21 the immunogenicity resulting in antibody formation and in a
22 decreased serum half-life. The immunization process takes
23 advantage of the specificity of the monoclonal antibody
24 ~~that decreases immunogenicity and results in a prolonged~~

1 serum half-life. Zenapax has achieved this, and you'll see
2 from our clinical data that we have a safe and effective
3 biologic product which allows for prolonged dosing and
4 coverage through the critical first few months post-
5 transplant.

6 We conducted two randomized, double-blind,
7 placebo-controlled trials where Zenapax was added to
8 standard immunosuppressive therapy, with the goal of
9 preventing acute rejection in renal transplant patients.
10 We tried to keep the study design as similar as possible
11 for the two studies so that data could be looked at side by
12 side.

13 The similarities in the two studies include the
14 fact that all patients on both studies were receiving a
15 transplant from a cadaveric donor. Only first transplant
16 patients were entered into the studies. All patients
17 received the same dose of Zenapax. Our dosing regimen was
18 1 milligram per kilogram given every 2 weeks, for a total
19 of five doses. The first dose was given prior to
20 transplant, so patients received the antibody on Days 0,
21 14, 28, 42, and 56. In both studies the primary efficacy
22 endpoint was the incidence of acute rejection at 6 months
23 post-transplant.

24 ~~There were differences between the two studies,~~

1 and I'll refer to them as the double-therapy study and the
2 triple-therapy study. The double-therapy study had
3 baseline immunosuppression with cyclosporine and steroids.
4 This study was conducted primarily in Europe, Canada, and
5 Australia, and there were 19 centers on this study. Two
6 hundred and seventy-five patients were entered. The
7 triple-therapy study was cyclosporine, steroids, and
8 azathioprine. This was a primarily U.S.-based study, and
9 there were 260 patients. So we did not have a geographical
10 distinction between the two studies, but rather we allowed
11 the centers to choose what would have been the standard
12 regimen at their center that Zenapax was added to.

13 The other important differences had to do with
14 the use of some medications. It was not possible to get
15 investigators from 19 centers and nine different countries
16 to agree on a standard steroid regimen for either
17 prophylaxis or treatment of rejection, and so the agreement
18 there was that on the double-therapy study, the use of
19 steroids for both treatment and prevention of rejection
20 would be per institutional protocol.

21 The same was true for CMV prophylaxis. On the
22 triple-therapy study, the centers agreed to use a pretty
23 rigorous proscribed regimen for steroid use. CMV
24 prophylaxis was required on the triple therapy study for

1 all patients except those who were CMV-negative and
2 received their kidneys from a CMV-negative donor. As I
3 mentioned, on the triple-therapy study, only CMV-
4 positive/negative pairs were required to have prophylaxis,
5 and it was optional for other groups, and it was at the
6 discretion of the center.

7 Once again, the primary efficacy endpoint was
8 the incidence of biopsy-proven acute rejection by local
9 histopathologic review at 6 months post-transplant. We had
10 a number of secondary efficacy endpoints. We looked at the
11 time to acute rejection, the number of acute rejection
12 episodes per patient, and the number of patients who
13 experienced more than one rejection.

14 Since Zenapax was given prior to transplant,
15 there was some concern about the potential for damage to
16 the transplanted kidney, so we looked at the incidence of
17 delayed graft function as an efficacy endpoint. We used
18 the use of anti-lymphocyte therapy to treat rejection as a
19 surrogate marker for severity of rejection, and we also
20 looked at the cumulative dose of corticosteroids.

21 We have data on infectious episodes for the
22 first 6 months post-transplant. We have data at 6 and 12
23 months for patient survival, graft survival, and the
24 incidence of lymphomas and other malignancies. We

1 evaluated renal function by serum creatinine and GFR at 6
2 and 12 months, and at 3 years we plan to collect data on
3 all patients for patient survival, graft survival, renal
4 function, and malignancies.

5 We chose a dose regimen that we believed would
6 be safe and effective in preventing acute rejection in the
7 greatest proportion of patients. This dose regimen was 1
8 milligram per kilogram every 2 weeks, for five doses. This
9 was based on a variety of data from preclinical and
10 clinical studies. Our preclinical data show that you need
11 a serum level of about 5 to 10 micrograms per mL to
12 saturate the receptor and prevent IL-2 binding. The five
13 doses allow for saturation for about 4 months post-
14 transplant. The majority of rejection episodes occur in
15 the first 3 months post-transplant, so we felt it was
16 really critical to have the antibody bound to the receptor
17 for at least 3 months, and a little extra wouldn't be bad
18 either.

19 This slide shows some data to support this.
20 This is pharmacokinetics modeling from our Phase I dose-
21 finding study, where, on the left, we have a milligram per
22 kilogram given every 2 weeks and half a milligram per
23 kilogram given every 2 weeks. The dotted line is 5
24 micrograms per mL. As you can see, with the milligram per

1 kilogram every 2 weeks, we are above 5 micrograms per mL
2 for the majority of the 70 days post-transplant, but this
3 is not achieved when one doses with half a milligram per
4 kilogram.

5 This slide shows the percent of peripheral
6 blood lymphocytes that express to Tac antigen. This was in
7 10 placebo patients and 10 patients who received Zenapax.
8 This is days post-transplant, with the days of the dose of
9 Zenapax noted here. Immediately after transplant, the Tac
10 receptor is not detected by the fluorescein antibody in
11 this assay, because it is blocked by the exogenous Zenapax.
12 At 4 months post-transplant, still not there. Our next
13 time point at 6 months shows the receptor is free to bind
14 to exogenous anti-CD25, and the levels have returned to
15 that of the placebo group. This also demonstrates the
16 reversibility of this therapy.

17 We also knew there was no dose-limiting
18 toxicity to Zenapax, so a dose of 1 milligram per kilogram
19 should not raise any safety concerns, nor would dosing for
20 2 months. And we had some preliminary efficacy data from
21 an uncontrolled Phase I study, where 16 patients received
22 five doses of Zenapax on a triple-therapy regimen, and the
23 only patient who experienced rejection was the one who
24 received .5 milligrams per kilogram.

1 As I mentioned, the studies were randomized,
2 and the randomization was successful. Each study was
3 balanced for 10 of the baseline characteristics and
4 demographic factors, except that in the triple-therapy
5 study, in the Zenapax arm there were more CMV-
6 negative/negative pairs than compared to the placebo group.

7 We planned to have 260 patients on each of the
8 studies. We actually exceeded that, with 275 on the
9 double-therapy study, and we had 260 on the triple therapy.
10 All patients are included in all analyses.

11 Over 80 percent of patients completed the five
12 doses of Zenapax or placebo. The most common reason for
13 dropping out was delayed graft function. If a patient
14 experienced delayed graft function and the investigator
15 chose to stop cyclosporine and give ATGAM or OKT3, then the
16 patient did not receive anymore study drug, because it
17 wouldn't have been possible to evaluate efficacy, and we
18 didn't know what the consequences would be in terms of
19 immunosuppression of having Zenapax on top of ATGAM and
20 OKT3. So this accounts for about half of the 20 percent of
21 patients who dropped out. The other half were various
22 administrative reasons and some infections. But all
23 patients were followed for the 6 months post-transplant.

24 Moving on to the efficacy data, we achieved our

1 primary efficacy endpoint and we have demonstrated that the
2 addition of Zenapax to double or triple immunosuppressive
3 therapy results in a significant decrease in the incidence
4 of acute rejection 6 months post-transplant. For the
5 double-therapy study, this represented a 40 percent
6 decrease in acute rejection. In the triple-therapy study,
7 this was a 37 percent decrease in acute rejection.

8 This is the Kaplan-Meier estimated probability
9 of acute rejection at 6 months post-transplant, and you can
10 see there's a significant increase in the time to acute
11 rejection in patients who have received Zenapax. This is
12 the triple-therapy study. There is a comparable increase
13 in time to first rejection for the double-therapy study.

14 There were a small number of patients who did
15 not have biopsy-proven rejection, but received a course of
16 therapy for rejection. They either had a medical
17 contraindication to having a biopsy or had a biopsy that
18 was read as negative, but the patient received the
19 treatment anyway because the clinical signs and symptoms
20 suggested rejection. These patients were counted as having
21 presumptive rejection, and when those patients, which are
22 equally distributed in the four different arms, are added
23 to the patients who had biopsy-proven rejection, the
24 benefit to receiving Zenapax remains.

1 There was no difference in the incidence of
2 delayed graft function between the two treatment arms,
3 although there was a difference between the two studies.
4 In the double-therapy study, the incidence of delayed graft
5 function was higher than on the triple-therapy study. This
6 may reflect the practices in Europe with the handling of
7 the kidneys and the fact that on the double-therapy study,
8 there may be a tendency for patients to receive more
9 cyclosporine in the early post-transplant period.
10 Nonetheless, patients on the double-therapy study were no
11 more likely to drop out for delayed function than they were
12 on the triple-therapy study.

13 There was less anti-lymphocyte therapy given to
14 patients who received Zenapax for the treatment of
15 rejection. Patients on the double-therapy study had less
16 anti-lymphocyte therapy, and this achieved statistical
17 significance, but was not significant on the triple-therapy
18 study.

19 The results show a significant decrease in the
20 cumulative dose of corticosteroids at 6 months on the
21 double-therapy study, but there was no difference on the
22 triple-therapy study. It's important to remember here that
23 on the triple-therapy study, the investigators were asked
24 ~~to follow a pretty rigorous steroid regimen for both~~

1 prevention and rejection, but on double therapy there was a
2 much wider range of steroid use, based on the institutional
3 protocol.

4 This slide shows the data from the analysis of
5 graft survival, and we have data from 6 and 12 months. At
6 6 months there was a significant improvement in graft
7 survival in the patients on the Zenapax arm on the triple-
8 therapy study. The P value was 0.02, but at 12 months the
9 P value became 0.08.

10 Patient survival was excellent in both studies.
11 In fact, at 6 months on the double-therapy study, there
12 were no deaths in the Zenapax group, and only one patient
13 had died at 1 year. The differences between Zenapax and
14 placebo patients on the double-therapy study were
15 significant at both 6 and 12 months. There were very few
16 deaths in the U.S. study, but there were fewer on the
17 Zenapax arm. It's important to note that there was only
18 one death from infection in the Zenapax group overall in
19 the two studies, but there were seven deaths from infection
20 in the placebo group in the two studies at 1 year.

21 We did an exploratory analysis of what's often
22 referred to as a combined endpoint, looking at acute
23 rejection, patient survival, and graft survival. Here it
24 just says "graft failure" because any patient who died with

1 a functioning graft was counted as having had graft
2 failure. When one looks at 12 months at this combined
3 endpoint, there is a statistically significant benefit to
4 having received Zenapax in both studies.

5 In conclusion, the efficacy data from these two
6 randomized studies show that Zenapax is effective in
7 reducing acute rejection in patients receiving first
8 cadaver transplants. There was a 37 to 40 percent decrease
9 in biopsy-proven rejection at 6 months post-transplant.
10 Patients on the double-therapy study received less
11 corticosteroids and less anti-lymphocyte therapy to treat
12 rejection. There was improved patient and graft survival,
13 and there was a benefit in the combined endpoint in both
14 studies at 12 months.

15 As one would expect with a humanized monoclonal
16 antibody with a very specific target, Zenapax has an
17 excellent safety profile, and I will go through some of the
18 safety data, including the adverse event profile:
19 laboratory abnormalities, infectious episodes, CMV
20 infections, lymphoproliferative disorders, and anti-
21 daclizumab antibodies.

22 As Dr. Smith mentioned earlier, we did pool the
23 data from the four studies for the safety analysis to
24 increase our chance of detecting a rare event that might be

1 attributable to Zenapax. I've discussed the two studies,
2 the double therapy and the triple therapy. The Phase I
3 study refers to the uncontrolled, open-label study where
4 there were 19 patients entered. Sixteen completed five
5 doses of Zenapax. The CellCept combination study entered
6 76 patients, only 75 were transplanted and received study
7 drug, and I'll discuss this study in more detail in a few
8 moments. The numbers for the safety database are 293 in
9 placebo and 336 in the Zenapax group.

10 There was no difference in overall adverse
11 events between the two treatment groups. Again, these
12 patients are undergoing renal transplant the day they're
13 receiving their first dose of Zenapax, and so it's not
14 unexpected to have such a high incidence of adverse events.
15 There was no difference in the serious adverse events
16 reported. There was no difference in the number of
17 patients who had premature withdrawal for adverse events.
18 In fact, the only difference that we observed was in the
19 number of deaths -- this is 1 year from the four studies --
20 4.4 percent versus 1.5 percent.

21 As I mentioned, when we first looked at the
22 adverse event profile, it was clear that most of the
23 adverse events that were being reported were a consequence
24 of undergoing transplant and taking certain of the

1 immunosuppressive medications, and there are no differences
2 here between the treatment groups. These are in decreasing
3 order of frequency.

4 We looked at specific toxicities that one might
5 expect to see with the administration of a protein, and I
6 think it's interesting to note that except for
7 hypertension, which was not significantly different between
8 the two groups, the other events were reported more
9 frequently in the placebo group.

10 We did not see any difference in marked lab
11 abnormalities between the Zenapax patients and the placebo
12 patients, although the high fasting glucose stands out
13 here. Fasting glucose was not a study that was required by
14 the protocol, and so the sample size here is actually very
15 small. It doesn't represent the whole population, and I
16 think it should not be interpreted as such.

17 Now, the infectious episode data was collected
18 differently on the CellCept study, so here when I present
19 the data on infectious episodes, we have a slightly smaller
20 sample size, 268 and 286. But overall there was no
21 difference in the overall infectious episodes between the
22 placebo group and the Zenapax group.

23 Looking at specific infections, again, very
24 comparable incidence. There was an increase in cellulitis

1 and wound infections of borderline significance here. Most
2 of these were mild and not to be of any clinical
3 consequence.

4 CMV is the infection that I think is of
5 greatest concern to the transplant community, and there was
6 no difference in the incidence of CMV infections between
7 the two treatment groups. Actually, CMV, as an
8 opportunistic infection, was collected separately on the
9 CellCept study. We're now back to the pooled database with
10 293 patients and 336, so of the 16 percent of the placebo
11 patients with CMV, 14 percent had viremia and 2 percent had
12 tissue-invasive disease. Here it was 12 percent viremia
13 and 2 percent tissue-invasive disease, and there were no
14 deaths from CMV.

15 We saw no increase in lymphomas or other
16 malignancies in our studies, although our sample size and
17 the follow-up is of somewhat short duration. There were
18 two lymphomas in the placebo group and two lymphomas in the
19 Zenapax group at 1 year, comparable numbers of non-melanoma
20 skin tumors -- I should mention that most of these were in
21 Australia -- and one patient who had a hepatic malignancy.

22 We looked very carefully and very arduously for
23 anti-daclizumab antibodies, and we had a highly sensitive
24 assay, and in fact we did detect antibodies to daclizumab

1 in 32 of 208 patients that were evaluable. This represents
2 a 15 percent incidence of antibodies. Although this
3 incidence was higher than we expected, we believe that
4 these antibodies are of no clinical significance, and I can
5 show this in the next few slides. We didn't see a decrease
6 in the serum levels of daclizumab in patients who were
7 antibody positive, there was no increased rejection in this
8 group, and there were no clinical adverse events suggesting
9 any kind of allergic response.

10 Now, these are serum levels at different time
11 points. Again, the fifth dose is the last dose, so Days 70
12 to 84 are after the dosing is completed, and the hatched
13 bars here are the patients who were antibody negative, and
14 the solid bars are those patients who scored positive on
15 our assay, and there's no difference. We know from our
16 experience in the primate model that when you give Zenapax
17 and the monkey develops antibodies, this is accompanied by
18 a very noted decrease in serum levels of Zenapax and
19 clinical occurrence of rejection.

20 We broke down the patients who scored positive.
21 On the double-therapy study, there were 22 patients who
22 scored positive. Five of those had rejection, 22 percent.
23 The antibody-negative patients, 32 had rejection, 31
24 percent. Triple therapy, two of the ten had rejection, and

1 13 of 73. So having an antibody in our assay did not
2 correlate with any increase in rejection, so our conclusion
3 is that these antibodies are not clinically relevant and
4 may represent some very low-affinity antibodies that the
5 body has produced.

6 We know that CellCept has become an important
7 part in the transplant regimen, so we started a study
8 before we completed our clinical trials to collect some
9 preliminary safety and PK data on the use of CellCept with
10 Zenapax in renal transplant patients. Again, we used the
11 same dosing regimen. We decided to conduct the study as a
12 double-blind, placebo-controlled trial so that we could
13 accurately interpret the adverse event reporting, so we
14 chose to do a two-to-one randomization. That way we would
15 have a little more data on the Zenapax/CellCept
16 combination. As I mentioned, there were 76 patients
17 entered and 75 who received drug.

18 The combination was very safe and well
19 tolerated. There was no pharmacokinetics interaction
20 between daclizumab and mycophenolic acid, and there was a
21 trend toward less rejection in the patients who received
22 quadruple therapy, although with this low incidence of
23 rejection and this small sample size, we could not achieve
24 statistical significance.

1 Pediatric patients represent a small percent of
2 the overall transplant population, but they represent a
3 population that is at high risk for acute rejection. So we
4 are doing a study in pediatric patients to see if Zenapax
5 can be safely used in this population, because we believe
6 they could benefit from Zenapax. This study is an open-
7 label, single-arm trial. Again, the goal is safety and PK
8 data. We're using the same dosing regimen, but here we've
9 allowed the centers to use their standard immunosuppressive
10 regimen so we could collect data that would be applicable
11 to real-world use of Zenapax. The goal is to have 60
12 patients, with 20 in three different age groups, and we've
13 actually filled the teenage age group, we've got about
14 seven kids in the 0-2 group, with the remainder in the
15 school-age group.

16 We have done a safety update, and we have about
17 25 patients in the database at this point. The median
18 follow-up is 8 weeks. As you can see, half of the patients
19 have received the five -- actually, more than half have
20 received the five doses. The patient who received six
21 doses got a dose of Zenapax before a living transplant, and
22 the transplant was postponed, so a few weeks later when it
23 came time for the transplant, he received, of course, his
24 five doses. As you would expect in this group, about two

1 thirds of the patients had living donors.

2 The point of this slide is that the majority of
3 patients are receiving CellCept, so the data from the
4 pediatric study will add to our database on the use of
5 Zenapax and CellCept together.

6 We have some very preliminary pharmacokinetics
7 data from about five patients on this study, and it looks
8 like the serum levels are slightly lower than what we saw
9 in the adult patients. Because it was an open-label study,
10 we were doing the FACS analysis, looking at anti-CD25 in
11 all patients, and we're seeing very good saturation. Now,
12 the data on this slide is only from a small number of
13 patients, looking here at about seven at the early time
14 points to two at the end, but Dr. Ettinger has just
15 received some data from his thirteen patients at UCLA which
16 corroborate these findings. So we're achieving very good
17 saturation despite the fact that serum levels may be a
18 little bit lower in the kids.

19 The adverse event profile that we're seeing in
20 the kids is very similar to what we saw in the adults. I
21 think the one adverse event that we didn't see in the
22 adults was dehydration, which may be associated with
23 diarrhea in the younger children and may be related to
24 CellCept use. We had 10 patients who reported 19 serious

1 adverse events, again, none that appear to be unusual or
2 unexpected or related to Zenapax.

3 Of the 25 patients that we have in our
4 database, only one patient has experienced one rejection
5 episode, which was reversible. One patient had delayed
6 function, and that was reversed. And there was one patient
7 who experienced graft loss due to a renal vein thrombosis.
8 So although our database is small and the follow-up is
9 short, we have not to date seen any adverse events or
10 anything that would expect that Zenapax would be
11 problematic in children. In fact, our preliminary data are
12 very encouraging.

13 In conclusion, overall I think the data that we
14 have show that Zenapax is effective in reducing the
15 incidence of acute rejection in the first 6 months, that we
16 have improved patient and graft survival, and that there's
17 an excellent safety profile with this humanized monoclonal
18 antibody. The addition of Zenapax to a double- or a
19 triple-therapy regimen with either Imuran or CellCept does
20 not have an increased risk.

21 I'd now like to ask Dr. Kirkman to present some
22 concluding remarks.

23 DR. KIRKMAN: My name is Bob Kirkman. I'm a
24 transplant surgeon at the Brigham and Women's Hospital in

1 Boston. I've been involved in three of the clinical trials
2 that you've just heard presented, and I've also been
3 involved for some time in the laboratory and preclinical
4 investigations which have brought us to the point that we
5 are at today, and I hope you will pardon me a very brief
6 historical retrospective that I think may put Zenapax in
7 some perspective.

8 The idea that the alpha chain of the IL-2
9 receptor might be an appropriate target for
10 immunosuppressive therapy was first developed in the early
11 1980s, and first shown to be true in a vascularized heart
12 transplant model in mice in 1985, a model in which the
13 short-term administration of an antibody against the mouse
14 IL-2 receptor alpha chain produced indefinite graft
15 survival. Those were exciting findings and led to a study
16 and a primate model of kidney transplantation using murine
17 anti-Tac, which is the forerunner antibody of Zenapax, the
18 antibody from which its complementarity determining regions
19 have been taken.

20 Those studies showed that the use of that
21 antibody would prolong an allograft in syngeneic monkeys
22 for approximately 1 week. They were followed by a two-
23 center randomized controlled trial of murine anti-Tac in
24 clinical renal transplantation, which demonstrated that for

1 the period of time which the antibody was administered,
2 approximately 10 days, the patients experienced an
3 extremely low incidence of acute rejection.

4 It was clear, however, from both of those
5 studies in the primate model and in man that the ability to
6 target the IL-2 receptor and to use this as
7 immunosuppressive therapy was limited by the length of time
8 for which we could give a murine monoclonal antibody, and,
9 indeed, most of the monkeys and most of the patients who
10 were tested had developed anti-mouse protein antibodies,
11 and that limited the effectiveness of this particular
12 approach.

13 I think what we have seen today is that that
14 barrier to using a monoclonal antibody against the alpha
15 chain of the IL-2 receptor for immunosuppressive therapy
16 has been removed, and that Zenapax, because it is a
17 humanized antibody with very limited immunogenicity, has
18 made possible this approach to immunosuppressive therapy in
19 transplantation in a highly successful way, and I believe
20 that the data that you have seen presented this morning
21 establish Zenapax as an effective and safe
22 immunosuppressive agent for renal transplantation.

23 The clinical benefits that one sees by the use
24 of Zenapax are fairly straightforward. There are fewer

1 rejection episodes in patients who receive Zenapax than in
2 patients who do not, and that has a number of various
3 obvious benefits for my patients and for all of us who take
4 care of clinical kidney transplant patients. It is, after
5 all, rejection episodes which lead to the eventual loss of
6 a graft from acute rejection, and if one can prevent those
7 acute rejection episodes, one would expect to reduce the
8 loss of grafts from acute rejection, and I think that's
9 indeed the case.

10 It is the need to treat acute rejection that is
11 the most common cause of morbidity and, indeed, mortality
12 in renal transplant recipients, and, therefore, if we can
13 reduce the number of patients who require that therapy, we
14 will decrease the morbidity and, indeed, the expense of
15 renal transplantation. I think you've seen that this leads
16 to an increase in graft survival. That has important
17 benefits in this field that is so limited by its most
18 important resource -- namely, the organ for
19 transplantation. If we can decrease the need for
20 retransplantation, that resource can be spread over a
21 larger patient population.

22 Finally, I think very importantly, we know that
23 the most important risk factor for the development of
24 chronic rejection is the occurrence of an acute rejection

1 episode in the first few months following transplantation,
2 and, therefore, I think it likely, although not yet proven,
3 that the reduction in acute rejection that we see with this
4 agent will lead to a decrease in chronic rejection in the
5 future.

6 These benefits have been achieved at relatively
7 level cost. There is no non-specific toxicity of the
8 administration of Zenapax. It's hard to tell when you're
9 giving this whether you're giving the placebo or not. In
10 fact, you can't tell, because the patients don't have any
11 reaction to the administration of this monoclonal antibody,
12 and in particular they don't have the cytokine release
13 syndrome that's so prevalent with the only other approved
14 monoclonal antibody in transplantation, OKT3. The
15 administration of Zenapax is not associated with an
16 increase in opportunistic infection or of an increase in
17 lymphoproliferative disease, the two most important markers
18 of overimmunosuppression in transplant patients, and as
19 you've seen, the use of this agent is not associated with
20 an increase in mortality.

21 Therefore, I think the data that you have seen,
22 from a clinical standpoint, clearly show a very favorable
23 benefit-to-risk ratio and support the indication of Zenapax
24 for the prevention of rejection in renal transplantation.

1 I think that the reason that we have seen this very
2 favorable benefit-to-risk ratio has to do with the very
3 highly selective nature of this particular agent. It is
4 indeed the most selective agent yet introduced for
5 immunosuppressive therapy.

6 And, finally, for those of us who have been
7 involved for a long time in biologic approaches to
8 immunosuppression, we thought that with the introduction of
9 monoclonal antibody technology, we might finally have the
10 tools which would allow us to manipulate the immune
11 response in ways that would be favorable for transplant
12 patients. We really haven't been able to do that until now
13 because of the limitations of the response of the host to a
14 foreign protein, and I think that in many ways Zenapax
15 represents the fulfillment of the promise that we first
16 hoped for with the introduction of this monoclonal antibody
17 technology, now more than two decades ago.

18 Thank you.

19 DR. BROUDY: I would like to thank the speakers
20 for Hoffmann-La Roche, and I would like to ask if any of
21 the members of the committee have any questions for the
22 speakers.

23 Dr. Hunsicker?

24 DR. HUNSICKER: My question for Dr. Light is,

1 she referred to patients who dropped out but were followed
2 for the full period of the study, and my question is simply
3 whether they were included in the efficacy analysis as well
4 as in the toxicity analysis.

5 DR. LIGHT: Yes.

6 DR. HUNSICKER: So this was a true intent to
7 treat.

8 DR. LIGHT: That's right.

9 DR. BROUDY: I'd like to ask, are there other
10 cells that are known to express the IL-2 receptor? When
11 you block the alpha chain, would you be blocking any other
12 cells in the body? Other hematopoietic cells, for example?

13 PARTICIPANT: Other than T cells, IL-2 alpha
14 subunits can be expressed on activated macrophages and K
15 cells. There's no evidence for the Tac receptor to be
16 expressed on non-lymphoid cells.

17 DR. BROUDY: Thank you.

18 Dr. Berman?

19 DR. BERMAN: I had a question for Dr. Light,
20 and it concerns Slide Number 34, which said that Zenapax
21 patients had significantly better outcome at 12 months. In
22 the previous two slides, it showed no difference between
23 graft survival or patient survival, and yet in Slide 34
24 there appeared to be significant improvement. Can you

1 clarify that for me?

2 DR. LIGHT: I think I'd like to ask our
3 statisticians for help with that.

4 PARTICIPANT: This is a combined endpoint to
5 look at the number of patients with biopsy-proven acute
6 rejection or graft failure. So, therefore, it has more
7 patients reaching the endpoint, and, therefore, it has
8 better statistical power in detecting the treatment
9 difference.

10 DR. BERMAN: It's just that in the previous two
11 slides there was no difference at 12 months in either of
12 the two studies in terms of graft survival or patient
13 survival.

14 PARTICIPANT: Yes, you're correct, but when you
15 look at the combined endpoint, there is strong treatment
16 difference in terms of acute rejection. The power is
17 tremendously increased due to the number of events. It's a
18 combined endpoint.

19 DR. BROUDY: Dr. Hunsicker?

20 DR. HUNSICKER: Just lest there be any
21 confusion, this endpoint that you see here includes the
22 primary endpoint, which is significantly different. If you
23 include with the primary endpoint, which is significantly
24 different, two endpoints which are not much different,

1 you'll still get a significant difference.

2 DR. BROUDY: Dr. O'Fallon?

3 DR. O'FALLON: That same slide indicates that
4 this was an exploratory analysis of some sort, and yet we
5 have quoted P values and --

6 DR. LIGHT: It was exploratory in the sense
7 that it was not something that was in the protocol when we
8 submitted the protocol. We did this after we submitted the
9 protocol.

10 DR. O'FALLON: Okay. Since I have the
11 microphone clutched firmly in hand here, let me continue
12 with a couple of questions.

13 (Laughter.)

14 DR. O'FALLON: It's almost a necessity and a
15 huge advantage to do studies like this over many, many
16 centers, but we didn't hear from you as to whether there
17 were any centers that seemed to have different results than
18 the results that were summarized over all centers.

19 PARTICIPANT: Again, this is the same event
20 statistician from Roche. We did a Fisher's Exact Test to
21 test across centers. We did not see a significant
22 difference in terms of the treatment by center interaction.
23 Therefore, we feel it's appropriate to put the centers in
24 our analyses.

1 DR. ANDERSON: There was a comment, though,
2 during the side effects -- it was just sort of a toss-away
3 comment and probably not significant -- that there was more
4 of one type of side effect in the Australia arm.

5 DR. LIGHT: That was skin cancer, and skin
6 cancer is extraordinarily common in Australia.

7 DR. ANDERSON: Okay.

8 DR. O'FALLON: Back to that test of
9 interaction, which, of course, probably didn't have a real
10 high power, were there many centers in which there were
11 very small numbers of patients entered into the studies?

12 DR. LIGHT: Yes, there was a range. There was
13 one center that entered two patients, and the highest
14 center had 52 patients. When I looked at the data per
15 center, what was interesting is that the centers where
16 there appeared to be a little difference, it was because
17 the placebo patients were doing very well, but I don't
18 think there were centers where the trend was in the other
19 direction.

20 DR. O'FALLON: Let me continue. Your endpoint
21 is at 6 months, and yet you showed us some very highly
22 significant Kaplan-Meier curves that were highly
23 significant on the basis of log rank test. So what you're
24 saying is that the time to acute rejection is delayed, even

1 if the differences at 6 months sometimes were a little
2 closer together. I'm a statistician, and I don't know if
3 that -- is that a very helpful characteristic of this, to
4 delay the time?

5 DR. JAY SIEGEL: We have not permitted use of
6 -- and with consultation with this committee -- use of time
7 to rejection as a primary endpoint. We consider it an
8 important finding, but theoretically an immunosuppressive
9 drug could eliminate rejection episodes for a period of
10 time during which it had effect, and then you could see
11 simply a higher incidence occurring after its effect wore
12 off. So we looked for a landmark analysis at a time period
13 long enough to accommodate that, but we do consider the
14 time informative and important.

15 DR. O'FALLON: Okay.

16 MR. BURDICK: Jim Burdick. Since we didn't
17 really answer the question, I'd just like to point out that
18 I would certainly agree that time to rejection is a small
19 thing, but the practical point is that if you can have
20 rejection occur reliably never before 2 months and after at
21 some point when things are much cleaner and more easily
22 handled, it would be a small clinical benefit. So it's not
23 irrelevant.

24 DR. O'FALLON: Two more points. Some of the P

1 values that we saw were modest. We go back to examination
2 of the power statement that seemed to be based on the
3 presumption that the failure rate in the placebo group
4 would be about 50 percent, and it certainly was not in one
5 of these studies even close to that. What is the
6 explanation of that difference? Usually you can predict
7 pretty well what's going to happen in the placebo group.

8 DR. LIGHT: I think the difference is a result
9 of chronology, that when we had our investigators meeting,
10 we asked the investigators, you know, "What rate of acute
11 rejection are you seeing in your patients?," and the quote
12 was 50 percent. Shortly after we started our study, the
13 data from the mycophenolate randomized trials came out, and
14 it turns out that on the study that was comparable in
15 design to ours, the rate was about 35 percent.

16 I think there's a tendency in controlled trials
17 to have a slightly lower rejection rate than you might see
18 overall. So I think that's where our mistake in judgment
19 was, in estimating the acute rejection rate.

20 DR. O'FALLON: Okay. There was a rather
21 sophisticated appendix presented to us, but not presented
22 here, regarding a time-dependent covariate analysis, in
23 which it was established that time to the acute rejection
24 was definitely associated with the occurrence of a failure.

1 But the two arms of the trial were not compared in that
2 analysis. I was just wondering if there was some reason
3 for that.

4 PARTICIPANT: Yes. I guess the assumption that
5 acute rejection leads to graft failure, you sort of would
6 expect the same thing would happen in both treatment
7 groups. I did, in the same model, try to include treatment
8 and also try to look at treatment and the time-dependent
9 rejection as an interaction, and then that statistical
10 significance still remains with the treatment effect in the
11 model. Therefore, there is strong evidence that acute
12 rejection leads to graft failure in those studies.

13 DR. HUNSICKER: What was the interaction
14 across --

15 DR. BROUDY: Please use the microphone.

16 PARTICIPANT: I tried three models. One model
17 was just the time-dependent covariate acute rejection, a
18 second model is with the treatment in addition to the time-
19 dependent acute rejection, and then the third model
20 included the interaction of both.

21 DR. HUNSICKER: And was the last interaction
22 significant?

23 PARTICIPANT: No.

24 DR. HUNSICKER: It would be very poorly

1 powered, but it wasn't significant.

2 DR. BROUDY: Dr. Miller?

3 DR. MILLER: The bone marrow transplant program
4 was discontinued. Was that based on efficacy, or were
5 there any specific toxicity or safety issues that may
6 contribute to our understanding of the safety of the
7 product?

8 DR. LIGHT: Yes. We had a study in the
9 treatment of steroid-resistant graft versus host disease
10 where efficacy was seen, about a 40 percent response rate,
11 and then we went ahead and did a randomized controlled
12 study in prevention of GVHD in matched unrelated donors,
13 and no efficacy was seen. So we have safety data. We
14 chose not to pool it with the renal transplant safety
15 database because the general condition of the patients is
16 different, but, again, we found no Zenapax-specific
17 toxicity in the GVHD patients.

18 DR. MILLER: Thank you.

19 DR. BROUDY: Ms. Meyers?

20 MS. MEYERS: Has it been studied in any other
21 types of transplants? Heart? Liver? None at all.

22 I'd just like to say from the point of view of
23 a consumer, there's a real problem with reimbursement for
24 ~~all transplant drugs, because Medicare patients only get~~

1 reimbursement for a short period of time, and what we've
2 found over the years is if there's any transplant drug
3 which is approved for kidney transplant, if it hasn't been
4 approved for heart or liver, even though it's widely used,
5 the patients don't get reimbursed. So are there any plans
6 to do clinical trials in liver, heart, et cetera?

7 DR. BROUDY: Would you like to answer the
8 question?

9 DR. LIGHT: Yes. We're on the verge of
10 starting a study in liver, and heart is a little further
11 along. But, no, we understand completely, and I think our
12 hypothesis is that the T cell is responsible for rejection
13 and the mechanism of Zenapax suggests that this could be
14 beneficial to these patients as well.

15 DR. BROUDY: Dr. Auchincloss?

16 DR. AUCHINCLOSS: Dr. Light, can you tell --
17 I'm sure you looked, and I guess there's probably an
18 answer, but was there any feature of patients who did have
19 rejection episodes that you were able to pick up?

20 DR. LIGHT: We did a series of subset analyses,
21 and I believe that FDA will be presenting some of that data
22 soon, and we didn't identify anything.

23 DR. AUCHINCLOSS: To ask the question the other
24 way around, if you looked at -- well, first question. Were

1 there any second transplants in --

2 DR. LIGHT: No.

3 DR. AUCHINCLOSS: If you looked at highly
4 sensitized patients, was there any difference? If you
5 looked at well-matched --

6 DR. LIGHT: You'll see that data soon.

7 DR. AUCHINCLOSS: So the bottom line is
8 nothing.

9 DR. LIGHT: I mean, mostly because the numbers
10 are very small. When you start out with a population of
11 130 patients on each treatment arm, the number in the
12 subset is going to be very small. So just to give a little
13 -- the punch line is that the trend was generally in favor
14 of the patients on Zenapax did better than the patients on
15 placebo, but you couldn't say anything statistically
16 because of the small numbers.

17 DR. BROUDY: Dr. Hunsicker?

18 DR. HUNSICKER: Actually, Ms. Meyers' question
19 brings up a question I'd like to put to the FDA, if I
20 might, and maybe it's premature, but this has to do with
21 the issue of extending the findings that have been
22 presented already here to new subsets of patients. You're
23 going to ask the question about pediatrics, for which I
24 have at least a preliminary answer, but the question is

1 really very similar to the situation with liver or heart
2 transplantation.

3 Where the mechanisms of rejection are
4 considered to be very similar, but where it might in fact
5 be very difficult to assemble the number of patients that
6 are required to get a significant thing, are you people
7 willing to accept similar reductions in risk fairly
8 consistently across groups, or do you actually require the
9 numbers to get a P value that is less than .05 or whatever?
10 In other words, what I'm asking is, how much more
11 information is really needed in order to extend an agent to
12 a new group of patients?

13 DR. BROUDY: I'm sure Dr. Siegel is willing to
14 comment on that from past experience.

15 (Laughter.)

16 DR. JAY SIEGEL: I suspect that my colleagues
17 in the Center for Drugs actually have a more extensive past
18 experience that we would want to make sure that we were
19 consistent with, but I would suggest that we do consider
20 different transplant organs to be different indications.
21 However, under our recently published -- earlier this year
22 -- guidance document on evidence of effectiveness, we lay
23 out the broad principles we use, which include,
24 ~~importantly, the~~ ~~that was designed largely to address~~

1 supplemental indications include, importantly, the fact
2 that evidence of effectiveness in related indications with
3 related mechanisms of action is considered supportive.

4 So what that would mean would be that probably
5 in this setting that the evidentiary standard to show a
6 different organ would be easier with the supportive
7 evidence of efficacy and renal failure. But I would not
8 extend that to the extent to say that statistically
9 insignificant data would suffice to meet that standard.

10 DR. BROUDY: Dr. Grimm?

11 DR. GRIMM: My question goes back to the
12 biology of Zenapax. I noticed in the information that the
13 committee was given that there seems to be a bit of an
14 increase in renal insufficiency, renal damage, and
15 thrombosis, and in the pediatric data there was some
16 thrombosis. Is there any evidence that the Zenapax is a
17 partial agonist of the IL-2 receptor? For example, in
18 activated macrophages, if it was, it might increase
19 production of tissue factor and lead to thrombosis and
20 delayed graft function. Have you looked at any evidence of
21 activation of the clotting cascade or anything in this
22 regard?

23 DR. LIGHT: No, we haven't. I think that we
24 have done some more detailed look at the data of those

1 particular adverse events, and in each case we can find
2 some explanations that don't implicate Zenapax. But we
3 have no specific data on clotting cascades.

4 DR. GRIMM: Okay. Thanks.

5 DR. BROUDY: Dr. Auchincloss?

6 DR. AUCHINCLOSS: I'd like to go further with
7 the biology question. Can you tell us more about how you
8 think this works and address a few things which I think I
9 know? There's no T cell depletion, as I understand it.
10 It's simply a coating of the receptor that persists for as
11 long as you give the antibody, but then the cells are
12 potentially still there. Can you tell us from the
13 experimental studies, can you immunize an animal to tetanus
14 toxoid or whatever during the time that you're getting the
15 drug? Can you immunize subsequently if you tried once
16 while you're getting the drug?

17 Just tell us a little bit more about how this
18 works and what we might expect. Particularly what I'm
19 thinking about is, what might you expect to happen to
20 children who haven't been exposed to many environmental
21 pathogens who are getting this drug?

22 DR. AKIMI: Hi. I'm John Akimi from Preclinic,
23 La Roche. The mechanism of Zenapax and the anti-CD25
24 antibodies, as we know it, is really as an IL 2 receptor

1 antagonist on activated cells. We do not have any other
2 evidence that this antibody as you've seen would induce
3 lysis or any depletion of the activated cells from the
4 circulation of tissues. I believe its mechanism in this
5 case, because we're using a humanized antibody, is that
6 we're now, for the first time, allowed to block the IL-2
7 receptor for a long period of time, and that gives us
8 prolonged depletion of IL-2 activated cells. So that is
9 what I believe its primary mechanism is.

10 We have done no other studies to demonstrate,
11 under the long-term treatment with Zenapax, whether you can
12 in fact produce immunization with tetanus toxoid or any
13 other potential vaccines, unless some of that information
14 may be buried in the literature. But I think you'd have to
15 look at the data with Zenapax because of the long-term
16 exposure, and I don't believe that's the case. Just
17 remember that Zenapax treatment is for a limited period of
18 time, so --

19 DR. AUCHINCLOSS: Well, let me extend the
20 question. First of all, I guess I'm a little surprised
21 that there isn't any animal information about whether you
22 can immunize an animal to a new environmental pathogen or
23 whatever, antigen, during the time of treatment or not, or
24 whether you can subsequently.

1 But aside from that, let me ask the bigger
2 question. How long do you think or how long does the
3 company think you could treat a patient with this reagent
4 for safely? Forever?

5 DR. FORTIN: Eric Fortin. I work in
6 ophthalmology. We're presently conducting a Phase I/II
7 trial of Zenapax in the treatment of chronic uveitis, and
8 so far we have treated some patients close to a year, with
9 different time points for infusions of the drug, and the
10 efficacy has impressed us as of yet, and so has the safety
11 data. So we have some patients who have received some 13
12 or 14 infusions of the drug over a 10- to 11-month period,
13 and we've encountered no significant problems so far, other
14 than two adverse events that I can detail some more, if
15 you'd like.

16 DR. AUCHINCLOSS: Can you tell me how you get
17 immunosuppression without immunosuppression?

18 DR. FORTIN: Well, let me tell you a little bit
19 about the trial itself. We're dealing with patients with
20 chronic uveitis who have necessitated treatment with
21 immunosuppressive agents, including prednisone,
22 methotrexate, or cyclosporine, for long periods of time.
23 What we're doing is tapering their immunosuppressants over
24 a period of 8 weeks, while we start infusing Zenapax

1 initially every 2 weeks. So after this 8-week period, they
2 remain on Zenapax monotherapy, and we monitor them for
3 signs of reactivation of the uveitis, which we measure --
4 our endpoints are decrease in 10 letters in vision or
5 increase in vitreal haze. So they do remain on Zenapax
6 monotherapy for a prolonged period of time.

7 I should add that these patients are patients
8 for the most part who have been on these immunosuppressants
9 for some as long as 10 years and have tried to come off the
10 immunosuppressants more than once in each case, and we've
11 been impressed so far that we've only had one reactivation
12 of uveitis over some eight patients that have received the
13 drug so far.

14 DR. AUCHINCLOSS: Let me ask a hypothetical
15 question of the company. If there was a child receiving
16 this drug, actively receiving the drug, who had their first
17 exposure to chicken pox, what does the company think would
18 happen?

19 DR. ETTINGER: I'm Bob Ettinger, pediatric
20 nephrologist from UCLA, so I can't speak to what the
21 company would think would happen, but with regard to an
22 exposure to chicken pox, hopefully, number one, that will
23 be rendered moot by the fact that all dialysis patients are
24 now receiving immunization. But that notwithstanding, one

1 would treat them in the same way that one would treat them
2 now, which is to watch them carefully and treat them with
3 acyclovir as necessary.

4 DR. AUCHINCLOSS: I'm sorry. I'm not making my
5 point. I'm asking the company, do they actually think that
6 they have a magic bullet that gives organ immunosuppression
7 without immunosuppression?

8 DR. LIGHT: Well, I think that Zenapax has only
9 been used in conjunction with other immunosuppressant
10 drugs, so I think that there is a specificity to Zenapax
11 that's unique among the other drugs that are available, and
12 I think that that's important. When we get to the point
13 when we don't have other drugs, we could answer that.

14 DR. AUCHINCLOSS: Presumably you think that any
15 activated T cell gets suppressed by this reagent. Is that
16 not true?

17 DR. LIGHT: Yes, it looks that way.

18 DR. AUCHINCLOSS: Any activated T cell to an
19 environmental pathogen that might enter at the time that
20 you were giving the drug, not just the organ transplant.

21 DR. LIGHT: That's expressing the CD25, yes.

22 DR. BROUDY: Dr. Kirkman?

23 DR. KIRKMAN: I'll make two comments with
24 respect to that. One, this is a hard question to answer in

1 an animal experimental model, because the reagents don't
2 exist to really allow you to do that for a prolonged period
3 of time. You can't give the Zenapax to a primate model for
4 a prolonged period of time, because it's still a foreign
5 protein to the monkey, so even though it's less immunogenic
6 than the murine antibody, it's impossible to do the
7 experiment for a very prolonged period of time in a monkey.

8 The only data that really, I think, is relevant
9 to the question you asked is the CMV data from the adult
10 study, because there were patients that were exposed to CMV
11 for the first time at the same time that they were
12 receiving Zenapax -- that is, recipients who were negative
13 and who received either a blood transfusion or an organ
14 from a CMV-positive donor -- and the fact is that there was
15 not an increased incidence of CMV in the patients who were
16 treated with Zenapax compared to the controls, and when it
17 did occur, it was a manageable problem.

18 So I think your theoretical concern is one that
19 those of us who have been involved in this for a long time
20 have always had, but the only data that directly speaks to
21 it suggests it's not a problem.

22 DR. BROUDY: Dr. Suthanthiran?

23 DR. SUTHANTHIRAN: I actually have four easy
24 questions. The first one is to Dr. Light on Slide 19 about

1 the data. I think it's very clear when you give the
2 Zenapax antibody, you don't detect CD25-positive cells.
3 There are two possibilities for this: one, as you said,
4 the saturation, so you're not able to access the Tac
5 antigen; the other possibility is, since you don't have an
6 IL-2-dependent signal, there is no clonal proliferation of
7 T cells. I'm sure you considered these, too, and do you
8 have any indirect immunofluorescence data to suggest that
9 in fact you have Zenapax antibody on the surface of these
10 cells but are negative for the CD25 antigen?

11 DR. LIGHT: Yes. For the sake of simplicity,
12 we only showed the data with the anti-CD25, but we have
13 data with 7G7, which is another antibody which recognizes a
14 different epitope on the alpha chain, and you'll see on
15 this slide that the levels of 7G7, which picks up the chain
16 that's on the cells, remain fairly high. Some are lower,
17 which means there may be some small depletion. The yellow
18 on the previous slide was down here, and you weren't
19 detecting any CD25. But 7G7 does bind to the cells.
20 You're seeing fewer cells, but it's not zero. So I think
21 we are detecting that there still is a receptor on the
22 cells.

23 DR. VINCENTI: Maybe I could just add another
24 ~~comment to this. The epitope to which Zenapax binds is~~

1 saturated right away, it goes down pretty close to zero.
2 The 7G7 shows a gradual decrease, suggesting that there is
3 some modulation of the receptor. Either there is increased
4 shedding or there is decreased expression of the receptor.

5 DR. SUTHANTHIRAN: I think this result is quite
6 anticipated in terms of what IL-2 would do to T cells, that
7 you would expect a certain amount of lesser percentage of
8 CD25-positive cells.

9 My second question has to do with the
10 antibodies administered every other week. Did you notice
11 any difference in terms of the timing of rejection? When
12 rejection happened in this group of patients, did they
13 happen further away from the antibody administration? Was
14 there any relationship to the concentration?

15 DR. LIGHT: Well, I think we have the Kaplan-
16 Meier curves on for time to rejection in the two studies,
17 so I guess the only way to answer that would be to take one
18 of the Kaplan-Meiers from the triple therapy, and you could
19 sort of put in the marks where the rejection occurred, but
20 there certainly were no blips right before an infusion. I
21 think that the saturation data suggests that you really
22 have a pretty constant level of saturation, even when your
23 serum levels go down. One possibility is that there's a
24 reservoir. These patients have fairly high levels of

1 soluble IL-2-R, which binds with the added Zenapax, and
2 that may serve as a reservoir. So even though your serum
3 levels may go down, you may have a reservoir that allows
4 for saturation in the absence of high serum levels.

5 But we're dosing on Day 0, Day 14, Day 28, Day
6 42, Day 56. This part of the curve is going up pretty
7 quickly in both groups. We certainly don't see a peak 14
8 days after the last dose.

9 DR. BROUDY: Dr. Siegel?

10 DR. JAY SIEGEL: I'd just like to comment in
11 regard to that issue of the saturation being constant, that
12 saturation is not the same as blockade; that equilibration
13 between interleukin-2 and between antibody to the receptor
14 occurs in vitro, at least, in a relatively rapid time
15 phase; that the affinity of interleukin-2 for the receptor,
16 for the alpha, beta, gamma, is about 2 logs higher than the
17 affinity of this antibody -- this antibody is in the 3
18 nanomolar range, whereas we're talking about the 10
19 picomolar range for a high-affinity IL-2 receptor, so it's
20 a 2 to 3 log difference; furthermore, that interleukin-2
21 will activate cells and trigger the receptor, even if it
22 has a very low level of receptor occupancy, if it's only
23 occupying a few percent of it.

24 ~~So really what may matter at any given site is~~

1 not whether you have a blockade, but the relative levels of
2 the anti-Tac and the interleukin-2 in the region. If you
3 have 100-fold excess anti-Tac, molar excess, that will lead
4 to roughly equivalent affinity and could lead to as much as
5 50 percent occupancy. To effectively block occupancy, you
6 need about a 4 log molar excess of antibody, which, since
7 the antibody weighs about four times what the cytokine
8 does, or a 5 log excess by weight, 100,000-fold excess.

9 So not to say there isn't blockade here, but
10 simply to say that the time course over time in which you
11 show saturation will not necessarily be the same as the
12 time course in which a local concentration of interleukin-2
13 is unable to trigger those cells. That may be a different
14 issue than whether or not the receptors are saturated.

15 DR. BROUDY: That's an elegant discussion, and
16 I think we'll finish your questions, take a question from
17 Dr. Anderson, and then take a break.

18 DR. SUTHANTHIRAN: If you look at the incidence
19 of rejection, it appears that the more of the drug you
20 give, you're better in some way. The placebo with the
21 highest azathioprine brought it down, and if you add the
22 humanized anti-Tac, it's still further down. Given that
23 most of us would be using three drugs and very possibly
24 mycophenolate as the third drug, what kind of numbers are

1 we looking at to see from your projections that an addition
2 of an anti-Tac would reduce significantly the incidence of
3 biopsy-proven acute rejection?

4 DR. KIRKMAN: The only data that we have to
5 directly answer your question is from the Phase I/II study
6 that used Zenapax in combination with CellCept. That's a
7 study that was not powered for efficacy and was designed
8 primarily as a safety study, but in the group that received
9 both CellCept and Zenapax, the incidence of acute rejection
10 was 12 percent. So it was quite, quite low. And,
11 obviously, because the study wasn't powered for that, we
12 can't make a strong statistical statement, but the
13 incidence was extremely low.

14 DR. SUTHANTHIRAN: My last question. When you
15 actually look at the 1-year survival rate, there are
16 differences, and they're not very striking differences, and
17 you made an important point that we all share in the
18 transplant community, that if you reduce acute rejection,
19 one of our goals is that we would prevent chronic
20 rejection-dependent graft loss. Are you planning on
21 studying these patients in terms of at 1 or 2 years,
22 especially not only from a renal function point of view,
23 but also from a structural point of view?

24 DR. LIGHT: Well, at this point, the plan is to

1 collect data on patient and graft survival and renal
2 function and malignancies at 3 years post-transplant. I
3 think that will give us a nice comparison to the data that
4 we have at 1 year. I guess my concern is that the sample
5 size we have is relatively small to detect a difference,
6 and that we have no control over what immunosuppression
7 patients are receiving after the study was completed at 6
8 months, and one possibility is that any patient who has
9 experienced rejection could get switched from azathioprine
10 to mycophenolate, and at the end of 3 years it will be
11 impossible to figure out what was related to getting
12 Zenapax in the first 8 weeks post-transplant. But we will
13 collect the data.

14 DR. BROUDY: Dr. Anderson?

15 DR. ANDERSON: I'm not an immunologist, but I
16 continue to be amazed at how mysterious and magical things
17 happen with the immune system in the human body, so I have
18 a couple of questions on the biology side, and the answer
19 might be "No studies." That's okay. The first is, have
20 you looked at all at the TH1/TH2 balance to see if there's
21 any influence there?

22 PARTICIPANT: No, those studies haven't been
23 done, that I know of.

24 ~~DR. ANDERSON: Okay. And the second, which is~~

1 probably also going to be "Not done," and that is, have you
2 looked at all at the balance of CD4 to CD8 cells?

3 DR. VINCENTI: We did these studies in the
4 Phase I, and we did not find any differences compared to
5 controls.

6 DR. ANDERSON: Okay.

7 DR. BROUDY: I think Dr. Berman would like to
8 ask the last question.

9 DR. BERMAN: This is for Dr. Vincenti again.
10 In the United States, what are the proportion of people
11 having a living donor transplant versus a cadaveric
12 transplant?

13 DR. VINCENTI: Well, at our center it's about
14 30 percent living donors, both related and unrelated. As
15 you may know, the greatest growth area nowadays is the use
16 of living unrelated donors. But cadaveric transplantation
17 remains, obviously, the most common source of kidneys.

18 DR. BERMAN: But the Zenapax hasn't been
19 studied in that population?

20 DR. VINCENTI: No, we did. In the Phase I
21 study, we included -- actually, most of the patients were
22 living related, and in the Phase I/II using CellCept, we
23 had living related and living unrelated, and we're
24 currently doing -- oh, these are the numbers. So there

1 were 13 living donors in the Phase I and 16 living donors
2 in the CellCept combination study. So we've had a fair
3 experience using living donors.

4 I think, as an aside, if you have an effective
5 immunosuppressive agent that can block the strong
6 immunizing effect of a foreign graft, totally unrelated, I
7 think one could extrapolate that it's going to be equally
8 effective in living donors.

9 DR. BERMAN: Is the rejection rate the same in
10 the living donors, or does it depend on HLA matching?

11 DR. VINCENTI: In general, living donors have a
12 lower rejection rate than cadaveric recipients.

13 DR. BROUDY: Okay. Thank you. I think we'll
14 take about a 10-minute break here and reconvene in 10
15 minutes.

16 (Recess.)

17 DR. BONVINI: Dr. Broudy, distinguished members
18 of the advisory committee, ladies and gentlemen, I'm Ezio
19 Bonvini from the Division of Monoclonal Antibodies, and
20 I've come today to present the agency perspective on the
21 use of this agent in prophylaxis of kidney transplant
22 patients.

23 My presentation will be divided into five
24 parts. I will very briefly talk about study design, and I

1 will then enter into some patient baseline characteristics
2 and demographics. Most of my presentation will deal with
3 the primary endpoint analysis and related analysis, and I
4 will spend a little time on just a single secondary
5 endpoint, time to first acute rejection. After my
6 conclusions, Dr. Jeffrey Siegel will continue with the
7 presentation of the analysis of safety data for these
8 agents.

9 To save time, I will very briefly scan this
10 slide, just to mention that I will refer to the first study
11 as the double-therapy study, and that is the study that
12 tested placebo or Zenapax as an add-on to cyclosporine
13 corticosteroid. This was the mostly European study and did
14 not include any U.S. centers. The second study, the
15 triple-therapy study for the addition of cyclosporine,
16 corticosteroids, and azathioprine, included 11 U.S.
17 centers.

18 We have already heard and I just need to
19 reiterate one single point, and that is that antiviral
20 prophylaxes were specified or required for all high-risk
21 patients in the triple-therapy study, while it was left to
22 the individual institutions in the double-therapy study.

23 The two arms of both studies were fairly well
24 ~~balanced with respect to patient baseline characteristics,~~

1 with one exception, as we heard earlier, and this was due
2 to a statistically significant difference in the triple-
3 therapy study due to an increase in positive donors in the
4 placebo arm, which was accounted for by a corresponding
5 decrease in the negative CMV donors. Note, however, that
6 the donor positive/recipient negative category was well
7 balanced between arms.

8 To be able to generalize the results of a
9 study, the study design needs to reflect current practices,
10 and the patient demographics need to reflect the patient
11 characteristics of the population for which the agent is
12 intended. I would like to spend the next few slides
13 providing evidence and showing a number of key factors --
14 age group of the recipient population, sex distribution,
15 primary cause of renal failure, as well as ethnic
16 background -- of the patient population of the two studies
17 and how they compare to the U.S. transplant recipient
18 population.

19 In the top panel, we have the distribution of
20 the U.S. cadaveric kidney transplant recipients from the
21 UNOS database for 1995, the year during which the triple-
22 therapy study was conducted, and it shows that the age
23 group between 35 and 49 years old represents the bulk of
24 the recipients in the cadaveric kidney transplants. The

1 mean age and median age were between 45 and 47 in both the
2 double-therapy study and the triple-therapy study and is,
3 therefore, consistent with the distribution of age -- the
4 distribution of age groups in both studies is consistent
5 with this type of distribution.

6 Recipient sex. Sixty percent of both cadaveric
7 and living donor transplants -- this is the UNOS database
8 spanning transplants from 1987 to 1991 -- are males. Sixty
9 percent are males. A higher fraction of male recipients
10 was present in the double-therapy study, 68 versus 74. In
11 the triple-therapy study, the fraction of male recipients
12 was 60 percent in the placebo arm and 59, therefore,
13 consistent with the distribution of sex in the U.S.
14 transplant recipients.

15 Ethnic background, an important characteristic,
16 a prognostic factor in kidney transplantation. The double-
17 therapy study, being mostly European, is represented almost
18 exclusively by white Caucasian, 95 to 97 percent. The
19 triple-therapy study is consistent with the distribution of
20 ethnic background in recipients. Sixty-one percent of 1995
21 cadaveric kidney transplant recipients in the U.S. were
22 white, 24 black, 11 Hispanic, and a small percentage, 3
23 percent, Asian. Sixty-one and 67 percent of the recipient
24 population in the triple therapy study were white, 20 and

1 19 black, and 15 and 11 Hispanic. This distribution is,
2 again, consistent with the distribution of recipients in
3 the U.S. cadaveric kidney transplant.

4 Diabetes is an important prognostic factor for
5 kidney and graft survival and is captured in the UNOS
6 database for cadaveric and living donor transplants in 1987
7 through 1991. Twenty-two percent of all patients have
8 diabetes -- a small fraction consistent with the prevailing
9 European location of the double-therapy study of diabetes.
10 Seven percent or 3 percent were present in the double-
11 therapy study. In the triple-therapy study, 22 and 25
12 percent of the patients in the placebo and Zenapax arm,
13 respectively, had diabetes. The larger fraction in both
14 studies and in both arms were glomerular nephritis,
15 followed by polycystic kidney disease.

16 In conclusion, I would like to conclude there
17 were no major imbalances between treatment arm in either
18 study, with the exception of the CMV status distribution,
19 and the demographic data of the triple-therapy study are
20 consistent with the demographics of the U.S. kidney
21 transplant recipient population.

22 In December 1994 we asked this committee for
23 input on an issue pertaining to the design of clinical
24 ~~trials of biological agents as add ons to basic~~

1 immunosuppressive therapy for prophylaxis of kidney
2 transplant rejection. While it's impossible for me to
3 summarize here at this minute the consensus of that
4 meeting, I would like to make three specific points, and
5 that is that the incidence of first rejection episodes was
6 an acceptable endpoint for study of agents added to
7 background immunosuppressive therapy, that this incidence
8 should be measured between 3 and 12 months post-transplant,
9 and that the selection of the time interval for the primary
10 analysis should be commensurate with the expected duration
11 of biological effects of the agents in question.

12 The primary endpoint of both trials was the
13 proportion of patients who develop a first biopsy-proven
14 acute rejection episode within the first 6 months following
15 transplantation. Biopsy was necessary to confirm the
16 diagnosis, and I should add that all primary endpoint
17 biopsies were also retrospectively reviewed and rated for
18 severity according to the Banff classification by a central
19 reviewer, Dr. Kip Salas, with the University of Alberta,
20 and his review was last.

21 You've already seen this slide. This is the
22 primary endpoint efficacy analysis, which is a lower
23 incidence of biopsy-proven acute rejection in the Zenapax
24 arm of both studies, and this difference is statistically

1 significant in both studies.

2 I'd like to make a point, and that is that both
3 studies were designed and powered to detect a 20 percent
4 decrease from 50 percent with a power of 80 percent and an
5 alpha of .5, and the approximately 50 percent rejection
6 rate was indeed achieved -- somebody already asked that
7 question -- only in the double-therapy study. The triple-
8 therapy study achieved a 35 percent rejection rate, and,
9 therefore, this study was vastly underpowered.

10 A number of patients in both the double-therapy
11 and triple-therapy study had unknown outcome at the 6-month
12 post-transplant, four patients in the placebo arm of the
13 double-therapy and nine in the Zenapax arm of the double-
14 therapy study, two and three in the placebo and Zenapax,
15 respectively, of the triple-therapy study. These patients
16 were using the denominator to calculate the incidence of
17 rejection in the primary efficacy endpoint and, therefore,
18 were counted as successes.

19 The agency conducted an analysis of the impact
20 of these patients by excluding them or alternating the
21 attribution of success and failure. In the first analysis,
22 the patients with unknown outcome were excluded for the
23 analysis. The yellow bar represents the entire intent-to-
24 treat population. A small increase was observed. The P

1 value was .002 for the double-therapy and .03 for the
2 triple-therapy study.

3 Another analysis was to treat the patients with
4 no information as failures in either arm of either study,
5 and the results are shown here. An increase is observed,
6 of course, in every category, and the P value is .01 in the
7 double therapy and .04. A worst-case scenario is achieved
8 by assigning success to the placebo arm for those patients
9 with no known outcome and failures in the Zenapax arm.
10 This analysis is shown here, and the P value in the double-
11 therapy study is .04, and the P value of .08 is obtained
12 under the worst-case scenario in the triple-therapy study.

13 In conclusion, we conclude that the level of
14 significance is sufficiently robust to withstand alternate
15 assignment of outcome to those patients with no rejection
16 status.

17 A number of patients that had no rejection
18 episodes lost their graft or died within the 6 months post-
19 transplant. These patients are shown here, 11 in the
20 placebo arm of the double therapy, 10 in the Zenapax, 7 in
21 the placebo and two in the Zenapax of the triple-therapy
22 study. Again, these patients were computed in the
23 denominator and, therefore, were considered success.

24 ~~The agency performed an analysis of treatment~~

1 failure, defined as the combined incidence of biopsy-proven
2 rejection, graft loss, or death within 6 months from any
3 cause. The yellow horizontal bars refer to the biopsy-
4 proven rejection. The difference between this yellow bar
5 and the blue and red bar represents the incidence of
6 treatment failure. The analysis is statistically
7 significant, with a lower incidence in Zenapax for both the
8 double therapy and triple therapy. This analysis was not
9 prospectively defined and, therefore, is considered
10 exploratory.

11 It's important to also analyze the outcome by
12 subset, and as I said earlier, age, distribution, sex,
13 ethnic background, and underlying cause of renal failure
14 were all important characteristics that we thought it was
15 important to analyze with respect to outcome. First
16 analysis, shown here, shows the outcome by recipient age
17 group, 18 to 39, 40 to 59, and 60 or older. The number on
18 the bottom represents the denominator of this equation --
19 that is, the sample size for each individual group. The
20 yellow bar represents the overall response, and as you can
21 see, there is a lower incidence in the Zenapax in all three
22 categories. Again, this study, I should say, was not
23 powered -- none of the studies were powered to detect any
24 significant level in any of the subcategories.

1 The same analysis for the triple therapy, and,
2 again, a lower incidence in the Zenapax in all three age
3 categories, and, again, the yellow bar represents the
4 overall population, the total population.

5 Outcome by recipient sex, male and female,
6 yellow is the overall, and this is a difference which
7 appears to be consistent with the overall population for
8 both categories in the double therapy, and these are the
9 results for the triple-therapy study.

10 Recipient ethnic background. This analysis, of
11 course, is only meaningful to the triple-therapy study,
12 owing to the very small representation of non-white in the
13 double-therapy study. What I would like to note is that
14 the difference between Zenapax and the incidence of biopsy-
15 proven acute rejection in the non-white population is lower
16 both in blacks and in the "other" category, which captured
17 both Hispanic and Asian.

18 This complex slide is meant to provide an
19 overall view of the response, broken down by the different
20 primary underlying causes of renal failure. This is for
21 the double-therapy study. The number of cases is
22 relatively small. I would like you to focus your attention
23 on the glomerular nephritis, where we have 55 and 61
24 patients, and, again, we can detect a decrease in the

1 Zenapax arm compared to the placebo arm.

2 Diabetes is very poorly represented, only 10
3 and 4 patients in the double-therapy study. In the triple-
4 therapy study, 29 and 32 patients had diabetes. Forty and
5 33 patients were transplanted for glomerular nephritis.
6 The other denominators are relatively small, and, again,
7 this is meant to represent the overall view of the response
8 distribution by categories of primary cause of renal
9 failure.

10 In conclusion, there is in general a lower
11 incidence of biopsy-proven rejection in the Zenapax arm
12 compared to the placebo in the subset of patients defined
13 by the recipient age, sex, or the primary cause of renal
14 failure. There's a smaller difference in the incidence of
15 biopsy-proven rejection in non-Caucasian patients compared
16 to the Caucasian population.

17 A number of corroborating analyses were
18 conducted by the sponsor and by the agency. One such
19 analysis is a central review of the incidence of biopsy-
20 prove acute rejection. The central reviewer was somewhat
21 more conservative in the definition of a rejection, and I
22 remind you that the yellow bar represents a local review,
23 and this is the difference between the local review and the
24 central review. Again, a decreased incidence was observed

1 in the Zenapax arm. This was statistically significant in
2 the double therapy and had a P value of .06 in the triple
3 therapy.

4 The central review provided also rating of
5 severity by the Banff classification, and this is shown in
6 this slide. The entire intent-to-treat population was used
7 in this analysis. Four categories were identified:
8 borderline, Grade 1, 2, and 3. A lower incidence was
9 observed in the borderline category compared to that -- a
10 greater decrease was observed in the borderline category
11 compared to Grade 1 and Grade 2, where only a few patients
12 were present in Grade 3. This was also consistent in the
13 triple-therapy study, although a difference of similar
14 magnitude was also observed in the Grade 2 patients.

15 In conclusion, in both studies there was a
16 larger difference between Zenapax and placebo arms in
17 borderline category of rejection severity compared to the
18 other categories.

19 The sponsor already provided the review of the
20 incidence of biopsy-proven and presumptive rejection. The
21 rejection was considered presumptive if it was treated,
22 irrespective of whether a biopsy was performed or
23 irrespective of the result of the biopsy. The yellow bar
24 represents the biopsy proven rejection, and, therefore,

1 this is the difference between biopsy-proven and
2 presumptive. The difference between Zenapax and placebo is
3 statistically significant.

4 The reason I present this slide is because by
5 capturing all rejection, biopsy-proven or presumptive,
6 during the 6-month period, the number of rejections per
7 patient can be obtained, and this is shown in this slide.
8 This represents the incidence of patients with one, two,
9 three, four or more rejections. The entire intent-to-treat
10 population is using the denominator here, and as you can
11 see, there is a decrease in the incidence of rejection in
12 the Zenapax arm. This is for the double-therapy study, and
13 consistent results were observed for the triple-therapy
14 study.

15 In conclusion, a lower proportion of patients
16 with one or more biopsy-proven or presumptive rejection
17 episodes was observed during the first 6 months post-
18 transplant in the Zenapax arm.

19 I'd like to conclude with this slide, and this
20 is the result of the local review for the incidence of
21 biopsy-proven rejection at 1 year. The yellow horizontal
22 bar represents the 6-month data. A small increase in a
23 small number of events occurred from 6 months to a year in
24 the placebo arm of the double therapy study. No additional

1 events were observed in the Zenapax arm of the double-
2 therapy study, and this study, of course, is highly
3 significant. A small number of events do occur between 6
4 months and 1 year in the placebo arm of the triple-therapy
5 study. I think a non-commensurate higher number of events
6 occur in the placebo arm, and by now the difference is not
7 any longer significant with a P value of .09. This
8 suggests the possibility that the durability of response in
9 the triple-therapy study may be transient.

10 Information pertaining to the durability of
11 response can be obtained by an analysis of the time to
12 first biopsy-proven acute rejection, and I'd like to show
13 here Kaplan-Meier curves of cumulative probability of
14 rejection for the double-therapy study first. These are
15 extended all the way up to a year. As you can see, most
16 events occurred during the first 120 days, 3 months post-
17 transplant, both in the placebo arm, upper curve, and in
18 the Zenapax arm. This is consistent with numerous previous
19 reports showing that most rejection occurs within the first
20 couple of months, 3 months from transplantation.

21 In the triple-therapy study, the placebo curve
22 shows similar behavior. I should mention, of course, that
23 in either case, the cumulative probability of Zenapax was
24 lower than the placebo arm. Most events occurred by 120

1 days, while in the Zenapax arm, a monotonous continuous
2 increase is observed up to a year. There is a bump at the
3 end which is driven by a single event, with now an
4 effective sample size of only 10 patients; therefore, this
5 is meaningless. This suggests that the period at risk for
6 rejection of these patients is prolonged compared to the
7 period of risk for the patient in the placebo arm, although
8 the probability of rejection is lower.

9 I'd like to wrap up my brief presentation by
10 reiterating a number of conclusions. The first is that the
11 addition of Zenapax to double- or triple-therapy
12 immunosuppressive regimens is associated with a
13 statistically significant lower incidence of first
14 rejection episodes during the first 6 months post-
15 transplant. Although this endpoint was not prospectively
16 designed, a statistically significant decrease in the
17 combined incidence of first rejection, graft loss, or death
18 from any cause was observed in the Zenapax arm compared to
19 the placebo arm.

20 A statistically significant decrease in the
21 incidence of first rejection episode was also observed 1
22 year post-transplant in the Zenapax arm of the double-
23 therapy study. However, the difference in the incidence of
24 first rejection episode was no longer statistically

1 significant for the 1-year post-transplant results of the
2 triple-therapy study.

3 In both studies, the cumulative probability of
4 first rejection was lower in the Zenapax treatment arm
5 compared to placebo; however, in the Zenapax treatment arm
6 of the triple-therapy study, there is evidence that the
7 period of at risk for first rejection is prolonged compared
8 to that of the placebo arm.

9 I'd like to stop here and then give the podium
10 to Dr. Jeff Siegel for an analysis of the safety data,
11 unless there are any questions.

12 DR. JEFFREY SIEGEL: Thank you, Dr. Bonvini.

13 Distinguished members of the advisory
14 committee, my name is Dr. Jeffrey Siegel, and I'll be
15 presenting the safety assessment of Zenapax. In my
16 presentation this morning, I'll begin by giving you an
17 overall profile of the safety assessment of Zenapax, I'll
18 proceed by talking about the deaths and serious adverse
19 events seen in Zenapax-treated arms compared to controls,
20 then talk about infections, malignancies, and
21 lymphoproliferative disorders, talk about other adverse
22 events that we're seeing, and talk a bit about antibody
23 formation.

24 ~~The safety database which was assessed to look~~

1 at the safety of Zenapax consisted of 630 subjects enrolled
2 in four renal allograft rejection trials. This was the two
3 Phase III trials that you've heard about, as well as Phase
4 I trials. There was no higher frequency observed of
5 adverse events overall, attributable adverse events,
6 infectious episodes, malignancies, lymphoproliferative
7 disorders, or laboratory abnormalities.

8 First off, there was no higher frequency of
9 deaths observed in the Zenapax-treated patients. There
10 were 13 deaths in the placebo arm and five deaths in
11 Zenapax arm. The five deaths seen in the Zenapax-treated
12 patients consisted of two patients who died of suicide, one
13 from intracerebral hemorrhage, one case of
14 lymphoproliferative lymphoma, and one case of infective
15 endocarditis.

16 There was also no overall higher frequency of
17 serious adverse events. However, when the specific serious
18 adverse events were examined, several were observed at
19 slightly higher frequencies in the Zenapax-treated arm.
20 This was renal damage and renal insufficiency, as well as
21 thrombosis. The numbers are shown in the next slide, where
22 you can see that the overall serious adverse event rate was
23 slightly lower in the Zenapax arm, 40 percent compared to
24 44 percent.

1 Of the infectious episodes, there was no
2 overall increase in the number of infectious episodes in
3 all or in these specific categories of infectious episodes.
4 There's no overall higher frequency of viral infections,
5 including CMV infections, which were seen in 13 percent of
6 Zenapax-treated patients and 16 percent of control
7 patients. There was no overall higher incidence of fungal
8 infections, bacteremia or septicemia, or of pneumonias.
9 However, one specific category of infectious episodes was
10 observed at a somewhat higher frequency. This was wound
11 infections and cellulitis, which was seen in 8 percent of
12 the Zenapax-treated patients and 4 percent of the control
13 patients. The nominal P value for this finding was .05.

14 Fewer deaths were observed from infections in
15 the Zenapax-treated patients compared to placebo, a single
16 case versus seven cases in the control group.

17 We have 1-year follow-up data for malignancies
18 and lymphoproliferative disorders and 6-month follow-up for
19 these disorders in the Phase I study. Overall there was no
20 higher incidence observed of malignancies. In placebos the
21 incidence was 2.7 percent, with Zenapax 1.5 percent. In
22 the category of lymphomas, very few were seen, less than 1
23 percent in either group. This represented two cases in
24 each group. And one death was observed of lymphoma. This

1 was a subject who received a single dose of Zenapax, and
2 then it was stopped, and 7 months later developed an
3 intracerebral lymphoma and died.

4 Overall the rate of other adverse events was no
5 higher in Zenapax compared to controls, and the frequency
6 of most of the specific other adverse events was similar or
7 lower with Zenapax. However, a somewhat higher frequency
8 was observed of three specific adverse events, and these
9 consisted of hypertension, tremor, and the category of
10 impaired wound healing without infection. These numbers
11 are shown here, where the incidence of hypertension was 25
12 percent with Zenapax and 20 percent in the placebo arm.
13 Incidence of tremor was slightly increased to 19 percent
14 compared to 16 percent, and the incidence of wound healing
15 impairment without infection was observed in 12 percent of
16 the Zenapax-treated patients and 10 percent of the placebo.

17 To look at this information in more detail, a
18 subset analysis was performed. Beginning with
19 hypertension, the incidence of reports of hypertension as
20 an adverse event were assessed by age group, and what you
21 can see is that the major group where a higher incidence of
22 hypertension was observed in the Zenapax-treated patients
23 was the patients over age 60, with 34 percent compared to
24 16 percent treated with placebo. A smaller increase was

1 observed in the 18- to 39-year-old category, and there was
2 no change in the category of 40- to 60-year-olds.

3 When the results were subsetted by ethnic
4 group, most of the higher frequency of hypertensive adverse
5 events was observed among the non-Caucasians, where 29
6 percent of the subjects experienced a hypertensive adverse
7 event compared to 16 percent on placebo.

8 When the incidence of hypertension as an
9 adverse event was assessed based on the etiology of renal
10 failure, you can see that the higher frequency of
11 hypertension was accounted for by two of the etiologies of
12 renal failure, diabetes and hypertension, and essentially
13 no higher incidence was seen in the other etiologies of
14 renal failure. Among patients where diabetes was the
15 etiology of renal failure, there was an incidence of 26
16 percent observed in the Zenapax arm compared to 16 percent.
17 Among the patients with underlying hypertension, there was
18 an incidence of 27 percent compared to 10 percent in the
19 placebo-treated arm.

20 Antibody formation to Zenapax is important in
21 assessing the durability of the response. Anti-idiotypic
22 antibodies, as you heard before, were observed in some of
23 the patients treated with Zenapax. The incidence was 17
24 percent in patients treated with double therapy and

1 slightly lower, 12 percent, in those treated with triple
2 therapy. Rejection rates were similar in the patients who
3 did or did not develop antibodies. The incidence was 20
4 percent in those with antibodies and 18 percent in those
5 without. However, no change in mean serum levels of
6 Zenapax was observed in subjects who developed antibodies
7 to Zenapax, and the IL-2 receptors remained saturated
8 despite anti-Zenapax antibodies in these subjects.

9 So, in summary, our assessment revealed that
10 there were few safety concerns which came up looking at the
11 Zenapax-treated patients compared to controls. However,
12 some specific adverse events were observed with a higher
13 incidence, and some of these are also observed associated
14 with cyclosporine-A administration. These include
15 hypertension, tremor, and renal damage and renal
16 insufficiency. While no higher incidence of
17 lymphoproliferative disease and malignancies was seen in
18 the database as observed, there is a need for longer-term
19 follow-up to assess the long-term rates of these
20 complications, and the sponsor is planning on acquiring 3-
21 year data on these complications.

22 Thank you.

23 DR. BROUDY: Thank you.

24 ~~Are there any questions for either Dr. Bonvini~~

1 or Dr. Siegel from the committee? Yes?

2 DR. HUNSICKER: Just one question. This is Dr.
3 Hunsicker. You have made a point about the tremor and the
4 hypertension as, if I can put this in quotations,
5 "separate" adverse effects that appeared to occur more
6 frequently. Were they in fact correlated? That is to say,
7 did they occur in the same patients? In which case, if
8 that were the case, we would be looking at a single
9 evidence -- that is, the combination of hypertension and
10 tremor -- as evidence of cyclosporine toxicity which
11 occurred.

12 Given the number of examinations that you've
13 done, it would be much less suggestive that there was
14 anything specific about this. It would just likely be
15 noise. If they were separate, if they were in different
16 groups of patients, it might be slightly more convincing.

17 DR. JEFFREY SIEGEL: That's a very good
18 question. I don't have that information. Does the sponsor
19 have that?

20 PARTICIPANT: That can be answered later on.

21 DR. BROUDY: Dr. Jonsson?

22 DR. JONSSON: Thank you. That was sort of my
23 question as well. Those side effects, hypertension,
24 tremor, and renal damage, are really the three main side

1 effects of cyclosporine, so did you -- you might have said
2 this -- compare the cyclosporine dose adjusted for body
3 weight in those two groups? In addition, if you had a
4 higher cyclosporine level, you're less likely to have a
5 rejection as well.

6 DR. JEFFREY SIEGEL: We asked that question of
7 the sponsor, and the pharmacokinetics reviewer also looked
8 at that. There was no difference observed in the
9 cyclosporine levels between the two groups.

10 Dr. Trapnell, could you comment on that?

11 DR. TRAPNELL: The cyclosporine concentrations
12 that were obtained were really just part of the trial, and
13 they were not really done in any kind of formal
14 pharmacokinetics study sense, if you will. So it wasn't
15 detailed what doses the patients were receiving, and
16 cyclosporine inherently has a lot of variability both
17 between and within patients. So the only data that was
18 provided were mean data. When we looked at the mean data,
19 the doses were not different and the levels were not
20 different between the Zenapax arms and the placebo arms.
21 But the ability to break that data out to really look at it
22 in detail just wasn't provided.

23 DR. GRIMM: Was this just trough levels, or was
24 there more area under the curve or peak levels

1 DR. TRAPNELL: It was trough levels.

2 DR. JONSSON: And as a follow-up on that, it
3 would be interesting to know the levels early on and late,
4 because early levels -- rejection happens early after
5 transplant, so high levels early on prevent rejection.

6 DR. JEFFREY SIEGEL: Let me make one other
7 point, which is that if these adverse events are real --
8 and we don't know that they are -- and if they are
9 associated with cyclosporine-A toxicity, there are two
10 possibilities. One has been mentioned, that you might have
11 higher levels of cyclosporine-A in Zenapax-treated
12 patients, or it could be that Zenapax somehow potentiates
13 the effect of cyclosporine-A, and I think further studies
14 may help assess that.

15 DR. BROUDY: Let me ask a quick question about
16 the renal damage. In your Table 18, it actually looks at
17 the 6-month period that the mean serum creatinine was lower
18 in the Zenapax arms and the GFR was higher in the Zenapax
19 arms. In Table 18 on page 17. So it's hard for me to
20 understand why you're concluding that Zenapax causes renal
21 damage and insufficiency.

22 DR. JEFFREY SIEGEL: The renal damage and
23 insufficiency that's shown here are serious adverse events
24 that were reported. When I looked at the case report

1 corresponding to these small number of events, what I found
2 is that many of these patients were -- patients who
3 developed an elevated serum creatinine were admitted to the
4 hospital for renal biopsy and were found, generally
5 speaking, to not have transplant rejection. Many of these
6 patients were thought to have cyclosporine-A toxicity, and
7 the dose was adjusted. So it may not have shown up in the
8 mean creatinine levels.

9 DR. BONVINI: Let me clarify also one point. I
10 guess the question also should be addressed to the sponsor,
11 but in Table 18, which were data provided by the sponsor,
12 the patients who lost their graft were excluded. So this
13 refers only to those patients with a functioning graft.

14 DR. BROUDY: Other questions? Dr. Auchincloss?

15 DR. AUCHINCLOSS: I've got a total of four.
16 First of all, for the FDA in general, I don't detect any
17 unhappiness on your part with taking rejection episode
18 frequency as the endpoint for this, and a satisfactory
19 endpoint. You're not going to worry at all about graft
20 survival. Is that correct at this point?

21 DR. BONVINI: No, this is not entirely
22 accurate. We are concerned with the impact, and, again, I
23 couldn't summarize the entire consensus expressed in the
24 1994 advisory committee meeting, but certainly there should

1 be no negative impact on graft survival and patient
2 survival.

3 Indeed, we normally suggest that the study be
4 powered to detect no decreased graft and patient survival
5 at 1 year post-transplant, and we usually recommend longer
6 follow-up to assure that graft and patient survival is
7 preserved. And we like to power the study as an
8 equivalency study to make sure that there is no decrease in
9 graft and patient survival. This study was not necessarily
10 designed that way; however, there is no negative impact on
11 graft and patient survival in either study at 1 year.

12 DR. AUCHINCLOSS: My feeling is that this is
13 excellent. Would there be in fact other surrogate markers
14 that you would accept? For example, supposing rejection
15 rates were identical, survival rates in patients and grafts
16 were identical, but the treatment arm was on half the
17 amount of immunosuppression 1 year later. Would the FDA be
18 interested?

19 DR. BONVINI: I think so. I will let Jay
20 comment on that. We've debated it in the past, and I think
21 we will be looking favorably, provided that sufficient
22 safeguards were introduced to guarantee that patient and
23 kidney survival were preserved.

24 Jay, would you like to comment?

1 DR. JAY SIEGEL: We discuss all proposals we're
2 faced with. It is in fact the case in some other diseases
3 that require chronic steroid therapy, that steroid sparing
4 as a -- the ability to taper off steroids as an endpoint
5 for clinical trials, when you either add in placebo or a
6 drug, is considered a measure of benefit. And we'd have to
7 discuss that. Of course, just as the issue with -- while
8 we recognize rejection episodes is a real benefit and one
9 that the committee felt in these days of relatively high
10 graft survival out at least to a year or two is a more
11 pragmatic one to look for and one that is likely to predict
12 more meaningful outcomes, it's also the case that the more
13 meaningful the benefit, the easier it is to weigh against
14 toxicities.

15 So a graft survival benefit in a drug, for
16 example, that is going to carry a risk of serious infection
17 or lymphoproliferative disorder is going to hold up a lot
18 better than is a steroid-sparing effect, for example. And
19 we weigh all of that in together.

20 DR. AUCHINCLOSS: And I think the point simply
21 is that these are the real clinical endpoints that we're
22 working with in clinical transplantation at this point.

23 Now, my second question would be about risks
24 and looking for safety. I would think that I guess Bob

1 Rubin, my colleague, would have taught me that the sentinel
2 chicken in this kind of study would be the patients who got
3 the immunosuppressive agent had a rejection episode and
4 then got OKT3 to rescue their kidney. That's probably as
5 vigorous an amount of immunosuppression as you could come
6 up with. Was there any indication that there was in that
7 group a surprising incidence of anything?

8 DR. BONVINI: I think this question should be
9 addressed to the sponsor. My answer is that the database
10 is fairly small.

11 DR. AUCHINCLOSS: I understand that.

12 DR. BONVINI: And I don't recall specific
13 events of lymphoma or any other problems with patients
14 receiving OKT3, but I'll ask the sponsor to confirm that.
15 However, only a very small number of patients received
16 OKT3.

17 DR. AUCHINCLOSS: I think the answer is no,
18 because there's such a small incidence of things like
19 lymphoproliferative disease, that I can't believe it's
20 going to be yes. But I think it's an important question,
21 because if you were going to see it, that's the group where
22 you would see it, I think.

23 My third question for you is back on this CMV
24 issue. Bob Kirkman has pointed out and I think

1 correctly -- that perhaps the best test of a new pathogen
2 being introduced during the time that this reagent is in
3 place would be the CMV-positive donor to a CMV-negative
4 recipient. As I look at your table, there are probably 60
5 such patients treated with Zenapax in the two trials. On
6 the other hand, if I understand the protocols correctly,
7 all of those patients would have been treated with
8 prophylactic anti-CMV therapy. Is that correct, and what
9 were the outcomes of CMV infection in that subgroup, the
10 donor positive/recipient negative?

11 DR. BONVINI: We asked the sponsor the same
12 question, and you have a slide, I guess.

13 DR. LIGHT: You were asking about the incidence
14 of CMV infection based on risk groups. So positive into
15 positive, 10 percent Zenapax, 17 percent --

16 DR. AUCHINCLOSS: Yes. It's the next group
17 down that I think we're interested in.

18 DR. LIGHT: Okay. So positive and negative, it
19 was 25 percent and 31 percent.

20 DR. AUCHINCLOSS: But it's also true, is it
21 not, that all of those patients are receiving --

22 DR. LIGHT: Prophylaxis. That's correct.

23 DR. AUCHINCLOSS: I think these data are very
24 impressive for safety, but I think we do have to remember

1 that it's safety in the presence of drugs specifically
2 designed to keep the infection from happening.

3 DR. GRIMM: Is that purely viremia, or is that
4 tissue-invasive disease?

5 DR. BROUDY: There were two tissue-invasive in
6 each category. The rest were viremias.

7 DR. LIGHT: Yes. I have to tell you, we had a
8 very liberal definition of CMV. Our trial was geared
9 toward collecting the most accurate data with respect to
10 rejection, and we were very liberal. Any patient who had
11 serologic evidence of CMV, regardless of what test was used
12 at their center, was counted as having CMV. So
13 theoretically a patient could have come in with a fever,
14 had some blood drawn for CMV, turned out to have a urinary
15 tract infection that caused the fever, but the lab test
16 came back that the patient had seroconverted, and that was
17 counted as a viremia. So it was a very liberal definition
18 of CMV.

19 DR. AUCHINCLOSS: Seroconverted or antigenemia?

20 DR. LIGHT: Antigenemia.

21 DR. AUCHINCLOSS: They had detectable CMV
22 infection.

23 DR. LIGHT: Yes. So those patients were in the
24 same group as those who had clinical symptoms that were

1 culture-positive. So we just lumped everything together,
2 and there was just 2 percent in each group with tissue-
3 invasive disease.

4 DR. AUCHINCLOSS: My last question for the FDA
5 in general, as a prelude to the later discussion that we'll
6 have, does the FDA have any experience with an
7 immunosuppressive agent that is shown to have efficacy for
8 one organ, one solid organ, that does not subsequently turn
9 out to have efficacy for some other solid organ? I'm not
10 talking about bone marrow transplantation. I'm talking
11 about kidney versus liver versus heart. Is there any
12 example of an agent that works for one and not the other?

13 DR. JAY SIEGEL: I would think the panel might
14 be better prepared to answer that question, since so much
15 of the data regarding that comes from uses that have not
16 been submitted to the agency, I suspect.

17 DR. AUCHINCLOSS: I'm not aware of any, but, of
18 course, we are all aware that, I think, all of the drugs
19 that have been licensed for treatment for prevention of
20 rejection in transplantation have been licensed originally
21 with an organ-specific labeling, and, of course, the label
22 that you've come up with for this one here is organ-
23 specific, and I'm wondering why and do we need to stick
24 with that. I'm on Abbey's question again.

1 DR. BROUDY: Maybe we could get to this issue
2 during the discussion period.

3 Okay. I think that concludes our question
4 period. Thank you very much.

5 I think we'll move on now to the questions for
6 the advisory committee, and if we could move to Question 1,
7 Question 1a is for discussion purposes, and this is,
8 "Please discuss the extent to which the results of the
9 double-therapy and triple-therapy studies can be
10 generalized to the various current U.S. practices." Would
11 one of the transplant nephrologists like to tackle this
12 issue?

13 DR. SUTHANTHIRAN: Usually Larry always takes
14 the mike. I'll let Larry speak.

15 (Laughter.)

16 DR. HUNSICKER: I don't know at what point in
17 the discussion we want to broaden the issue. Let me get at
18 what I think is the most direct issue, which is that we've
19 already heard from the FDA that the patients in the triple-
20 therapy arm very closely resemble the American kidney
21 transplant recipients, and, therefore, that study clearly
22 is extrapolatable. Everything that we've seen from the
23 double-therapy arm is consistent with what we've seen in
24 the triple therapy arm, and I would assume that that would

1 be the case, too. Therefore, my answer would be, yes,
2 sure, this is extrapolatable.

3 However, I do want to pick up at some point --
4 and I'll leave it to the chairman's decision when -- on
5 Hugh's question, because it is very closely related to the
6 question that I put to the FDA, who is now being
7 distracted, early on that had to do with how much more
8 information is needed. As I scan my memory, I can think of
9 no circumstance in which an agent that has been shown to be
10 effective in prophylaxis for rejection in one organ has not
11 been shown to be -- at least of the vascularized organs we
12 deal with -- has not subsequently been shown to be
13 effective in others as well.

14 We're going to have questions -- there are no
15 pediatric patients in this particular study, so we're going
16 to be asked whether this could be extrapolated to pediatric
17 patients. There are no living donor patients in these two
18 studies, and so we're going to be asked whether the data
19 are extrapolatable to living donor recipients. And, just
20 so that we're complete about this, there are no second and
21 subsequent transplants in this data set, and if we aren't
22 going to be asked, we should have been asked whether these
23 data are extrapolatable to patients receiving second and
24 subsequent transplants. And the answer is that everything

1 in our experience has suggested that this is the case, that
2 they are extrapolatable.

3 Now, I think that extrapolation of these data
4 to second and subsequents is a little easier, although not
5 all that much easier, than the extrapolation to living
6 donor and to pediatric recipients, and perhaps the most
7 distant is the extrapolation to other organ types. But
8 there are some real practical issues both for the
9 transplant community -- and I want to say here I'm speaking
10 for the transplant community and not for the sponsors. It
11 can be extremely difficult to have adequately powered
12 studies in some of these subsets. It might be very
13 difficult to have an adequately powered study of recipients
14 of second transplants. It might be very difficult to have
15 an adequately powered study of pediatric patients. It's
16 probably achievable to do some of the others. But to
17 require this before the community is considered blessed in
18 using these agents in these other groups is, I think,
19 unreasonable. So we have to have some sense of how much
20 more information is required in order to be able to
21 extrapolate.

22 So what I would like to suggest is what some of
23 the particular questions are that come as we do this. I
24 can't think of any that particularly relate to the second

1 and subsequent recipients. The general rule in these
2 things is that the higher the underlying basic risk is, the
3 more likely you are to see a benefit. So presumably
4 there's no reason that we should not expect that there
5 would be a benefit in second and subsequents.

6 The converse is true with respect to living
7 donors. The baseline rate of rejection is modestly less,
8 although if you exclude the recipients of HLA identical
9 transplants, I'm not sure it is substantially less. So one
10 could ask whether the potential benefits which are going to
11 be proportionately smaller will still be in excess of the
12 potential risks in the living donor population. Since
13 there are so few risks in the use of this drug, it appears,
14 I think that the answer to that is still yes.

15 With respect to the pediatric patients, the
16 issue arises as to whether the same rules hold for kids,
17 and here the direction in the two studies is a little
18 contradictory. There was a trend which was not analyzed in
19 the FDA analysis toward more efficacy in older people in
20 the double-therapy study and a trend to more efficacy in
21 the younger patients in the triple-therapy study. To my
22 statistical brain, these totally cancel out so that there's
23 no evidence of any age effect whatsoever. But you could
24 ask, do we need to show in pediatric groups with respect to

1 efficacy that there is good efficacy? And, unfortunately,
2 the study which I had thought was going to give a great
3 deal of clarity to this turns out to be an uncontrolled
4 study, so it really won't. But you could ask that.

5 And then, finally, one can ask the question, if
6 we're going to go to other organ types, how much more
7 information does the FDA need before the community will be
8 free to conclude that this agent which works in one
9 transplant type, like other agents that have subsequently
10 been proved to work in other transplant types, might be a
11 reasonable thing to use in other organ recipient types?

12 A couple of years ago I might not have said
13 this, but we are increasingly being constrained in the
14 transplant community from use of new agents that are
15 potentially expensive, and I have no reason to doubt that
16 Hoffmann-La Roche is going to get everything that it can
17 out of this particular agent. We're increasingly
18 constrained in the use of these agents unless we can show
19 an FDA indication. So it's conceivable that the people who
20 are transplanting heart and lung and liver and so forth
21 might in fact be constrained in the use of this agent
22 pending the further information, which should be obtained.
23 And I think this issue should probably be addressed.

24 ~~But to get back to the first, I don't think~~

1 that there's any question but the data are extrapolatable
2 at least to the primary cadaveric kidney transplant
3 recipients in the United States.

4 DR. BROUDY: All right. I think we've roamed
5 and actually answered almost all of the questions already.

6 (Laughter.)

7 DR. BROUDY: But maybe I'd like to get a second
8 opinion. Dr. Suthanthiran?

9 DR. SUTHANTHIRAN: I don't have the time to be
10 brief, but --

11 (Laughter.)

12 DR. BROUDY: Dr. Suthanthiran has already told
13 me he brought 50 slides.

14 (Laughter.)

15 DR. SUTHANTHIRAN: I think this agent has been
16 tried in the context of CSA-based immunosuppressive
17 therapy, and that's the most common protocol we use in
18 clinical transplant. The other one would be FK, and the
19 data suggest CSA and FK work more or less similarly, except
20 for a slight reduction in acute rejection. So from that
21 perspective, I think the data that was presented to us
22 today can be generalized to the overall cadaver renal
23 transplant population.

24 It was very impressive that in the

1 mycophenolate group, the rejection incidence went from 20
2 percent to 12 percent, and the 20 percent is not an
3 unlikely number for a living related transplant, so I would
4 anticipate even in a living related transplant, except for
5 the two haplotype match, it may be beneficial.

6 We were told that the demographics of the
7 patient population is quite representative of the U.S.
8 population, so my answer would be yes to Question 1a, that
9 this data could be generalized to the current U.S.
10 transplant population.

11 DR. BROUDY: And I would agree. In fact, many
12 of those patients were U.S. transplant populations. So
13 let's move on to Question 1b --

14 DR. AUCHINCLOSS: Well, I don't quite agree,
15 Virginia.

16 DR. BROUDY: Okay.

17 DR. AUCHINCLOSS: I agree in principle. What
18 I've learned this morning is that this is an
19 immunosuppressive agent that's effective, and there are, as
20 has been pointed out, a large number of special cases, and
21 I don't know for which ones this is an appropriate agent to
22 use.

23 The most important one is the mycophenolate
24 combination, and, of course, this company, which produces

1 both mycophenolate and this agent, is going to push the
2 notion that this agent should be added on top of triple-
3 drug therapy that includes mycophenolate. I mean, that's
4 absolutely inevitable, assuming licensing occurs here. And
5 I don't feel all that comfortable that we know that in fact
6 it's safe in that combination. I think it's effective, but
7 I don't know where the safety line is.

8 My view of this is that you don't get
9 immunosuppression without immunosuppression. If you take
10 the rejection rate down from 20 percent to 10 percent, you
11 probably pay a price for that in terms of complications of
12 immunosuppression. I don't know where it's going to come
13 out. I believe the transplant community will figure out
14 how it's going to come out.

15 The point is that you can't make an absolute
16 generalization from these data that it's going to be
17 equally efficacious and equally safe in all the possible
18 combinations, in all the possible treatment groups.

19 DR. BROUDY: Thank you.

20 Other opinions? Yes, Dr. Jonsson?

21 DR. JONSSON: He was here first.

22 DR. BROUDY: Go ahead.

23 DR. WOODLE: I would agree with you. I mean,
24 ~~there was a single limited study of 75 patients, of which~~

1 50 were studied with a combination of MMF and Zenapax. So
2 this is really a Phase IV issue for the FDA and the
3 company, and I think the answer should be, it should be
4 taken care of and addressed in a Phase IV recommendation to
5 the company.

6 DR. BROUDY: Dr. Jonsson?

7 DR. JONSSON: Just a comment on Question 1a,
8 how this therapy applies to various current U.S. practices.
9 I think more and more kidney transplant programs are now
10 using as the primary immunosuppression tacrolimus,
11 CellCept, and steroids, and I think that the pendulum is
12 swinging more and more that way, and I'm just curious to
13 know if this drug has been used in combination with
14 tacrolimus and if there are any problems identified with
15 that.

16 DR. BROUDY: Would anyone from the company like
17 to comment on that?

18 DR. VINCENTI: We really don't have experience
19 using Zenapax in combination with tacrolimus. Personally,
20 quite frankly, I feel that still the main thrust of triple
21 therapy involves cyclosporine, CellCept, and prednisone,
22 with tacrolimus being used primarily for the high-risk
23 patients. If you look at the Phase III study, though, of
24 ~~tacrolimus, tacrolimus was used with anti lymphocyte~~

1 agents, OKT3 and ATGAM, and I think if we can substitute a
2 biologic agent that is more specific and it's clear does
3 not have major adverse events, I think one could very
4 easily extrapolate that it may be better to use it with
5 tacrolimus, and it's probably going to be safer than
6 combining tacrolimus with OKT3 or MLG that have such broad
7 immunosuppression and are well known to increase the
8 incidence of lymphoma or opportunistic infection.

9 DR. JONSSON: I think many programs are now
10 using tacrolimus, prednisone, and MMF, without using either
11 OKT3 or ATGAM. I think that's actually the most common way
12 of using it.

13 DR. BROUDY: I guess the question is whether
14 the FDA should require studies with these various
15 permutations or not, and that's the question we're really
16 debating now.

17 Ms. Meyers?

18 MS. MEYERS: But there's another question,
19 which is, once the drug is out on the market, they're going
20 to be using it for all organ transplants. I mean, that's
21 happened with all of these drugs, even though they're
22 labeled. So my question is, the company is going to submit
23 pediatric information to the agency, and maybe Jay can
24 answer this. Are you going to put something on the label

1 about what is known about pediatric dosages, based on that
2 small, incomplete thing, but at least pediatricians will
3 have some information?

4 DR. JAY SIEGEL: Yes. That reflects our
5 current policy that any reliable data we have, even if
6 inconclusive regarding pediatric use, would appear in the
7 label.

8 MS. MEYERS: So if you had information on the
9 use of this drug with liver transplant or heart transplant
10 or lung transplant, would you also put that on the label?

11 DR. JAY SIEGEL: If we have information on
12 drugs that off-label use is unsafe or dangerous sometimes,
13 we put that in the label. We do not put unproven uses or
14 unapproved uses -- efficacy data about unapproved uses in
15 the labeling of drugs.

16 MS. MEYERS: So the company would have to
17 submit data on its use with other organ types. Is that
18 correct?

19 DR. JAY SIEGEL: Well, we don't have a decision
20 about how broad a label we'd write. I'm hearing a lot of
21 information from this committee and some recommendations.
22 We will incorporate that information and those
23 recommendations together with an assessment of what the
24 current status of the data are, as well as what current

1 practices are. It is not likely that we will act in a
2 manner inconsistent with the way we act with other drugs
3 used in transplantation, unless we decide to redirect the
4 way we deal with all of those drugs. Now, an individual
5 drug may have different data or different reasons to act
6 differently.

7 I should add perhaps, in response to Dr.
8 Auchincloss' earlier question, that while we may be unaware
9 of immunosuppressive drugs active for one type of
10 transplantation and not another, that there exist efficacy
11 issues, as some of the panel members have mentioned,
12 regarding quantitative efficacy, which is to say that in
13 some populations where the likelihood of rejection is much
14 lower, the possibility for benefit is, therefore, much
15 lower, and there are always safety issues. Every type of
16 organ transplant has different underlying diseases and
17 different potentially vulnerable organs as targets for
18 toxicity, and the relative risk and benefit of each
19 situation is a separate issue. So data are desirable.

20 I heard a comment that potentially not
21 approving certain uses might restrict the ability of
22 surgeons to use it in that area. On the other hand,
23 promoting studies in those areas, whether on label or new
24 indications, is probably desirable, given the fact that the

1 information content is different.

2 So I'm going to step back on this issue and
3 simply ask the committee for advice and integrate that
4 advice with data and with practices and try to figure out
5 what's the right thing to do.

6 DR. BROUDY: I think Dr. Grimm has a comment.

7 DR. GRIMM: Yes. The discussion which revolves
8 around all the special cases is especially germane to
9 pediatrics, and I'm sorry to jump to Question 6, but it
10 seems to be that's the way the conversation is going.

11 The children are at a special risk, because
12 there's a higher rate of acute graft rejection, a higher
13 rate of graft loss. Children's immune systems are
14 different, and that has been shown in a number of ways.
15 And we've had bad experiences in the past with just
16 introducing cyclosporine without enough data in advance,
17 and so in the early 1980s the pediatric patients didn't
18 really have the same benefit from cyclosporine that adults
19 did, and I'd be reluctant to just openly release this drug
20 for use in everyone, for the same concerns.

21 In pediatrics, at least the registry data from
22 the North American Pediatric Renal Transplant Cooperative
23 Study suggest that you need to use an anti-T cell agent
24 like OKT3 or ATG prophylaxis up front to get better

1 outcome. So in looking at use of Zenapax, the way I look
2 at it is, it's an either/or, either OKT3 or ATG or Zenapax,
3 and the question that I have is, is there similar efficacy?
4 Now, true, it looks like Zenapax is definitely a reduced
5 side effect profile compared to OKT3, but the question
6 remains what will the long-term efficacy be. In a child
7 who is age 4 and you're doing a transplant, if the average
8 cadaveric graft survival half-life is 8 or 9 years, you're
9 looking at transplanting that person again at 12, at 20, at
10 28, and it's not good enough.

11 So my concern about just releasing it in a drug
12 which isn't necessarily proven to be as efficacious as some
13 of the other anti-T cell agents, I have a big concern about
14 that.

15 DR. BROUDY: Dr. Auchincloss?

16 DR. AUCHINCLOSS: Jay, it seems to me that
17 labeling does two things. Sometimes it prevents patients
18 from getting reimbursed for treatment that their doctors
19 and everybody else, frankly, agree is worthwhile for them,
20 and, secondly, labeling drives the future studies that the
21 company initiates. Not all future studies, because the
22 transplant community will do future studies as well, but
23 the ones that the company cares about are those that will
24 broaden the labeling.

1 The current labeling that you have down for --
2 not you particularly, but that is listed for this agent
3 restricts it to renal transplantation, and that will drive
4 the company to test it in hearts and livers, which,
5 frankly, I think, is a waste of time, because the
6 transplant community will test it there and will know the
7 answer to that, and I think we can really be very confident
8 that we know what the answer is.

9 I am very concerned about the pediatric
10 population, and I could imagine defining other populations
11 that you might exclude from the labeling, and that's where
12 I think I'd use your power, if you will, to get the trials
13 to happen where in fact they really will be useful to you.

14 DR. BROUDY: Yes?

15 DR. GRIMM: There are only about 400 pediatric
16 kidney transplants done a year in North America, and so I'm
17 expecting Larry to comment that you'll never get that trial
18 done, and that's a very valid concern, and one of the
19 issues that leads to is how well the pediatric community
20 does and has supported multicenter studies. Look back at
21 the history of cancer therapy with the advent of CCSG and
22 POG, where the only way they really have made the
23 tremendous advances that they made was by forcing
24 ~~tremendous multicenter cooperative studies to answer~~

1 specific questions as they came up, and perhaps it's just
2 that in the pediatric transplant community, with the
3 support of the regulatory and the companies, we have to
4 pursue that even harder to capture every available renal
5 transplant being done in North America to get them into a
6 study to answer the questions as they come up.

7 Because as Dr. Vincenti said much earlier on,
8 this is just the opening of the flood. There are eight or
9 nine agents which are going to be coming up in the next few
10 years, and the same questions we'll be sitting here
11 debating in 3 or 4 years if we don't do those studies.

12 DR. BROUDY: Dr. Anderson, you had a comment?

13 DR. ANDERSON: Yes. I'm going to take Jay
14 Siegel up on his final comment, which was that he was going
15 to step back and throw this issue open to the panel, and
16 I'd like to look at it in a more global way, and the issue
17 is labeling.

18 DR. HUNSICKER: Is which?

19 DR. ANDERSON: Labeling. I had asked our
20 chairman privately is this the right time to talk about
21 this, and she said yes, it is, and so that's all you need.

22 (Laughter.)

23 DR. BROUDY: Since we seem to be discussing it.

24 DR. ANDERSON: Historically, if one looks at

1 the FDA and looks at the debate over FDA reform over the
2 last 2 or 3 years, a number of issues were clearly very
3 emotional, but discussed in some detail, and one of the big
4 issues -- and Abbey Meyers was one of the leaders in this
5 -- was that the FDA should never be put in the position
6 that it is passing off snake oil to an unsuspecting public.
7 Therefore, many of the suggestions for FDA reform that
8 included allowing drugs to be used prior to the time that
9 they're actually fully tested and so on were not considered
10 to be the ideal way to go.

11 But if we narrow it down a bit and look at the
12 present reality of this country, third-party payers are the
13 reality. The payment for drugs and biologics are dependent
14 upon FDA approval, and it is perfectly valid and I
15 understand where the FDA is coming from in saying, "Here's
16 our mandate, here are our rules, here are our regs, here
17 are our guidelines." What happens in terms of third-party
18 payment really isn't addressed in your specific guidelines,
19 but nonetheless it's the real world, and Abbey as well as
20 others can give examples -- probably everybody around this
21 table can give examples of where individuals who have
22 transplants then cannot be reimbursed for the cyclosporine
23 or whatever, and something needs to be done, and it isn't
24 obvious what can be done.

1 So one possibility would be, is it within --
2 well, I won't word it that way. One possibility would be
3 that the FDA could reexamine this issue, now that the major
4 debate for FDA reform is now resolved, and see if perhaps
5 in certain situations -- and this is perhaps one of those
6 situations -- the labeling could in fact give sufficient
7 wording that third-party payers could reimburse for solid
8 organ transplants, but to make clear that full experimental
9 studies had not been done and to mandate that the company
10 does basically Phase IV trials to basically answer the
11 questions. And, as Hugh says, if the transplant community
12 is going to do it anyway, you might not have to mandate it,
13 whatever, but basically to get some sort of compromise so
14 that the FDA gives sufficient approval to allow third-party
15 payments in certain situations, while still maintaining its
16 mandate to be certain that you don't get FDA approval
17 unless drugs are fully tested.

18 DR. BROUDY: Jay, would you like to handle that
19 one?

20 DR. JAY SIEGEL: Well, this isn't an unusual
21 circumstance in that regard. There is no drug or no
22 clinical trial in which there are not both included within
23 the population of patients studied subsets of biological
24 interest ~~those with more severe or less severe disease,~~

1 people with a certain underlying cause of disease, or
2 elderly or children -- that are included but not,
3 obviously, independently powered or prospectively
4 identified to where you can make an independent
5 contribution. So even within the population studied, you
6 have to make decisions about how broadly you can
7 generalize.

8 If this study had been open to children and had
9 three children in it, would we then say, well, we now know
10 it's okay to label for children as well because they
11 included children? And then outside the population that's
12 studied, there is an infinite range. That's always the
13 case.

14 So there never has been a crisp answer to how
15 narrowly or broadly you define an indication, and there is
16 plenty of precedent for indications to include use in
17 populations and even in manifestations of disease that some
18 might consider a different disease or a separate disease
19 and to exclude others. So it is always there as an issue.
20 It's a difficult issue.

21 As to specifically having a tiered type of
22 approval system, that was discussed in a number of circles
23 as part of the FDA reform, is there such a thing as a
24 ~~partial approval that might or might not impact~~

1 reimbursement in a way, and what would reimbursers do with
2 that, and whatever. It was largely rejected by those who
3 were considering it in various places. I can't, by
4 recollection, be too specific. I know the debate came up
5 as an approach. We write labels that do or don't in
6 various ways. You know, somebody does a study in heart
7 attacks, and everybody there has ST elevations and
8 everybody came within 6 hours, then we have to decide
9 whether the indication says that it's only people with
10 those criteria or whether we note that in the clinical
11 pharmacology section, and it's all judgmental, and it all
12 depends basically on inference that is dependent on expert
13 opinion, since it isn't statistically proven.

14 So that leaves me where I was before, and there
15 are important policy implications that extend beyond
16 reimbursement and future studies. They extend to what
17 detail men can promote, they extend sometimes to litigation
18 issues and whatever. We try to focus more on the
19 scientific questions, but are not oblivious to those
20 concerns and are interested in input. It's hard to give a
21 general answer, because it's such a complex issue that
22 doesn't lend itself to a simple answer.

23 DR. ANDERSON: May I ask the chairman,
24 ~~regarding this issue, if we can return to this to see what~~

1 the panel's recommendation would be?

2 DR. BROUDY: Yes, I think we will hit actually
3 all of these issues in going through the questions.

4 Dr. Miller?

5 DR. MILLER: Given that increasingly
6 transplantation of all types are being done under capitated
7 systems, I think the reimbursement issue is important, but
8 should be secondary. What I'm saying is, we should give
9 the clinicians who are making these decisions enough data
10 to be able to make the decisions and make sure that the
11 company supports and provides that data, because we're
12 actually going to be making the decisions on how we're
13 going to optimally use the resources that we have to
14 transplant so many patients under the new care system.

15 So I understand labeling issues and
16 reimbursement issues, but the primary thing is data, and I
17 think that has to be paramount.

18 DR. BROUDY: I guess I agree with you
19 completely that I would feel uncomfortable approving this
20 in a pediatric population when we haven't seen the data
21 from the pediatric population, knowing that the
22 neuroblastoma group has been able to achieve transplant
23 studies, and perhaps thinking that response to new antigens
24 is more important in the pediatric population, having seen

1 a certain absence of data in that regard, I think it would
2 be important to do studies in the pediatric population.

3 Dr. Kleinerman?

4 DR. KLEINERMAN: I just want to raise a couple
5 of points. I think that I disagree a little bit with Dr.
6 Grimm's statement that the oncology community, the CCSG and
7 the POG, have made considerable progress. I think the
8 studies that have come out of CCSG and POG have largely
9 been follow-up studies to novel approaches that have been
10 done in large centers, large cancer centers, and that the
11 questions that they answer are not really all that
12 exciting. So I'm not really -- and working in a
13 cooperative group, I think it's very difficult. What comes
14 out is very watered-down studies.

15 So appreciating what you're saying, I'm not
16 exactly sure what I would recommend, but I would caution
17 that I don't think the answer is to have a cooperative
18 group do the answer and you're going to get the answer that
19 you want, because I think when you analyze the data, when
20 you have 15 pediatric centers doing it, that the data --
21 you'd be amazed at how people aren't consistent with the
22 protocols and the data is watered down.

23 The other thing I'm concerned about is, in
24 oncology we have a great deal of problem getting new agents

1 for our patients. Companies are usually reluctant to give
2 the new agents to kids because of side effects or whatever,
3 so I really applaud Hoffmann-La Roche for taking the lead
4 and going ahead and doing the studies in pediatrics. I
5 think we do need more studies, but I would tend to agree
6 with Dr. Anderson that some inclusion in the label of what
7 we know about giving pediatrics may make the pediatric
8 transplant community construct the studies that need to be
9 done and I think the company needs to be encouraged to
10 support.

11 So I agree that there's not enough, but yet I
12 think we need to give the transplanters the tools to make
13 that decision and not rely on a cooperative group study to
14 do that.

15 DR. BROUDY: Dr. Hunsicker?

16 DR. HUNSICKER: I'd like to make three
17 comments, if I might, which I hope will prove to be
18 helpful. The first is that there are, in all of these
19 evaluations, really two issues to be dealt with. One is
20 safety, and one is efficacy. My arguments for broadening,
21 if you will, are really efficacy-related, where I'm
22 concerned that we may not be able in a timely fashion to
23 get more data to demonstrate efficacy in a subgroup in
24 which efficacy is prima facie very likely.

1 The issue of safety is quite a different one,
2 and there I would be much more conservative. Perhaps later
3 on I will extend Dr. Auchincloss' concern about safety
4 particularly in children, and I think that if I were to
5 come down with a recommendation, which I suppose I am sort
6 of finding myself oozing toward, Dr. Siegel, I would say
7 that you ought to require additional studies, but that they
8 should be focused on establishing safety within different
9 communities, and that if those studies, which might be
10 underpowered to show you efficacy, come up with a relative
11 risk reduction which is comparable with what was seen in
12 the major efficacy studies, that then one would be able to
13 assume that that was showing the same efficacy and now we
14 have demonstrated safety. So I guess I would focus on the
15 issues of safety.

16 The second thing is that with respect to the
17 extended use of this agent, it should be remembered that
18 there is something unique about transplant drugs as opposed
19 to drugs for treatment of common viral infections or
20 whatever, and that is that these drugs are used almost
21 exclusively by a group of physicians and surgeons who are
22 specialized in transplantation and that they're not likely
23 to be misused or trivially -- or at least less likely to be
24 misused or trivially used than an agent which is being used

1 by the entire physician population of the country. To this
2 end, it would be reasonable to include in the labeling for
3 this agent, just as it is for most of the other agents used
4 in immunosuppression, that its use should be restricted to
5 people with expertise in immunosuppression.

6 The third thing is that one of the traditional
7 problems of post-approval studies is the issue of
8 ascertainment. You hear a whole lot more about the bad
9 effects, but you don't really quite know what the
10 denominator is. This is also with transplantation a unique
11 situation, in that we have a census of the population being
12 followed in the UNOS database, and it may have been
13 mentioned that I'm this year's president of UNOS, so I'm
14 particularly aware of that issue. It seems to me that the
15 FDA would do well to speak with UNOS about some of these
16 things where we need to make certain we include in our data
17 collection the questions that need to be answered so that
18 we can have a proper denominator to these things.

19 The question came up about the possible late
20 rejection episodes in the American triple-agent trial. To
21 get further information on this, which is a small subset of
22 all of the patients, is going to require a huge trial and
23 an immense period of time. It probably is the kind of
24 thing that is ideally suited to a post approval

1 surveillance, where in fact with transplantation we could
2 give you a census of all the patients and could look at
3 this in a very clear fashion if we have the appropriate
4 information captured in the UNOS database.

5 That's my three comments.

6 DR. JAY SIEGEL: Just for clarification, your
7 comment about focusing on safety data, was that intended to
8 apply across the board to issues of pediatrics and new
9 drugs, but also other organs? Heart and liver?

10 DR. HUNSICKER: Exactly. Exactly. I look at
11 the interaction of two issues. One is feasibility, and the
12 other is the need for information. Now, these are 500 or
13 something like that patient studies. You can get that in
14 liver, you can get that in heart. That's not impossible,
15 and it's not unreasonable to require those populations to
16 have properly done studies. But you're not going to get
17 this easily in pediatrics, and I would hate to stick
18 approval in pediatrics to a study that's going to be
19 virtually impossible to do. The issue with children is
20 safety.

21 DR. BROUDY: Dr. Grimm, would you like to
22 comment on that?

23 DR. GRIMM: I can't argue with that issue, and
24 it looks like the Zenapax safety data is very good.

1 However, I still am concerned about comparing the efficacy
2 of Zenapax with the efficacy of the other biological
3 response modifiers that we use, OKT3 and ATG, because I
4 don't see any data suggesting similarity, one is better,
5 one is worse, and I do have a concern in 2 or 3 years when,
6 if Zenapax were freely available to the pediatric
7 transplant community, it is likely that it would be used
8 extensively fairly rapidly because of its lack of side
9 effects, and then we may never know or we may have lost the
10 opportunity to determine whether it is as good as previous
11 therapy and how do you compare it to other therapy.

12 I just have a big concern about that.

13 DR. BROUDY: Maybe we could move through the
14 questions specifically now. I think we've had a very good
15 discussion on Question 1a, and now I'd like to move on to
16 Question 1b, and this is a question we need to vote on.
17 "Do the data from the double-therapy and the triple-therapy
18 studies establish the efficacy of Zenapax in reducing the
19 incidence of renal allograft rejection?" Who would like to
20 start the comments on this?

21 DR. HUNSICKER: Yes.

22 DR. BROUDY: Dr. Hunsicker, yes. That's terse
23 and concise.

24 ~~DR. SUTHANTHIRAN: Should I elaborate on that?~~

1 (Laughter.)

2 DR. BROUDY: Yes.

3 DR. SUTHANTHIRAN: [Inaudible] biopsy-proven
4 acute rejection at 6 months. Both the two-drug and the
5 three-drug studies support that. I think if the question
6 is focused on that, I think the answer is yes.

7 DR. BROUDY: Thank you.

8 Dr. Jonsson, would you like to comment?

9 DR. JONSSON: I would like to see the
10 cyclosporine data a little bit broken down, but yes --

11 DR. BROUDY: Please use your microphone.

12 DR. JONSSON: I'm sorry. The short answer is
13 yes.

14 DR. BROUDY: Good. Are we ready to take a
15 vote, or are there other comments on this question before
16 we vote? Anyone else like to make a comment?

17 (No response.)

18 DR. BROUDY: Okay. All who would vote yes that
19 the data from the double-therapy and triple-therapy studies
20 establish the efficacy of Zenapax in reducing the incidence
21 of renal allograft rejection, please raise your hand.

22 (Show of hands.)

23 DR. BROUDY: Are there any no votes?

24 (No response.)

1 DR. BROUDY: Okay. Thank you.

2 Let's move on now to Question 2a, and this is
3 for discussion only. "In light of this observation, please
4 discuss whether and how labeling should address the
5 monitoring and management of patients who receive Zenapax
6 as an add-on to triple immunosuppression."

7 DR. WEISS: The "this observation" was the
8 observation that the period at risk for rejection in the
9 triple-therapy study may extend beyond the first 3 months
10 and could have implications in terms of management and
11 monitoring.

12 DR. BROUDY: Dr. Hunsicker?

13 DR. HUNSICKER: I think that the status of our
14 information is that we have a suggestion that there may be
15 a difference in triple therapy, we do not know that there
16 is, and that the labeling should indicate that surveillance
17 for late rejection is particularly appropriate in this
18 group of people.

19 DR. BROUDY: Dr. Auchincloss?

20 DR. AUCHINCLOSS: I just want to make the
21 overall point that as opposed to the labeling of the
22 indications for use, this kind of labeling for this kind of
23 drug, I think, is of minor importance, which is to say the
24 ~~people who use this kind of reagent will know much more~~

1 about it than you're going to be able to include in the
2 fine details.

3 DR. BROUDY: I agree. And they'll be following
4 the patients closely. I agree.

5 Other comments?

6 DR. WOODLE: I'm sure this is going to be a
7 recommendation, but I think that a closer look at the
8 patients who are experiencing late graft rejection in the
9 triple-therapy study in a comparison to those who remain
10 free of rejection would be something the FDA would want to
11 have the company do, to try to see if there are risk
12 factors to determine who is at risk or at higher risk for
13 rejection in those patients. And although there's some
14 cyclosporine data in the tables presented by the company,
15 there's no data beyond 3 months about cyclosporine.

16 DR. BROUDY: Okay. Let's move on to Question
17 2b. "In light of this evidence of diminished long-term
18 durability of response in the triple-therapy study, should
19 studies of longer-term treatment or other forms of
20 treatment optimization be encouraged?"

21 Dr. Hunsicker?

22 DR. HUNSICKER: I think my comments would be
23 that such studies are going to be virtually infeasible.

24 ~~The numbers of patients if you look at the incremental~~

1 numbers of rejections in that period of time, it is so
2 small that it's going to be extremely difficult to do this
3 as a prospective design trial. This is the kind of post-
4 approval surveillance that I think will be possible on a
5 census of patients if we in fact get the company or the FDA
6 to work with UNOS to make sure that those data are
7 collected.

8 DR. BROUDY: Ms. Meyers?

9 MS. MEYERS: I really disagree, because these
10 very rare cases like pediatric transplantation, it's an
11 orphaned indication. There have been orphan drugs approved
12 by studies of 10 people. Do it. Ask the company to do it.
13 I really think that the company should be asked to do
14 studies on other organs, because we know that FK506 came on
15 the market for several years only for liver transplant.
16 But the fact is, FDA should request the company to do these
17 studies of pediatric indications. They don't have to tell
18 them to study it on 1,000 children. They know there aren't
19 1,000 children. But they could say, "Do it on 10, 15, 20
20 kids," and that could be done.

21 DR. BROUDY: Well, maybe this is the time,
22 then, to specifically discuss the issue of what should be
23 done in other organ transplant settings, other than the
24 cadaveric kidney transplant setting. I'm sure this is an

1 area of interest to the FDA. What should we do in the
2 setting of the heart transplant or liver transplant?
3 Should we request another study of the company?

4 Dr. Miller?

5 DR. MILLER: Well, yes, of course. At this
6 point, the approval is for renal, and unless we vote to say
7 let's open it up to approval for all different organs, the
8 company will be required, if they want to extend the label,
9 to do studies. I do agree with Dr. Hunsicker that
10 potentially the studies do not have to be huge randomized
11 trials. They can compare to what is the standard of care.
12 Well-controlled Phase II trials that could adequately
13 assess the efficacy and safety of a drug in a specific
14 population could be adequate. But I think they should be
15 done.

16 DR. BROUDY: Dr. Auchincloss?

17 DR. AUCHINCLOSS: First of all, specifically
18 with respect to 2b, frankly, it scares me to death to think
19 that people are going to start using this drug long term,
20 because apparently they think that it's risk-free, and
21 immunosuppression is not. So the fact that in fact
22 everybody's talking about using it long term leads me to
23 think that, yes, long-term trials are something that I do
24 want to see the company do.

1 Now, with respect to your bigger question, no,
2 I would not ask for trials of heart. I would specify solid
3 organ allografts in adults, is the way I would do the
4 labeling.

5 DR. BROUDY: Dr. Hunsicker?

6 DR. HUNSICKER: Just to show that I'm not
7 entirely consistent, I would actually probably like to see
8 or require a study in hearts and in livers. I would not
9 require two pivotal studies. I would require one, because
10 I think that if it is consistent with the very -- and I say
11 this because it is feasible. It's not too big a deal to do
12 that. A major focus, as I've already indicated, should be
13 toxicity.

14 I actually will change what I said about long-
15 term studies with respect to Hugh's comment about the -- I
16 had not assumed that you meant that people were really
17 going to be studying longer use of this agent, although
18 that's one possibility. I would actually probably first
19 have asked whether that stuff that appears in the American
20 study after 6 months is real or a fluke. I think it may be
21 a fluke. I don't know, and we have to look and see about
22 that.

23 But if in fact there is any suggestion that the
24 use of this agent would be extended beyond its current

1 time, that has to be based on additional safety data. Or
2 at least it has to require additional safety data.

3 DR. BROUDY: We're really addressing two issues
4 here, both the other organs and the long term. Maybe we
5 should focus on the other organ issue and then get to the
6 long term.

7 DR. HUNSICKER: The other organs, I would just
8 stick with what I've said with respect to pediatrics, since
9 that came up. I've already said I think it would be very
10 hard to do those, and so I would not require an efficacy
11 study in children, but I would require more safety
12 information.

13 DR. BROUDY: I guess I would also like to see
14 safety information on other solid organ transplants.
15 Speaking as the one who takes care of all the post-
16 transplant lymphoproliferative disorders in the solid organ
17 transplant recipients at the University of Washington, in
18 which we have about a 5 percent incidence in our heart and
19 particularly maybe even higher in our liver transplant
20 recipient population, I see a lot of PTLD, and I would very
21 much like to see this agent studied, since I think it may
22 have cost since it is a very effective immunosuppressive
23 agent, to make sure that it does not increase the risk of
24 particularly PTLD in the liver transplant population. So I

1 would also like to see those safety studies done in other
2 solid organ transplants.

3 DR. WEISS: But would you be able to do that in
4 a single-arm study comparing to what is known, basically a
5 historically controlled type of setting with things like
6 lymphoproliferative diseases?

7 DR. BROUDY: Well, I'd have to look at how many
8 liver transplants are done.

9 Perhaps you know this, being a member of UNOS,
10 how many are done in the states and whether one could do a
11 two-arm study.

12 DR. HUNSICKER: It would be possible to do a
13 two-arm study. It would not be excessively difficult.

14 DR. BROUDY: I think a two-arm study would be
15 better.

16 DR. SUTHANTHIRAN: That's very interesting, and
17 a selective immunosuppressant is being evaluated, and we do
18 have data that back our approach. So I would support an
19 organ-specific safety study.

20 DR. BROUDY: Dr. Auchincloss?

21 DR. AUCHINCLOSS: I don't want you to think for
22 a second that I don't want the studies to be done. The
23 fact is, I know they will be done, no matter how you label
24 this. I can tell you that there will be six presentations

1 at the American Society of Transplant Physicians and
2 Surgeons a year from now that will include heart and will
3 include pancreas and will include lung, and you'll have
4 more trials than you can possibly deal with.

5 What you may not have are some of the ones that
6 we're particularly talking about here. Those are the ones
7 that I want the company to focus on, rather than spending
8 their money doing the liver trial.

9 DR. WOODLE: But, Hugh, what you won't have is,
10 you won't have the financial backing and the rigor with
11 which these studies will be done as if they were done under
12 an FDA prospectus.

13 DR. AUCHINCLOSS: I understand that, but
14 that's --

15 DR. WOODLE: So I'd like to just exercise a
16 note of caution. I agree that we need to address the issue
17 of reimbursement, but I think we need to be very careful
18 about sacrificing the science to try to achieve that. I'm
19 not sure from a statutory perspective that it's within the
20 realm of the FDA to try to address that issue. That may be
21 something for another agency of the government to try to
22 address the issue as to reimbursement, whether or not these
23 insurance providers should be able to deny payment.

24 ~~MS. MEYERS: But only if you get it on the~~

1 label. If it's not on the label, they can legally refuse
2 reimbursement. So all of your studies won't do any good if
3 that company doesn't put it on the label.

4 DR. WOODLE: I would agree wholeheartedly that
5 the requirement for two pivotal-based retrials for an
6 extension of an indication to another organ is probably
7 excessive, and that there are other ways to achieve those
8 goals through less extensive trials to facilitate the
9 ability of these pharmaceutical companies to extend their
10 indications.

11 DR. JAY SIEGEL: Such a requirement doesn't
12 exist. We don't have any absolute number of trials --

13 DR. WOODLE: [Inaudible.]

14 DR. JAY SIEGEL: Yes. But I called attention
15 earlier to our document in March of this year regarding
16 efficacy standards, which notes in particular that the need
17 for confirmatory data for new indications can frequently be
18 satisfied by the existence of data from related
19 indications, and I think that this is probably an area in
20 which, based on the advice of this committee, that would be
21 an important consideration. Certainly, that's what I was
22 alluding to before.

23 The other thing noted in that policy is that if
24 the way those data happen to be generated, unfortunately,

1 was through a trial that did not have the benefit of
2 company financing and FDA input, if I might flatter
3 myself --

4 (Laughter.)

5 DR. JAY SIEGEL: You know, obviously, we would
6 prefer to get data from as rigorously designed and
7 conducted trials as possible, but we are open --
8 particularly recognizing the situation of how data are
9 generated with agents already on the market, that same
10 document clarifies that we have an open policy to
11 acceptance and analysis of data generated in that way,
12 providing that there is sufficient basis to ensure the
13 reliability of the data.

14 DR. WOODLE: Jay, one of the things that the
15 FDA did the last time the FDA asked a question in this
16 manner back in 1994, when they asked the question basically
17 was acute rejection an appropriate endpoint for clinical
18 trials in transplantation, they brought it to the advisory
19 committee, and I think that the answer out of the advisory
20 committee was reflected in the study that was done today
21 and some other studies that have come before. It's
22 probably time once again to address this issue of extension
23 of indications and what's required and bring that to the
24 committee formally and dedicate a day for that.

1 The other issue that Hugh touched on earlier is
2 just as important, and that's the issue of are there new
3 indications that need to be considered. As everybody
4 around this table knows, the issue of acute rejection as an
5 endpoint is now almost moot. Drug companies cannot do
6 trials anymore with that as a primary endpoint. Instead of
7 going on an ad hoc basis within the agency, I would urge
8 the agency to bring that issue to committee and ask the
9 question, what are the appropriate endpoints that need to
10 be addressed? It's time for that to be done, as the field
11 is moving rapidly forward.

12 DR. BROUDY: Dr. O'Fallon?

13 DR. O'FALLON: I was just going to comment that
14 we as a committee would have one awful time trying to
15 assess the results of half a dozen perhaps controlled
16 different ways or uncontrolled studies on two or three of
17 these other organs, and we'd be an awful lot better off
18 with another study of the type that we had here today to
19 make this assessment and this generalization. So I agree
20 that other studies will be done, but it's going to make
21 life very difficult around here.

22 DR. BROUDY: All right. Well, why don't we get
23 back to the questions, and then we'll touch again on the
24 ~~issue of the pediatric population and the living related~~

1 donors in the future.

2 To finish Question 2b, the issue of the long-
3 term therapy with Zenapax, should studies of longer-term
4 treatment be encouraged, and what would the proposed
5 duration of therapy be, what endpoints should be used to
6 assess efficacy, et cetera?

7 Dr. Hunsicker, should we do studies beyond five
8 weekly doses of Zenapax?

9 DR. HUNSICKER: Yes, if we're going to use it
10 longer than that. I think the first question is to find
11 out whether there's really a signal out there or whether
12 that's noise, and that may be a matter of surveillance. I
13 don't think that the safety of this drug for a longer
14 period of time has been established, and we get back to
15 this maybe when we get on to 3a. There is a question that
16 needs to be answered that I have not heard answered.

17 But, yes, I would require longer studies for
18 safety if in fact people seriously consider a longer use of
19 the agent.

20 DR. BROUDY: Dr. Jonsson?

21 DR. JONSSON: From what I've learned about this
22 drug here today and in the material provided, it doesn't
23 appear to me that this is a drug that should be used longer
24 term, and if people will seriously think about doing that,

1 studies are obviously needed.

2 The other question that I sort of had is, is
3 this a drug that perhaps could be used the second time
4 around or the third time around for recurrent or persistent
5 rejections? If so, that needs to be studied.

6 DR. BROUDY: Well, I think the concern about
7 that is the toxicology data provided in Appendix 1. Would
8 anyone from the FDA like to comment on that, the data on
9 rechallenge with the drug?

10 MR. ESSAIN: Hi. I'm David Essain.
11 Unfortunately, there are no human studies looking at
12 delayed rechallenge. It's well known that generation of
13 Type 1 hypersensitivity reactions require late rechallenge
14 after initial antigen exposure. The only study that looked
15 at this was in the preclinical model in synamologous
16 monkeys. In that study, there were three different dose
17 levels administered to synamologous monkeys of the
18 humanized anti-Tac. In parallel, a second study was done
19 with the murine anti-Tac. In Appendix 1 you'll see a brief
20 table of the results. The animals were rechallenged at Day
21 42, after an initial dosing schedule between Day 1 and Day
22 14.

23 In the humanized anti-Tac-treated groups, no
24 reactions were seen at the two lower levels, but at the

1 upper level, one of the four animals underwent an
2 anaphylactic reaction which did respond to standard
3 pharmacologic therapy for anaphylaxis. Interestingly, the
4 parallel study with the murine anti-Tac, four out of four
5 animals at the lowest dose level had a similar reaction,
6 and that study was, therefore, ceased at that point. The
7 middle and upper dose levels were not rechallenged.

8 However, it is also well known that following a
9 systemic anaphylactic response, antigen-specific IgE may
10 transiently disappear and may not be present for 4 to 6
11 weeks -- detectable for 4 to 6 weeks after such a response.

12 In regard to characterization of those
13 antibodies, it was shown that the animals challenged with
14 the murine anti-Tac seemed to generate a mixture of anti-
15 isotype and anti-idiotypic antibodies; however, those
16 challenged with the humanized anti-Tac generated almost
17 exclusively anti-idiotypic antibodies, which, when fine
18 mapped, the epitopes seemed to be related to the CDR region
19 H1, H2, and L3. These are antibodies similar to the anti-
20 idiotypic antibodies that have been reported in patients
21 receiving the humanized anti-Tac.

22 DR. BROUDY: Would any of the immunologists
23 here like to comment?

24 ~~DR. SUTHANTHIRAN: I'm not sure I want to~~

1 comment about that particular aspect, but when we have
2 time, I would like to comment about the 2b aspect when we
3 get back to that issue.

4 DR. BROUDY: All right. Well, why don't you go
5 ahead and comment about 2b.

6 DR. SUTHANTHIRAN: In this particular question
7 about the duration of therapy, there are actually three
8 components here. One is the duration of therapy, the other
9 is the endpoints to assess efficacy, and the third is what
10 kind of safety information we want. I think the data we
11 have, what was presented to us, show that this particular
12 course of therapy that was given was quite efficacious in
13 reducing the incidence of acute rejection at 6 months. So
14 that's all the data we have, and I'm pretty comfortable
15 with that duration of therapy.

16 But I would like to isolate the endpoints to
17 assess efficacy and apply it to what has already been
18 presented to us. If we look at the data here at 1 year in
19 terms of graft survival, it's quite similar both in the
20 two-therapy group and the three-therapy group. So we're
21 not able to appreciate an improved outcome at 1 year. One
22 of the major benefits of acute rejection, we all believe,
23 is that we can prevent chronic rejection and we will see
24 some improvement. So I think it's very important when we

1 approve a drug such as this that we really have data to
2 support the original premise under which we are approving
3 this therapy, and we ought to get an endpoint that exists
4 besides this 6 months, but get an endpoint at 2 years of
5 function, and even preferably some tissue, to tell us that
6 there is in fact a beneficial effect from reducing the
7 acute rejection.

8 So I would take the endpoints to assess
9 efficacy not in terms of making a longer duration of
10 therapy, but applied to the current duration of therapy and
11 ensure that we are seeing the benefit.

12 DR. BROUDY: And I think the company does plan
13 to obtain 3-year data, is my understanding.

14 Yes, Dr. Hunsicker?

15 DR. HUNSICKER: Since the question has been
16 asked, I will try to give an answer, and that is with
17 respect to repeat therapy. This question will in fact
18 arise, because a fraction of patients lose their graft and
19 will come up for retransplant. We haven't the foggiest
20 idea of what's going to happen, and a second course -- not
21 a second dose, but a second course of therapy should only,
22 in my opinion, be given under a protocol so that we are
23 absolutely certain we know the answer to the question of
24 whether there is an adverse reaction.

1 So I would think that the indication should say
2 that at least at the present time, a contraindication to
3 the use should be a prior course of this thing until such
4 time as we have evidence about safety of a repeat course.

5 DR. BROUDY: Thank you. I will completely
6 agree with that, given the data that were just presented.

7 Other comments?

8 DR. GRIMM: With regard to the efficacy issues
9 of longer use, when you're dealing with such a low rate of
10 graft failure, [inaudible] are going to be important. One
11 aspect is [inaudible] or GFR in 3 years, but [inaudible] or
12 a biopsy and using standardized criteria, such as the Banff
13 criteria or [inaudible] criteria.

14 DR. BROUDY: Let's move on to Question 3a.
15 This is a voting question, so we'll discuss it first, then
16 we'll take a vote. "Is the safety profile adequate to
17 support the use of Zenapax as an add-on to double or triple
18 immunosuppression?"

19 Dr. Hunsicker?

20 DR. HUNSICKER: Here's where I want to put my
21 question to the company, and it's a follow-on to Dr.
22 Auchincloss' question, and it has to do with safety. I
23 will say up front that I have no qualms about the safety of
24 this agent for the period of time that it's being used in

1 adults. The issue is that it has been suggested to us that
2 what this agent does is simply to turn off the immune
3 system for new antigens for the period of time that the
4 agent is being administered. But clearly that is not the
5 case, because if all it did was to turn off the immune
6 system for that period of time, when the drug was stopped
7 you would have an incidence of rejection that was similar
8 to what you would have expected in the beginning.

9 So the immune system has not just been turned
10 off, it has been conditioned. It's conditioned so that in
11 fact the future rejection of these new antigens that it has
12 been seeing has been altered.

13 The particular concern I have has to do with
14 children, and it reflects Hugh's concern, which is that
15 they are being exposed to any number of new antigens during
16 this period of time, infectious agents and the like, and we
17 haven't the foggiest notion of what the long-term impact is
18 of this modification of the immune system that doesn't
19 simply give you a void, but actually may condition people
20 to be receptive of those antigens in the future.

21 I think this was behind what Hugh asked earlier
22 on when he was trying to extract from the company what the
23 impact is on the immune things that you're exposed to. Do
24 we have any idea what happens to subsequent responses,

1 direct hypersensitivity responses, humoral immune
2 responses, to antigens that are introduced first under the
3 cover of this agent? Do we know whether this in fact is
4 altering the long-term response to antigens that we may not
5 want the recipient to become accepting of?

6 DR. LIGHT: I think the short answer is that
7 Zenapax is reversible at the end of 4 months. At the end
8 of 6 months the T cells are back expressing Tac.

9 DR. HUNSICKER: But the response to the antigen
10 is not the same had the immune system simply been blotted
11 out during that period of time.

12 DR. LIGHT: So you're talking about tolerance.

13 DR. HUNSICKER: Pardon?

14 DR. LIGHT: You're talking about tolerance?

15 DR. HUNSICKER: Well, "tolerance" is a very
16 specifically used word, but they are certainly more
17 accepting of the graft than they would have been had they
18 never seen this stuff.

19 Dr. Kirkman is nodding his head there. Why
20 don't you comment on this? You've had more experience than
21 anybody else.

22 DR. KIRKMAN: There's no way to answer your
23 question with data at this point. I think that your
24 ~~statement is probably~~ I believe your statement is

1 correct, that something happens during the 3-month interval
2 during which these patients are exposed to an antigen at
3 the same time that their T cells are turned off, are
4 incapable of responding, that produces a prolonged effect
5 beyond the exact period that the drug is being
6 administered. I think that's correct, but since we don't
7 know exactly how the drug works in that way, it's hard to
8 provide you with a definitive answer to the question.

9 The only data that I think is directly relevant
10 to the question that you've posed so far is the CMV data
11 that we've presented. That's the only antigen that we can
12 clearly identify that has been presented at the time that
13 this drug is effective and for which we have adequate data
14 to follow. That experience suggests that for that virus,
15 and taking into account Dr. Auchincloss' caveat that
16 prophylaxis was provided, that this is a safe thing to do.

17 But I think that all of us who have thought
18 about anti-IL-2 receptor therapy for a long time now were
19 worried about this issue that you're presenting. I think
20 that the data that you've seen are reassuring as far as
21 they go so far.

22 DR. GRIMM: May I make a comment?

23 DR. BROUDY: Yes, please.

24 DR. GRIMM: I just wanted to point out, perhaps

1 I'm not quite so concerned as you are because of the CMV
2 data, but also the fact that the HAT therapy may not be 100
3 percent blocking of IL-2. You know, it was pointed out
4 that IL-2 itself is two orders of magnitude more -- has a
5 higher affinity for the receptor. So local immune
6 responses may continue to occur, especially once you get
7 past the first few weeks when you're really blasting the
8 patient with steroids and higher levels of cyclosporine.
9 So I have a bit less anxiety about that issue.

10 The other thing is, there may be some change in
11 the graft over that period of time when they're heavily
12 immune suppressed and you lose the passenger leukocytes and
13 antigen presenters, and so there may be different stimuli
14 to rejection later on than there is earlier. So I'm not
15 quite so worried.

16 DR. BROUDY: Dr. Hunsicker?

17 DR. HUNSICKER: I agree that it is reassuring,
18 what we've seen. However, I would suggest to the FDA with
19 respect to this that this is an area that, quite apart from
20 the label, you should encourage Hoffmann-La Roche to
21 characterize. We need to know what's happening to these
22 immune responses.

23 With respect to labeling, I will say that I
24 think that the safety profile is adequate to support the

1 use of Zenapax as an add-on to double or triple
2 immunosuppression, at least in adults. That I will vote
3 for. With respect to children, I'm conflicted, because I
4 do not want to preclude the use of this agent, which
5 appears to be effective in a special group of patients.
6 I've been concerned for a long time that we leave our kids
7 behind.

8 DR. BROUDY: Other comments before we vote on
9 this issue?

10 (No response.)

11 DR. BROUDY: Okay. Let's vote on the question,
12 "Is the safety profile adequate to support the use of
13 Zenapax as an add-on to double or triple
14 immunosuppression?" All voting yes, please raise your
15 hand.

16 (Show of hands.)

17 DR. BROUDY: Are there any nos?

18 (No response.)

19 DR. BROUDY: Okay. The vote is 12 in favor and
20 no one opposed to Question 3a.

21 Let's move on now to Question 3b. "Please
22 discuss the management of patients receiving Zenapax and
23 cyclosporine and manifesting signs of cyclosporine
24 toxicity. Should dose adjustments of either agent be

1 recommended?" Would one of the transplant nephrologists
2 like to address this?

3 DR. SUTHANTHIRAN: I think if one is convinced
4 that they're dealing with cyclosporine, but with respect to
5 whether someone would alter the humanized anti-Tac, I
6 seriously doubt that they would be interacting together.
7 The mechanisms of action, at least as we understand it at
8 the present time, are so distinct. So I don't foresee any
9 alterations in the dosage of anti-Tac.

10 DR. BROUDY: Any other comments on that issue?
11 Dr. Grimm?

12 DR. GRIMM: I would just support Dr.
13 Suthanthiran. It's hard to understand how this interaction
14 would take place.

15 DR. BROUDY: I didn't find the data very
16 convincing that the agent itself caused renal insufficiency
17 or a decrease in the GFR. They're pretty small numbers.
18 So I would completely agree one should adjust the
19 cyclosporine dose if one thinks there's cyclosporine
20 toxicity.

21 We have a consensus on one issue here.

22 (Laughter.)

23 DR. BROUDY: "In the triple-therapy study, the
24 ~~antiviral prophylaxis was prespecified and mandatory for~~

1 all high-risk patients. Should CMV prophylaxis be
2 routinely recommended when Zenapax is used with triple
3 immunosuppression therapy in high-risk patients?"

4 Dr. Hunsicker, do you have an opinion on this?

5 DR. HUNSICKER: I've got an opinion on
6 everything.

7 (Laughter.)

8 DR. BROUDY: That's why I called on you.

9 DR. HUNSICKER: I have great difficulty making
10 an argument in any direction in the absolute and total lack
11 of information. We have no information whatsoever of what
12 would happen in the absence of the use of CMV prophylaxis.
13 I will say that personally I think that you're dumb to not
14 give immunoprophylaxis for the high-risk patients anyway.
15 I mean, that's pretty much the standard of practice, and so
16 it's a non-issue to some extent.

17 Because of the concerns that Dr. Auchincloss is
18 about to recommend, I think that we should say specific
19 consideration should be given to coverage during this
20 period of time.

21 DR. BROUDY: Dr. Auchincloss?

22 DR. AUCHINCLOSS: It's just a non-issue. I
23 mean, these people are being treated anyway. I don't think
24 you even need to consider it.

1 DR. BROUDY: Dr. Suthanthiran?

2 DR. SUTHANTHIRAN: I think CMV prophylaxis
3 should be considered on its own.

4 DR. BROUDY: And please define for the FDA the
5 high-risk patient.

6 DR. SUTHANTHIRAN: The high-risk patient at the
7 present time is a donor positive and recipient negative.

8 DR. BROUDY: Thank you.

9 Any other comments about this question?

10 (No response.)

11 DR. BROUDY: I think we have consensus here.

12 Let's move on to Question 4. "Please comment on the
13 adequacy of the available data to support the use of
14 Zenapax in association with MMF, corticosteroids, and
15 cyclosporine."

16 Dr. Hunsicker?

17 DR. HUNSICKER: This is likely to be the
18 commonest combination within the next -- probably now. If
19 this agent were approved now, the majority of people
20 receiving it will be receiving it in the setting of
21 cyclosporine, mycophenolate, and prednisone.

22 Earlier on I wanted to point out to Dr.
23 Suthanthiran that although the study with mycophenolate was
24 ~~not powered to be statistically significant and wasn't~~

1 statistically significant, the reduction in risk of
2 rejection was exactly the same, 40 percent, as was the
3 reduction in risk of rejection in every other circumstance,
4 and the presumption is that this is going to be an agent
5 which has an independent action and will be additive in its
6 effects.

7 This is an area where I would reiterate that
8 what we need is just enough safety information to make sure
9 that we're not getting into problems with runaway tumors
10 and the things that you were worried about and so forth
11 like that, and I would be willing to accept a relative risk
12 that was in the same ball park, without worrying too much
13 about P values.

14 DR. BROUDY: Dr. Suthanthiran, would you like
15 to comment on this question, the issue of use with MMF,
16 steroids, and cyclosporine?

17 DR. SUTHANTHIRAN: Next time I'd like to go
18 before Larry Hunsicker.

19 (Laughter.)

20 DR. SUTHANTHIRAN: I think, as Larry said, this
21 is probably the most likely combination. I don't think we
22 really have good data to support it, but from what
23 [inaudible] immunobiology, I think it would be reasonable
24 to support this approach.

1 DR. BROUDY: Yes, Dr. Weiss?

2 DR. WEISS: If you have a concern about an
3 increase, you nevertheless still have to do a relatively
4 large trial to try to detect that difference. So I guess I
5 have a question about how much safety is enough.

6 DR. HUNSICKER: No amount of safety is ever
7 enough, and so you divide your studies into those things
8 that are planned and which detect big signals and do your
9 post-release surveillance, which in this case, because
10 you're dealing with transplants and we have a census of the
11 population, can be done with great sensitivity. So I think
12 I would just aim for the big stuff to make sure that we're
13 not producing with this combination more -- I think that
14 probably the most sensitive thing would be infections.
15 You'd want to make sure that you aren't getting a whole lot
16 more viral infections in this group.

17 You're not going to have enough sensitivity
18 without a huge study that's not really feasible to look at
19 the issue of tumors, and that's going to have to be done
20 with post-release surveillance.

21 DR. BROUDY: Dr. Auchincloss?

22 DR. AUCHINCLOSS: Again, in the real world,
23 this is a huge concern, but not a concern to us. Why?

24 ~~Because this one company makes both agents, and, of course,~~

1 they're going to try to convince the transplant community
2 that we should use them both. So I have confidence that
3 I'm going to see the data.

4 DR. VINCENTI: May I make one comment? Another
5 potential approach, we have just started to participate in
6 a multicenter trial whereby we're using Zenapax with selsa.
7 Basically, one can look at these immunosuppressive
8 protocols as adding more drugs. On the other hand, you can
9 look at Zenapax as a potential opportunity to look at those
10 drugs that are nephrotoxic, those drugs like steroids that
11 give a lot of long-term side effects, and see, well, how
12 could we use this new high-tech drug that has little
13 toxicity to minimize the toxicity of the additional drugs?

14 And the approach we're taking now is doing a
15 study in primary transplants, combining Zenapax, selsa, and
16 prednisone. No cyclosporine. We have had 14 patients.
17 The majority of patients have been followed for over 6
18 weeks. We have one patient followed for 4 months. So far
19 we have had no rejection. None of the patients developed
20 de novo hypertension, none have tremors, and the mean
21 creatinine of the patients was 1.0.

22 Now, obviously, it's still early to extrapolate
23 the ultimate success and the long-term success, but I'm
24 ~~throwing this out as an idea of the potential creative~~

1 approaches that maybe this drug is going to allow the
2 transplant community.

3 DR. BROUDY: Of the many permutations that
4 would be available. Thank you.

5 Okay. Any other comments about this issue?

6 (No response.)

7 DR. BROUDY: Okay. We're going to now move on
8 to Question 5, and this is a voting question. "Should
9 labeling restrict the use of Zenapax only to recipients of
10 cadaveric renal allografts? Please comment on the
11 requirements for generalizing the indication of prophylaxis
12 of kidney transplant rejection from recipients of cadaveric
13 renal allografts to include recipients of kidneys from
14 living related donors."

15 Dr. Suthanthiran?

16 DR. SUTHANTHIRAN: I think the issue of a
17 living related donor could actually be called a living
18 donor, because we not only have living related donors now,
19 we also do emotionally related transplants. So I guess
20 those patients would come under that category.

21 All but HLA-identical patients have an
22 incidence of rejection perhaps in the range of about 20 to
23 25 percent, very similar to what was presented for the
24 mycophenolate group. From my perspective and this is

1 something maybe Hugh might again say is a non-issue -- from
2 my perspective, I think even though the data we were
3 presented was confined to cadaver renal allografts, I'm
4 quite comfortable about including allografts from living
5 donors.

6 DR. BROUDY: Yes?

7 DR. GRIMM: The living donor long-term survival
8 is not that much different from the cadaveric long-term
9 graft survival, with graft survival half-life cadaveric, 9
10 years, 8 and a half years, and graft survival half-life in
11 the haploidentical living donor, 12 or 13 years. So it
12 doesn't make that much of a difference. So certainly for
13 the non-HLA-identical, I would support the use of this drug
14 in that situation.

15 DR. BROUDY: Yes?

16 DR. WOODLE: Just so that there's consistency
17 within the agency, this question has come up before the
18 committee before, and there's been not a formal
19 recommendation to the committee, but there have been
20 individual recommendations that if you're going to have
21 acute rejection as a primary endpoint, that living donors
22 that are non-HLA-identical should be acceptable for
23 inclusion in those trials. Indeed, there are pivotal
24 trials under way right now with other agents in which

1 living donors are included with acute rejection as an
2 endpoint.

3 So I think that if you're going to look at
4 labeling and you're going to look at design and execution
5 of trials, there needs to be consistency between the two.

6 DR. BROUDY: Dr. Hunsicker?

7 DR. HUNSICKER: That also applies to second and
8 subsequent transplants. It would have been helpful to have
9 at least some information. So long as Number 5 is read as
10 asking about the labeling of Zenapax for all kidney
11 transplants and not -- it doesn't stipulate here exactly
12 what we're talking about. I would support its labeling for
13 all kidney transplants, with the caveats I have previously
14 said about pediatrics.

15 DR. BROUDY: What about HLA-identical living
16 donors?

17 DR. HUNSICKER: You can leave that up to the
18 docs. I probably wouldn't use it for HLA-identicals,
19 because it's probably unnecessary, but there's no evidence
20 here I'm going to hurt them.

21 DR. BROUDY: Dr. Jonsson, a comment?

22 DR. JONSSON: I would just support that and
23 include all kidney transplants.

24 ~~DR. BROUDY: Would you include all kidney~~

1 transplants, Dr. Suthanthiran?

2 DR. SUTHANTHIRAN: Yes.

3 DR. BROUDY: Dr. Auchincloss?

4 DR. AUCHINCLOSS: Yes, for this vote, and then
5 I'd like to take a second vote and see how many of the
6 committee would like to actually broaden it to all solid
7 organ allografts.

8 DR. BROUDY: All right. Any other discussion
9 about whether the indication should be broadened to all
10 adult kidney transplants?

11 (No response.)

12 DR. BROUDY: Okay. Let's take a vote on this
13 issue. Voting yes would mean we should broaden the
14 indication to all adult recipients of renal allografts. If
15 you favor this broadening, vote yes.

16 (Show of hands.)

17 DR. BROUDY: Any no votes?

18 (No response.)

19 DR. BROUDY: All right. We have just voted to
20 broaden the indication to adult recipients of renal
21 allografts.

22 DR. HUNSICKER: We have pediatrics that quietly
23 got dropped, and I would --

24 DR. BROUDY: ~~That's the next question.~~

1 DR. HUNSICKER: Okay.

2 DR. BROUDY: And now, Dr. Auchincloss, tell us
3 what you'd like us to vote on, what you'd like an opinion
4 on.

5 DR. AUCHINCLOSS: That I think in fact the
6 indication should be all adult recipients of organ
7 allografts.

8 DR. BROUDY: I'd like to ask the FDA if it's
9 all right with them if we take a vote on this, or what
10 would you like us to do procedurally?

11 DR. JAY SIEGEL: Well, as I said before, all
12 opinions on this question are valued. I think it's an
13 interesting point about an independent discussion of this
14 issue, which is something we should consider. There is a
15 different subcommittee that advises the FDA, two of whose
16 members are here now, who certainly we would want to be in
17 the loop in considering such a question. It doesn't much
18 matter to me whether you vote or don't vote. We've heard
19 your opinions, and that's what --

20 (Laughter.)

21 DR. JAY SIEGEL: No, what I mean to say is that
22 it's your opinions that count, it's not what the number is.

23 DR. BROUDY: What he's telling us is that we
24 have a powerless vote.

1 (Laughter.)

2 DR. AUCHINCLOSS: All of our votes are
3 powerless in a certain sense.

4 DR. JAY SIEGEL: What I'm telling you is that
5 it's advisory, and your advice is important and will fit in
6 together with the other issues I've mentioned in helping
7 us. But if you'd like to vote, that's fine.

8 DR. BROUDY: Well, why don't we go ahead, then,
9 Dr. Auchincloss. Why don't we vote on the issue --

10 DR. HUNSICKER: Can we discuss it first?

11 DR. BROUDY: A comment from Dr. Hunsicker,
12 please.

13 DR. HUNSICKER: Well, Dr. Anderson first.

14 DR. ANDERSON: I wanted to ask a question of
15 both the panel and the FDA. If the panel were to vote yes
16 on this -- and, frankly, that's what I want to do -- is the
17 feeling of the FDA and the panel that it would be more or
18 less difficult to get the appropriate scientific studies
19 that everyone feels ought to be done? Or the same. Would
20 it be equally possible to get the scientific studies
21 done --

22 DR. JAY SIEGEL: Let me simply say this, that I
23 don't know if anybody can predict that. It would be
24 interesting to know what the company's perspective is. One

1 thing that we know is different is that if they don't have
2 that labeling, they cannot run ads in journals, send out
3 detail men, go to meetings and tout its efficacy based
4 either on no data or on the types of flimsy data that some
5 of you indicated might be generated.

6 So there would be that regardless of the
7 labeling, but certainly one of the impetuses of change is
8 the impetus regarding promotions and the impetus regarding
9 reimbursements, of course. Undoubtedly, the labeling would
10 give them a stronger basis. I mean, that's one of the
11 positives. But it is also one of the factors in the
12 opposite direction.

13 DR. BROUDY: I believe that fewer studies would
14 be done, and I feel uncomfortable, personally, voting to
15 approve something in an area in which we have not seen the
16 data supporting its use or the safety issues myself.

17 Dr. Hunsicker?

18 DR. HUNSICKER: I suppose I'm saying this to
19 explain to Hugh why I'm going to vote against this. I'm a
20 believer in process, believe it or not, and if there is
21 another committee whose job it is to consider this kind of
22 a thing, I'd rather have the decision come from that
23 committee. But I would not have any problem voting for a
24 motion to send to that committee the consideration that

1 these indications should be broadened in the future.

2 See, we're dealing with a situation where we
3 have two pivotal trials in kidney transplantation. What we
4 should do in the future is not have two pivotal trials in
5 kidney transplantation and then approve it for all organs,
6 what we should do is have one in kidney and one in liver so
7 that you can cross the information. I think we have to
8 make this change prospectively, and I think it needs to be
9 remanded to that committee to come to this, but I will vote
10 against doing that at this point now.

11 DR. JAY SIEGEL: Let me clarify the process,
12 since that is important. It is neither that committee nor
13 this committee that's going to make this decision. The
14 agency will make the decision, and you appropriately are
15 advising the agency on this question, and that will advise
16 the agency on the specific questions of approval of
17 specific drugs for specific indications.

18 So I don't at all mean to downplay the
19 importance of this committee or of that committee. It's of
20 critical importance, but it's neither that nor this that
21 are making the decision. They're both advisory committees
22 to the agency, and both are equally, I think, valid and
23 appropriate for advising us on this question.

24 ~~DR. HUNSICKER: So you've heard me say that I~~

1 would vote against extending this indication, but would
2 strongly suggest that the FDA consider designing the trials
3 in the future to answer the broader question rather than
4 the narrower question.

5 DR. BROUDY: Dr. Suthanthiran?

6 DR. SUTHANTHIRAN: Now that I know my advice
7 and word is very important, I think one of the nicest
8 things we have seen in the last few years with
9 immunosuppressive therapy has been these prospective
10 controlled, double-blind studies, which have not been done
11 in the past. I think the mycophenolate and neoral
12 represent good approaches. The data we have today is only
13 for renal transplantation, and that, too, only for CRD, and
14 we're willing to extend it to living donors.

15 Human nature being what it is, I think if we
16 approve this for all organs, I think the studies in other
17 organs would not be done. And I say this with a certain
18 amount of concern, because when we don't put it on the
19 label, there's going to be reimbursement issues and so on
20 and so forth. But, nevertheless, I think it's best for us
21 to confine this to renal transplantation and not have a
22 blanket coverage of all organ transplantation.

23 DR. BROUDY: Ms. Meyers?

24 MS. MEYERS: The third question is, if this

1 thing that we just voted on is only for adults with kidney
2 transplants, that means that the children will not be
3 reimbursed. So can we get another motion for a third
4 question about pediatric use?

5 DR. BROUDY: That's the next question, Number
6 6. We'll move on to that next.

7 Dr. Grimm, a comment?

8 DR. GRIMM: When we look after patients in
9 medicine, we serve two masters. On one side, we have the
10 individual patient that we see in front of us in need, and
11 if you really believe a drug is good, you want to get that
12 drug to that patient, and when you're in the clinic, that's
13 the thing that's most important. But on the other hand, we
14 also have to serve the master of science. We don't want to
15 be recommending a drug without decent supporting trials,
16 and I'm very much torn, and I recognize where you're coming
17 from, but I'd also have to vote no at this point.

18 DR. BROUDY: Do you wish to make a comment, Dr.
19 Auchincloss, before we vote?

20 DR. AUCHINCLOSS: I don't expect this vote to
21 come out in my favor.

22 (Laughter.)

23 DR. AUCHINCLOSS: I don't expect the FDA to do
24 anything about it even if it did. I actually honestly just

1 thought it would be interesting to get a sense of the
2 committee for them, and I would only conclude by suggesting
3 to the committee how inconsistent I think they are. I
4 think that the likelihood that this agent is efficacious
5 relative to risk for an HLA-identical kidney transplant is
6 so small compared to the likelihood that it's efficacious
7 for a heart transplant as to be not even in contention.

8 DR. BROUDY: Dr. Hunsicker, could you address
9 that question, please? I think you commented that you
10 would not use this agent for an HLA-identical kidney
11 transplant.

12 DR. HUNSICKER: I would personally not use it.
13 I think it would be unnecessary. The way to address Dr.
14 Auchincloss is to say that we are, I think, inconsistent
15 because the trial was designed to answer a kidney question
16 in an administrative setting, where everybody understood we
17 were going to do kidneys separate from livers. What I have
18 suggested is that the right way to do this -- and you
19 understand I have deep sympathy for your position -- is to
20 design the trials in the future with two pivotal trials
21 representing different organ transplant systems so that we
22 can in fact have the basis for generalization.

23 DR. BROUDY: Okay. I think we will now proceed
24 to a vote. Should the labeling for Zenapax be extended to

1 recipients of other solid organ transplants? All in favor,
2 please raise your hand to vote yes.

3 (Show of hands.)

4 DR. BROUDY: All opposed, please raise your
5 hand to vote no.

6 (Show of hands.)

7 DR. BROUDY: We have six yes votes and six no
8 votes on this question.

9 PARTICIPANT: That's the perfect outcome.

10 (Laughter.)

11 DR. BROUDY: I hope this has been helpful to
12 you, Dr. Siegel.

13 (Laughter.)

14 DR. BROUDY: Now let's move on to what will
15 probably be the most contentious issue in front of us
16 today, I think, Question 6. "Provided the data from this
17 study indicate an acceptable safety profile and are
18 adequate to determine dosing, what, if any, additional
19 studies would be required for the use of Zenapax in the
20 pediatric population? Specifically, would a separate
21 efficacy trial be necessary, or is prophylaxis of kidney
22 transplantation in pediatric populations similar enough to
23 adults to permit extrapolation of efficacy?"

24 ~~Dr. Grimm, as a pediatric nephrologist, would~~

1 you like to start this off?

2 DR. GRIMM: We've talked a lot about this
3 throughout this portion of the meeting, and there's not
4 much more that I have to say, but just a couple of points.
5 One is the issue about what is really pediatric. There are
6 different components of pediatrics -- for example, the
7 psychosocial and the growth and development aspects, which
8 extend into the late teens. Immunobiologically, I don't
9 really know what is pediatric. For example, if you were
10 going to limit the indication to non-pediatrics, then if
11 you've got a 15-year-old who would be an excellent
12 candidate for this drug, are you going to prevent that 15-
13 year-old from getting the drug? So one of the issues, I
14 think, is the age that we'd want to focus on.

15 The second thing is, I believe that children in
16 many ways are different than adults. Their immune system
17 is on a higher state of readiness. They're seeing new
18 infections for the first time. In pediatric
19 transplantation, acute CMV and Epstein-Barr virus infection
20 are much more significant and much more relevant and much
21 more of a problem.

22 In pediatrics, if we would just go ahead with
23 the use of Zenapax, my concern is that what it would mean
24 ~~is that we would stop using antibody mediated induction~~

1 with either OKT3 or ATG, and I just don't know which is
2 more efficacious or less. On the other hand, this drug
3 seems to be much less toxic than the drugs that we have
4 available, and if we were to make a blanket no, then it
5 would prevent these children from getting the benefit of
6 the drug. So I'm very much torn, again, serving my two
7 masters.

8 I raise the question whether, if we did leave
9 it as a blanket acceptance for all renal transplantation,
10 is there any way we could send the message to the company
11 that in doing so it would be expected that a proper study
12 of this drug in the pediatric age group would be done?
13 Because if the answer is no, then I would have a hard time,
14 and it's a very tough decision.

15 DR. BROUDY: Let me ask one quick question. Do
16 you think an adequate study could be done in the U.S.
17 pediatric renal transplant population to answer this
18 question?

19 DR. GRIMM: I don't know about whether it could
20 be done in just the U.S. population, but drug companies are
21 multinational. We're involved in Canada with a study of
22 mycophenolate which involves Australia, U.S., Canadian
23 centers. So it's possible, especially with the will on the
24 side of the company, to perform an adequate study if you

1 look at Westernized centers. I think in just looking at
2 the U.S., it might be difficult. But, again, you would
3 need to have the will for it.

4 DR. BROUDY: Dr. Hunsicker?

5 DR. HUNSICKER: I agree in large measure, but I
6 want to make sure that I come out so that you'll know how
7 I'm voting on this. First, a comment. It is not
8 traditionally the job of the FDA to determine whether this
9 therapy, Zenapax, is better than OKT3. The issue is, is it
10 better than placebo or is it better than something else.
11 So I don't think the company has to answer the comparative
12 question for you. I've already stated that I think the
13 major issue in pediatrics is safety, for the reasons that
14 we've discussed, and not efficacy. The likelihood of
15 efficacy is great.

16 Now, here we come to the difficult choice. We
17 don't know as much as we would like about safety in
18 children, and yet there is every reason to believe that
19 this agent will be as relatively effective in pediatrics as
20 it is in adults, and children have more severe and more
21 frequent rejections, and, therefore, the absolute benefit
22 in children will be larger than it is in adults. And there
23 is at least not yet a smoking gun, and Bobby's studies have
24 not turned up a smoking gun on sort of a preliminary safety

1 kind of thing.

2 Therefore, I would vote to approve extending
3 the indication to include children -- that is to say, all
4 kidney transplant recipients -- with the labeling proviso
5 that we aren't quite so certain as to the long-term impact
6 of the use of this agent during the time that people are
7 being exposed to new things, and with a clear commitment,
8 which I don't think is going to be hard to come by, from
9 the company that they will be studying this issue of
10 safety.

11 DR. BROUDY: Dr. Auchincloss?

12 DR. AUCHINCLOSS: Well, I'll vote against
13 including kids in the indication, because while I agree
14 with you that I think the potential benefit may be greatest
15 in this group, I am really scared that the risk is
16 potentially enormous in this group. So not only do I want
17 to see the follow-up on this trial before the indication is
18 extended to kids, I really would like to see some
19 additional specific testing in children of, does
20 immunization work during the time of treatment? What
21 happens if it doesn't work and you come back and reimmunize
22 later? Are they in fact tolerant? I really think there
23 are some very important questions that really should be
24 addressed before this should be brought to kids.

1 DR. BROUDY: Dr. Stein?

2 DR. WEISS: For the purpose of discussion here,
3 I'd like to ask Dr. Hunsicker, what are we looking at in
4 terms of numbers of transplants done in children under the
5 age of 2 who would not be fully immunized?

6 DR. HUNSICKER: Under the age of 2?

7 DR. WEISS: Yes.

8 DR. HUNSICKER: Well, under the age of 18, only
9 5 percent of transplants in the United States are in
10 children under the age of 18, and of those, roughly 5
11 percent are under the age of 5. So it's a tiny fraction of
12 transplants done in kids under the age of 2. But I want to
13 rush to say it is not simply immunization to those things
14 that we're immunizing. Far more important is immunization
15 to all those things that we don't even know the names of.

16 DR. WEISS: I understand that.

17 DR. BROUDY: Dr. Kleinerman?

18 DR. KLEINERMAN: Dr. Auchincloss, I'm going to
19 vote on the other side, because I think, as Dr. Grimm
20 pointed out, getting a study like you want done with the
21 small numbers of patients that we have is going to make it
22 impossible. And I would argue that the company may say --
23 the marketing people may come and say, "Look, the amount of
24 money it's going to take to put together this study will

1 never be offset by the increase in the product," so the
2 study will never be done, we'll never have the drug,
3 because there will be something on the label that will say,
4 "This has not been approved for use in children," and like
5 many of our oncology agents, we will be so far behind the
6 adult oncologists that it's really pathetic.

7 So I think there's a real danger in that by not
8 extending the ability to use this agent in children. At
9 the same time, I think that the company can collect other
10 safety data in small groups of children that receive this
11 agent as part of their transplant regimen. Looking at
12 immunizations during that time, I don't think that there
13 should be huge numbers that are required, and I don't think
14 an additional efficacy study needs to be done.

15 I think the thing that we're struggling with
16 is, we want to make sure that there's no increased risk of
17 infections or inability to mount an immune response, and I
18 think that can be done with small numbers of patients.

19 DR. BROUDY: Thank you.

20 Comment, please?

21 DR. ETTINGER: Bob Ettinger from UCLA. As a
22 pediatric nephrologist, I want to address the very narrow
23 point about immunizations during this period of time.

24 They, as a general rule, are never done because of the

1 concern that, if you will, the immunization will not take.
2 So almost always we attempt to immunize our patients during
3 the dialysis period, or we leave a window of time when we
4 do not give routine immunizations until the
5 immunosuppression has come down.

6 DR. BROUDY: Other comments on this issue?
7 Yes, Dr. Auchincloss?

8 DR. AUCHINCLOSS: The company -- and I am
9 impressed that they have done it -- has already, as I
10 understand it, initiated a study of 60 children. I am not
11 looking for more kids than 60 for my purposes. What we
12 have right now is a median of 8 weeks follow-up in 25 kids.
13 I want to see a year with the 60 or something like that,
14 and then I want to see -- and my immunizations obviously
15 doesn't work here, because I don't work with kids at all,
16 but I bet there are things that you can do to kind of find
17 out whether this drug, this agent, is dangerous.

18 DR. LIGHT: I think that unlike the pivotal
19 trials, where the follow-up was 6 months, the follow-up on
20 this study is going to be a year before the database will
21 be closed.

22 DR. BROUDY: Dr. Hunsicker?

23 DR. HUNSICKER: You know, a lot of the studies
24 could actually be done in, I believe, monkeys. You could

1 even do them with a murine-equivalent in mice. I mean, the
2 question that we have is, what is the impact of exposure of
3 an animal to an antigen during the period of time when his
4 IL-2 receptor is blocked? This ought to be required of the
5 company. We have to know what is the long-term impact on
6 the responses to that antigen.

7 And lest anybody be confused when we talk about
8 immunization, I'm talking about immunization in terms of
9 the way God made it to happen, we get infected with
10 something and we become immune to it. I'm not talking
11 about something that we have manufactured here on Earth.

12 DR. BROUDY: Thank you.

13 Ms. Meyers?

14 MS. MEYERS: I just feel that the repercussions
15 of saying that it's not approved for children are just so
16 terrible, I don't think, if you think about it, if it
17 happened to your child or your grandchild, that you would
18 ever want this committee or anybody to say, "Don't do it."
19 The company has that little bit of data. There should be
20 some type of caution on the label that "It's only been
21 studied in 10 or 15 children, this is the state of
22 knowledge, and, therefore, it may affect the dosage, we
23 don't know what will happen with immunization," et cetera,
24 et cetera. But please don't say that it's not approved for

1 children, because no one's going to get reimbursed.

2 DR. BROUDY: Let me ask a question of Dr.
3 Siegel. If what Dr. Auchincloss is recommending came to
4 pass, they completed the study and came back to you in a
5 year with 1-year follow-up data, would the company have to
6 bring this before the committee again, or could the FDA
7 decide to extend this application to children after review
8 of the safety data and the efficacy -- at least the safety
9 data in children?

10 DR. JAY SIEGEL: Yes, there's no requirement
11 that anything in particular be taken or not be taken to
12 committee, with the exception -- well, there had been, I
13 think, for devices, actually, but I don't even think that
14 exists anymore. So absolutely not, and we've had many
15 labeling revisions as new data acquire that don't come
16 through the committee, and occasionally we decide to bring
17 some, depending on the impact, the interest, and so on.

18 DR. WOODLE: Virginia?

19 DR. BROUDY: Dr. Woodle?

20 DR. WOODLE: I suspect that what we're talking
21 about here is including the word "adult" in the indication,
22 and to my knowledge, this would be the first time for a new
23 drug that that would be done. Was that done for tacrolimus
24 or mycophenolate? Is the word "adult" in the indication

1 for those drugs? Or cyclosporine?

2 DR. HUNSICKER: In the review for tacrolimus,
3 there were data on children presented at the time it was
4 approved.

5 DR. JAY SIEGEL: It wouldn't be the first time
6 for a drug, period, that that's done, but our current
7 pediatric policy suggests that if we feel that there are
8 either data or reasonable basis -- and this isn't an exact
9 quote of the wording -- to believe that the physiological
10 processes and the effects in children are likely to be
11 parallel to those of the adults, that we would generally
12 not restrict the indication and would generally put in
13 whatever pediatric data we have to guide its use.

14 Now, it sounds to me, if I'm correctly getting
15 the sense of this committee, that there is a reasonable
16 level of comfort probably regarding its efficacy, regarding
17 its impact on rejection, and there are some variable
18 levels, but not insignificant, of discomfort about
19 specifically its impact on recognition and response to new
20 antigens, which is, obviously, a somewhat different issue
21 for children from adults, and although this question -- if
22 that's the sense, if that answers our question, which is,
23 would we need separate efficacy data -- I think, though,
24 ~~that you're also helping us address a lot of other~~

1 questions, and certainly one approach, I guess, that Dr.
2 Hunsicker and Ms. Meyers have suggested that we certainly
3 can and do do in some cases would be, for example, not to
4 put the word "adult" in the indication, but to make sure
5 that the labeling indicates that there are theoretical
6 concerns which have yet to be appropriately addressed, and
7 also somebody else can in fact ask or even require a post-
8 marketing commitment from a sponsor to study those issues.

9 DR. WOODLE: Which is the way kids are usually
10 handled. That's the traditional way --

11 DR. JAY SIEGEL: Except for those diseases that
12 are truly a different disease in children from adults,
13 where there would be a lot of concern about extrapolation,
14 that's the way we usually handle it.

15 DR. BROUDY: Dr. Miller, did you have a
16 comment?

17 DR. MILLER: My comment was just that we
18 approve it as not excluding children but require that the
19 60-patient study be completed in a timely fashion and
20 reviewed by the agency as a basis for --

21 DR. BROUDY: Dr. Auchincloss, what do you think
22 about that suggestion? Would you be comfortable with that
23 suggestion?

24 DR. AUCHINCLOSS: It's obviously all a matter

1 of degree, as I think the previous vote was. I feel enough
2 uncomfortable that in this case I'd leave the kids out
3 until the data comes in, but I don't think we're talking
4 about anything that's very far apart in one position versus
5 the other.

6 DR. BROUDY: Yes, Dr. Grimm?

7 DR. GRIMM: If the data on the 60 patients
8 showed no significant concerns about side effects compared
9 to what we know from the normal population, I would be
10 reluctant to only leave the label as adult. Because of
11 that issue, we're never going to get this drug into
12 children. However, we need to send a message very clearly
13 that post-marketing surveillance is really critical so we
14 don't run into the same troubles that we have in previous
15 time points with cyclosporine when it was first introduced,
16 and even with the high rate of lymphoproliferative disorder
17 which was seen in the first pediatric patients which were
18 given FK506. I think it would be very important to keep a
19 very, very tight look at that for an extended period of
20 time.

21 DR. BROUDY: Precisely. Since more children
22 acquire EBV in the peritransplant period, they would be at
23 higher risk.

24 Yes, Dr. Suthanthiran?

1 DR. SUTHANTHIRAN: I would support the use of
2 this agent in pediatric transplant patients, for the
3 following reasons. One, in fact pediatricians use more of
4 an induction anti-lymphocyte therapy than adults do, and
5 it's very likely from the mechanism of action this may be
6 less of a broad-based immunosuppressant than OKT3 or ATGAM
7 is. Second, Hoffmann-La Roche may not like it, but this
8 agent is not a total immunosuppressant. It only brought
9 down the rejection episode in a significant fashion, but it
10 didn't completely abrogate it, so I'm not that much worried
11 about this agent being a global immunosuppressant and
12 exposing the children to a very high level of infectious
13 complication or to PTLD.

14 Maybe the children may be the best population
15 to see the beneficial effects of this drug, because they do
16 have an increased incidence of rejection, and that may be
17 more comparable to the placebo and two-drug group, which
18 are a 45 to 50 percent incidence of rejection. But these
19 three agents, I think it may be a better strategy to, say,
20 approve this drug for renal allograft recipients than just
21 to approve it just for adults.

22 DR. BROUDY: Dr. Kleinerman?

23 DR. KLEINERMAN: Sorry, one last thing. Just
24 as was made the suggestion prior that when studies are

1 brought before the FDA, rather than just having renal, have
2 renal and another organ, I think we really need to send a
3 message that companies need to start trials in pediatrics
4 early so that we won't continue to have this problem.

5 Because as somebody said, the traditional way to deal with
6 pediatrics is in Phase IV studies, and that's why we as
7 pediatricians can't get the drugs early on. If it was a
8 requirement to start the studies when you start the other
9 studies, then we would have had more data, and we wouldn't
10 be struggling with this issue.

11 So I think we really need to send a message
12 that the pediatric studies, as limited as they may be, need
13 to start at the same time that they start with adults.

14 DR. BROUDY: Dr. Siegel, would it be helpful to
15 you if we took a vote on the issue of use of this
16 medication in the pediatric population?

17 DR. JAY SIEGEL: Same answer. There's been a
18 lot of very helpful advice. I'm reasonably satisfied with
19 where we stand. And lest anybody take that the wrong way,
20 I don't mean at all to downplay the importance of
21 everything you say, but the numbers are -- you know, how
22 many hands go up in one way or another is not a critical
23 part of the process, I think.

24 DR. BROUDY: I think for Ms. Meyers' benefit

1 perhaps, I would like to take a vote for the pediatric
2 population, if you're comfortable with that.

3 DR. JAY SIEGEL: Yes.

4 DR. BROUDY: So I'd like to have those who
5 favor extending the use of Zenapax to the pediatric
6 recipient of a renal allograft, please raise your hand.

7 (Show of hands.)

8 DR. BROUDY: Nine in favor. Those who are
9 opposed, please raise your hand.

10 (Show of hands.)

11 DR. BROUDY: We have nine in favor and three
12 opposed.

13 Are there anymore comments before we close this
14 meeting? And I'd like to say that Dr. William Freas, Bill
15 Freas, would like to make a brief announcement.

16 DR. FREAS: I know we're late. FDA generally
17 sends to former advisory committee members certificates of
18 appreciation for their dedication and hard work. Today, by
19 sheer coincidence, we happen to have the certificate and
20 also a former member here at the table, and we would like
21 to take this opportunity to personally thank Dr. Steve
22 Woodle for his hard work and dedication on this committee
23 throughout the past years.

24 Thank you, Dr. Woodle.

1 (Applause.)

2 DR. FREAS: Because we have such a busy agenda,
3 we have reserved certain tables in the cafeteria next-door
4 for advisory committee members, and we're asking the
5 committee members to use those tables to speed up their
6 service. And during lunch we'll collect any confidential
7 material you wish to give us.

8 (Whereupon, at 12:38 p.m., the meeting was
9 recessed for lunch, to reconvene at 1:30 p.m.)

10

11

12

13 AFTERNOON SESSION (1:40 p.m.)

14 MS. DAPOLITO: Good afternoon, members of the
15 committee, invited guests, and public participants. I
16 would like to again welcome all of you to this, the 21st
17 meeting of the Biological Response Modifiers Advisory
18 Committee. Again, I am Gail Dapolito, the designated
19 federal official for this meeting.

20 At this time, I would like to announce that in
21 the absence of Dr. Julie Vose, Dr. Virginia Broudy will be
22 the acting chair of today's meeting, and for the benefit of
23 those just joining this meeting for this afternoon's
24 session, I would like to go around the table and have the

1 committee members introduce themselves again, please, and
2 we can start over here with Dr. Berman.

3 DR. BERMAN: Ellin Berman from Memorial Sloan-
4 Kettering Cancer Center in New York.

5 DR. GABRILOVE: Janice Gabrilove, associate
6 attending, Memorial Sloan-Kettering Cancer Center.

7 DR. ANDERSON: French Anderson, USC School of
8 Medicine.

9 DR. O'FALLON: Mike O'Fallon, Mayo Clinic.

10 DR. BROUDY: Virginia Broudy, University of
11 Washington.

12 MS. HEINEMANN: Kristina Heinemann. I'm the
13 patient representative.

14 DR. GOLDSBY: Dick Goldsby, Amherst College.

15 DR. AUCHINCLOSS: I'm Hugh Auchincloss from
16 Massachusetts General Hospital.

17 DR. MILLER: Carole Miller, Johns Hopkins
18 Hospital.

19 DR. CARDINALI: Massimo Cardinali, FDA.

20 DR. KEEGAN: Patricia Keegan, FDA.

21 DR. WEISS: Karen Weiss, FDA.

22 DR. JAY SIEGEL: Jay Siegel, FDA.

23 MS. DAPOLITO: Ms. Abbey Meyers, the consumer
24 representative, will be joining us shortly, and we have two

1 members who won't be here today, Dr. Hardigan and Dr. Hann.

2 At some point on the agenda, we shall have an
3 open public hearing. As part of the FDA advisory committee
4 meeting procedure, we hold an open public hearing for
5 members of the public who are not on the agenda and would
6 like to make a statement concerning matters pending before
7 the committee. I have not received any requests to speak.
8 Is there anyone in the audience at this time who would like
9 to make a presentation or address the committee in this
10 open public hearing for this afternoon's topic?

11 (No response.)

12 MS. DAPOLITO: Okay. I see no response, so I'd
13 like to turn the microphone over to Dr. Virginia Broudy.

14 DR. BROUDY: Thank you.

15 I think we'll move on now to Topic 2, and I'd
16 like to invite representatives of Schering-Plough to do the
17 presentation.

18 DR. PELLICCIONE: Good afternoon. My name is
19 Nick Pelliccione, senior director of regulatory affairs at
20 Schering-Plough, and on behalf of Schering-Plough, I would
21 like to thank the FDA and the Biological Response Modifiers
22 Advisory Committee for the opportunity to be here today.

23 We're here today to discuss the use of INTRON A
24 in conjunction with combination chemotherapy for the

1 treatment of clinically aggressive follicular lymphoma.
2 Our presentation today will provide you with information we
3 believe supports the use of INTRON A for the following
4 indication. INTRON A is indicated in previously untreated
5 patients with clinically aggressive follicular non-
6 Hodgkin's lymphoma, in conjunction with anthracycline-
7 containing combination chemotherapy.

8 First, Dr. Robert Spiegel, senior vice
9 president of clinical research at Schering-Plough, will
10 describe the framework upon which our application is based.
11 Then Dr. Howard Ozer, director and chief of hematology-
12 oncology of the Allegheny University of the Health Sciences
13 Cancer Center, and former chair of the NCI's Experimental
14 Therapeutics II Study Section, will provide an overview of
15 lymphoma and discuss the clinical characteristics of the
16 patient population that is the focus of our application.
17 Finally, Dr. Craig Tendler, clinical project director in
18 oncology at Schering, will present the results of our
19 pivotal trial and review other study data available in the
20 literature which address the use of interferon in the
21 treatment of lymphoma.

22 As you will see, this is not a straightforward
23 area, and our discussion will highlight the importance of
24 choosing the correct patient population for this therapy.

1 Also present today and available to respond to
2 questions are Dr. Phillipe Solal-Celigny, the principal
3 investigator of the pivotal study performed by GELF, the
4 follicular lymphoma study group in France; Drs. Nick Tio
5 and Harry Amcrougth from our biostatistics group; and Dr.
6 David Cigano of our quality of life research unit.

7 I'd like now to turn the podium over to Dr.
8 Spiegel.

9 DR. SPIEGEL: Thank you, Nick, and good
10 afternoon to the members of the advisory committee. My
11 remarks will be brief this afternoon, and we will try very
12 hard to keep the committee on schedule through our
13 presentation.

14 As you are aware, there has been considerable
15 interest in having pharmaceutical sponsors expand their
16 labeling to include additional indications. This has
17 benefit in providing accurate and appropriate information
18 to physicians about efficacy and safety, as well as
19 cautions for the use of their drugs. Additional labeling
20 can also influence patient reimbursement and treatment
21 guidelines.

22 In this regard, the FDA has recently endorsed
23 new cancer initiatives, one of the intentions of which is
24 to encourage submission of published information, as well

1 as information from sponsor-controlled studies. In fact, I
2 was pleased to see a handout available today as we came
3 into the room which describes the current FDA guidance to
4 sponsors and the steps to be taken by the FDA to minimize
5 formerly perceived barriers to having expanded indications
6 added to labeling of approved products.

7 Today, based on extensive discussion with the
8 agency that began in 1994, we are presenting the results of
9 a large, well-conducted randomized trial in a specific
10 homogeneous group of non-Hodgkin's lymphoma patients, with
11 extensive follow-up. We are also providing a large
12 composite clinical trial experience of interferon in non-
13 Hodgkin's lymphoma. We have included for review all Phase
14 III studies which have utilized interferon-alfa in
15 follicular non-Hodgkin's lymphoma. Some were done with
16 heterogeneous populations of NHL patients. Some were done
17 with a diverse group of chemotherapy drugs used alone and
18 in various combination regimens. Some studies used lower
19 doses of interferon or shorter duration than we might
20 recommend today, and some used interferon-alfa other than
21 our INTRON A.

22 What results is admittedly a complex dossier
23 with multiple well-controlled trials which do not each
24 provide clear duplication of activity in all endpoints.

1 However, for the most part, these are mature studies with
2 available results to assess progression-free survival and
3 overall survival, not surrogate endpoints. We believe the
4 overall message is that interferon clearly is active and
5 efficacious in NHL and has a role in combination with
6 chemotherapy. Interferon is used today outside the United
7 States in NHL as an approved indication, and it has been
8 used in the U.S. off-label without approval or guidelines.

9 The data provided to you should help define the
10 subpopulation of lymphoma patients who will derive benefits
11 from interferon. We look forward to working with you today
12 to define how to best describe this population and provide
13 appropriate labeling for prescribers.

14 I'd now like to turn the podium over to Dr.
15 Ozer, who will begin our discussion by describing the
16 setting of non-Hodgkin's lymphoma.

17 DR. OZER: Thank you, Bob.

18 My name is Howard Ozer from Allegheny
19 University in Philadelphia. I'd like to express my
20 appreciation for the attention of the committee members.

21 I'm going to spend a few minutes talking about
22 the classification of the lymphomas in as simple and short
23 a version as I can and try to point out what we're
24 ~~describing as clinically aggressive follicular lymphomas~~

1 and how they differ clinically and therapeutically from the
2 overall group of non-Hodgkin's lymphomas.

3 First of all, this slide represents the
4 epidemiology overall for the follicular lymphomas. The
5 SEAR data anticipate approximately 53,000, plus or minus,
6 new cases of non-Hodgkin's lymphoma in the United States
7 for this year. Of those, between 30 and 40 percent will be
8 low-grade lymphomas, as defined by the International
9 Working Formulation A, B, and C categories. The incidence
10 for lymphomas, particularly the follicular lymphomas, is
11 increasing probably as a result of environmental toxins.
12 It was 2.6 per 100,000 in the U.S. population between 1978
13 and 1979, and is 3.6 per 100,000 between 1991 and 1993, the
14 last date for which SEAR data are available. This
15 represents almost a 40 percent increase per decade. It
16 generally occurs in the middle-aged and elderly, and the
17 incidence is higher in whites than in blacks or Latinos.

18 This slide attempts to compare the
19 International Working Formulation with a modified Rappaport
20 Lukes Collins classification, and the IWF categories range
21 from A to J, low-grade, intermediate, and high-grade
22 lymphomas. I've highlighted here in yellow the follicular
23 lymphomas. These make up the vast bulk of the patients
24 that are described in the trials that you'll hear about

1 today. One or two of the trials did allow enrollment of a
2 small number of patients in the International Working
3 Formulation A and E categories.

4 Biologically, follicular lymphoma represents a
5 malignancy of small B lymphocytes from germinal center
6 cells. A high proportion of these cells are resting not in
7 S phase, and, therefore, it has a low proliferation rate.
8 The histological pattern is follicular or a mixture of
9 follicular and diffuse, but there is always an element of
10 follicular histology present to make the diagnosis.
11 Eighty-five percent of these lymphomas have a translocation
12 of the 14,18 chromosome, with a rearrangement of the bcl-2
13 proto-oncogene that controls apoptosis and is thought to be
14 etiologic. There is a tendency for these lymphomas to
15 transform to a large-cell lymphoma at relapse. They then
16 become highly refractory to further therapy.

17 Clinically, follicular lymphoma presents with
18 involvement of the lymph nodes and bone marrow and has
19 initial sensitivity to either chemotherapy or radiotherapy.
20 However, with each successive therapeutic intervention,
21 there is increasing resistance to treatment, and ultimately
22 the disease is, in all but a few exceptions, incurable. It
23 has a prolonged median survival, and the universe of
24 patients and I stress that it's the universe of all

1 patients -- has a median survival of 7 to 10 years, and
2 we're going to show you where the exceptions are to that.
3 Survival duration is highly dependent on prognostic
4 features that I'll describe in a moment. Generally, it's
5 not curable with any of the standard therapies available.

6 This is a slide of the standard Ann Arbor
7 staging criteria for the lymphomas, and the lymphomas fall
8 into two categories, limited- and advanced-stage disease,
9 and shown in yellow are the advanced-stage patients that
10 we'll be discussing this afternoon. Limited-stage patients
11 have single region or single extralymphatic organ
12 involvement or perhaps two regions of involvement for Stage
13 2 on the same side of the diaphragm. Stage 3 involves
14 disease on both sides of the diaphragm, and Stage 4 is
15 extranodal involvement. Each stage can be subdivided
16 according to the presence or absence of constitutional
17 symptoms, and the presence of constitutional symptoms
18 usually confers extensive high tumor burden disease.

19 Limited-stage follicular lymphoma is involved
20 in the minority -- 10 to 20 percent -- of patients. The
21 median survival for these patients ranges up to 15 years,
22 so they're on the very good end of the spectrum of
23 survival. However, in addition, these are the only
24 patients who may be cured. A small subset in whom local,

1 regional, or involved field radiation therapy can be
2 utilized will be cured.

3 Eighty to 90 percent of the patients, however,
4 present with advanced-stage 3 or 4 disease. Most of these
5 patients do achieve a complete response or a very good
6 partial response with initial therapy; however, ultimately
7 they will relapse. There is a spectrum of patients and
8 patients who are asymptomatic and have low tumor burden
9 disease who can be treated with deferred therapy if they
10 are highly selected, and this does not appear in that
11 patient subset to affect overall survival. The median
12 survival, again, for this group of patients, both the low
13 and high tumor burden, is 7 to 10 years.

14 With high tumor burden, which involves
15 approximately 60 percent or more of Stage 3 or 4 patients,
16 the story changes, however. These patients are often
17 symptomatic at presentation, and they do require immediate
18 therapy, and currently almost all physicians use
19 combination chemotherapy involving an anthracycline. Their
20 median duration of initial remission is 1.5 to 1.7 years,
21 and their median survival, therefore, ranges from 5 to 6
22 years.

23 The treatment options, therefore, that we have
24 available to us for Stage 3 and 4 disease also form a

1 spectrum that correlates with survival. Deferred therapy,
2 sometimes referred to as "watch and wait," was pioneered by
3 the Stanford group and, as I mentioned, in asymptomatic
4 patients doesn't affect survival. These patients can also
5 be treated with a single oral alkylating agent, such as
6 chlorambucil or cyclophosphamide, and combination
7 chemotherapy currently evolved toward CHOP, or
8 cyclophosphamide, doxorubicin, vincristine, and prednisone,
9 is preferred for the symptomatic patients. And, lastly,
10 for refractory patients or for relapsing patients,
11 intensive combination chemotherapy with stem cell rescue is
12 currently utilized.

13 This slide represents the overall survival
14 curve for the entire population of patients with low-grade
15 lymphomas, and it's derived from the Stanford experience
16 over approximately four decades. Despite a variety of
17 therapeutic interventions, the curve has remained constant
18 and is without plateau and appears to be unaffected during
19 various decades of therapy, and these are the data from
20 which the overall survival of 7 to 10 years is derived.

21 However, if we then look at the Stage 3 and 4
22 patients who have advanced high tumor burden disease, we
23 can determine that there are a number of adverse prognostic
24 factors. First of all, older age and less good performance

1 status both impact on outcome. All of the other measures
2 are either direct or surrogate measures of tumor burden. A
3 bulky tumor can be defined as anything greater than 5 or 7
4 centimeters, but patients may also have an elevated beta-2
5 microglobulin, elevated LDH, more than two nodal sites, and
6 constitutional symptoms as a surrogate marker, and this,
7 again, is the population of advanced-stage high tumor
8 burden patients that will be described in the subsequent
9 trials.

10 One group, the GELF group in France, looked at
11 a comparison of survival of the high tumor burden versus
12 low tumor burden patients with Stage 3 and 4 disease, and
13 you can see here that in fact they do experience a less
14 good survival, on the order of 5 to 6 years, as compared to
15 the low tumor burden same Stage 3 and 4 patients.

16 So the therapeutic approaches, again, form a
17 spectrum. Stage 1 or 2 disease with median survival of 10
18 to 15 years and occasional curability is generally best
19 treated with local radiation therapy. Stage 3 or 4 disease
20 with low tumor burden and a median survival of 7 to 10
21 years can be treated either with watch and wait or with a
22 single oral alkylator. In contrast, Stage 3 or 4 disease
23 with high tumor burden, usually with symptoms, has a 5- to
24 6 year median survival, and these patients are best treated

1 with an anthracycline-containing CHOP or CHOP-like regimen.

2 Shown here are attempts by several cooperative
3 groups internationally and two U.S. single institutional
4 studies to advance therapy for high tumor burden or adverse
5 prognostic factor Stage 3 and 4 aggressive follicular
6 lymphoma, and you can see here that the first point of the
7 slide is that the median survival ranges between about 45
8 and 55 percent. Each of these regimens are variations on a
9 CHOP-like regimen, some with higher and some with lower
10 doses, but all containing an anthracycline.

11 So, in conclusion, follicular non-Hodgkin's
12 lymphoma is both clinically and therapeutically
13 heterogeneous. There is no single best chemotherapy
14 regimen for advanced-stage patients, although an
15 anthracycline-based regimen is widely preferred by both
16 U.S. and international physicians. Prognostic features
17 which predict for high tumor burden also predict for a
18 reduced survival, and, therefore, this disease is not an
19 indolent lymphoma when high tumor burden is present, and
20 better therapeutic approaches are needed.

21 Alfa-interferon is a biologic which has been
22 shown to have both an in vitro and a clinical rationale for
23 therapy in the non-Hodgkin's lymphomas. In vitro studies
24 in tissue culture, as well as in vivo studies in animals

1 demonstrate synergistic anti-tumor effects with cytotoxic
2 agents, including anthracyclines, that enhance apoptosis
3 and allow for clonal tumor cell death. There are direct
4 anti-proliferative activities of interferon in vitro, and
5 interferon may activate cytotoxic T cells and then K cells,
6 if indeed we believe that they play a role in regulation of
7 the lymphomas.

8 Clinically, I've had the privilege of working
9 with Schering-Plough and developing interferon for a number
10 of years, and interferon-alfa has definite activity in a
11 variety of lymphoproliferative malignancies and, as a
12 single agent therapy for non-Hodgkin's lymphomas, can evoke
13 up to a 50 percent response rate.

14 With that, I'll turn the podium over to Dr.
15 Tendler.

16 DR. TENDLER: Good afternoon, members of the
17 advisory committee and FDA members. Today I would like to
18 review for you the data from the pivotal GELF trial, as
19 well as a variety of data from other studies' supportive
20 randomized trials of interferon for follicular lymphoma.
21 It is in this context which we hope to define the patient
22 population that's most likely to benefit from interferon
23 treatment -- namely, those with follicular lymphoma,
24 ~~advanced disease, and high tumor burden~~ specifically,

1 those patients in clinical need of treatment with
2 clinically aggressive disease.

3 In addition, we hope to provide data that will
4 delineate to you today how interferon can be integrated
5 with other anthracycline-containing regimens and other
6 effective chemotherapy treatments to achieve the benefit of
7 prolonged progression-free survival, which has consistently
8 been demonstrated across the majority of trials which I'll
9 be describing today.

10 Finally, we hope to further clarify the safety
11 profile of interferon when used in this setting, which is
12 associated with some additive toxicity, but is nevertheless
13 manageable with appropriate dose modifications.

14 I'd like to begin the discussion today by
15 reviewing the pivotal GELF trial, which compared a
16 doxorubicin-containing combination chemotherapy regimen
17 with or without INTRON A, again, in a very well-defined
18 patient population of clinically aggressive, large tumor
19 burden follicular non-Hodgkin's lymphoma. This study was
20 conducted by the French working group for follicular
21 lymphomas, known as GELF, which is the largest independent
22 cooperative group of hematologists in Europe. The chair of
23 this group is Professor Coiffier, and as was mentioned
24 before, Dr. Solal Celigny, who is with us today, is the

1 principal investigator for this study.

2 This study was conducted by qualified
3 investigators over 30 sites in France and one site in
4 Belgium. There were a total of 273 randomized patients to
5 the study, and the preliminary results of the study, as you
6 know, were first reported in the New England Journal in
7 1993. By early 1996, the study provided mature data from
8 which definitive clinically meaningful results could be
9 derived. After consultation with the FDA, the data from
10 this update were utilized in conjunction with supportive
11 data from similar studies in the literature as the basis
12 for our BLA supplement and will be reviewed in the
13 presentation today.

14 There are a number of reasons which need to be
15 stressed for why the GELF study was the one which was our
16 choice for inclusion as the pivotal trial in the BLA
17 supplement. First, it was a large, well-controlled
18 cooperative group trial with a high-quality database. This
19 study, as I mentioned before, was conducted in a
20 homogeneous, well-defined follicular lymphoma patient
21 population, all of whom had their initial diagnosis
22 established by lymph node biopsy and confirmed by both a
23 regional pathologist as well as by the central study
24 pathologist.

1 In addition, the patients all had evidence of
2 high tumor burden, as specified by prospectively defined
3 criteria in the protocol. As was mentioned before, these
4 criteria identified a patient population with adverse
5 prognostic features who overall had a poorer survival than
6 those with low tumor burden. Finally, with a median
7 duration of follow-up of 6.1 years, the GELF study provides
8 mature data from which clinically meaningful results can be
9 derived.

10 The primary objective of this study was to
11 determine the effect of INTRON A in conjunction with
12 combination chemotherapy on progression-free survival in
13 the clinically aggressive follicular lymphoma patients.
14 Secondary objectives included comparison of overall
15 survival, response rate, and tolerability between the two
16 treatment arms.

17 As shown on this slide, patients were
18 randomized to receive CHVP, a doxorubicin-containing
19 combination chemotherapy regimen, alone or in conjunction
20 with INTRON A at 5 million units three times a week for a
21 total duration of treatment of 18 months. The CHVP
22 chemotherapy was given monthly for the first 6 months and
23 every other month for the remaining 12 months. This
24 ~~particular doxorubicin containing regimen was chosen by the~~

1 GELF group because it delivered similar cumulative doses of
2 cyclophosphamide and doxorubicin as other regimens such as
3 CHOP, however, with theoretically less toxicity because of
4 the decreased dose intensity of both the doxorubicin and
5 the cyclophosphamide.

6 As shown on this slide, eligible patients for
7 the study all had follicular lymphoma, again, confirmed by
8 nodal biopsy on all patients. None of the patients had
9 received prior treatment. The initial diagnosis was made
10 within 3 months prior to study entry, so none of these
11 patients who had low tumor burden and then have progressed
12 would have been entered on this study. All patients were
13 less than 70 years of age, had Ann Arbor Stage 2 through 4,
14 and in addition, as mentioned before, every patient had one
15 of the following large tumor burden criteria: either a
16 tumor mass greater than 7 centimeters, three nodal sites
17 each greater than 3 centimeters, the presence of systemic
18 symptoms, substantial splenomegaly, the presence of a
19 compression syndrome, or a leukemia or blood cytopenia.

20 As you heard from Dr. Ozer, it is these large
21 tumor burden criteria which were used for selecting
22 follicular lymphoma patients for the GELF study, which
23 isolated a group of high-risk patients with poorer
24 prognosis as compared to other low tumor burden follicular

1 lymphoma patients.

2 The enrollment period for the study was from
3 October 1986 to June 1991. The rights of the patients were
4 respected under the Declaration of Helsinki. Again,
5 another feature of the study, which was mentioned, was the
6 central pathology review for all lymph node biopsies. At
7 the time of the first interim analysis, the boundary for
8 significant difference in progression-free survival was
9 crossed, with a P value of less than 0.02, and in
10 accordance with Pocock's rule, the randomization to the
11 study was stopped.

12 The results of the GELF study are based on a
13 reliable, high-quality database. To verify the accuracy of
14 the study data and to ensure its compliance with FDA
15 standards, Schering-Plough authorized an independent CRO to
16 conduct an extensive source data verification in 100
17 percent of the patients, as per an FDA agreed-upon
18 protocol. It included examination of baseline variables,
19 as shown on this slide, as well as the all-important
20 response variables. Results from the verification process
21 revealed minor findings requiring few corrections to the
22 database. None of the changes resulting from the
23 verification procedure significantly affected the efficacy
24 results which I'll be describing today.

1 In addition, to augment safety reporting from
2 the study, Schering-Plough authorized the medical monitors
3 from Etem to collect all adverse events noted in the
4 patients' charts. These were, again, all encoded and
5 incorporated into the original safety database. Finally,
6 the date of progression, the date of last follow-up, and
7 the date of death were verified in all patients in a
8 database sweep to update survival.

9 A total of 273 patients were randomized to the
10 study. As shown on the slide, five patients -- three in
11 the chemotherapy-alone arm, two in the chemotherapy-plus-
12 INTRON arm -- were randomized, not treated, and have no
13 follow-up data. These five patients are excluded from all
14 intent-to-treat analyses, thus the intent-to-treat
15 population consists of 268 patients, on which all of the
16 efficacy analyses which I'll be presenting to you were
17 performed. In addition, there were 26 other patients who
18 had ineligible diagnoses discovered during the course of
19 study treatment. Thus, the efficacy population consists of
20 242 patients. The results for all the major efficacy
21 comparisons were similar between the intent-to-treat
22 populations and the efficacy patient populations.

23 On this slide, you see depicted the baseline
24 patient characteristics for the entire study population.

1 At study entry, the clinical characteristics of the
2 patients were well balanced between the two treatment arms.
3 At initial diagnosis, approximately 80 percent of the
4 patients had Stage 4 disease. About 75 percent of the
5 patients had one or more sites of extranodal involvement,
6 and about 55 percent of the patients -- again, equal on
7 both treatment arms -- had evidence of bulky tumors usually
8 greater than 7 centimeters in size.

9 The important thing, again, to emphasize is
10 that all of these patients were in clinical need of
11 treatment, could not be managed with the watch-and-wait
12 approach.

13 This slide shows you the overall response which
14 was seen on both arms of the study. The analysis was
15 performed for 258 patients for which there was response
16 data available and was analyzed for response after 6 months
17 of treatment, as well as best response to treatment. One
18 can see a significant improvement in overall response for
19 patients receiving chemotherapy with INTRON A over
20 chemotherapy alone, 90 percent overall response versus 74
21 percent with the chemotherapy alone, and this difference
22 was statistically significant with a P value of .001.

23 As I mentioned before, in this analysis the 15
24 ~~patients who did not have response data were excluded, but~~

1 if they are included as treatment failures, the results
2 remain statistically significant.

3 Here are the estimated Kaplan-Meier
4 progression-free survival curves for each treatment group,
5 as depicted in the slide. A statistically significant
6 improvement of nearly 18 months was seen in terms of the
7 median progression-free survival for patients treated with
8 chemotherapy plus INTRON A, median progression-free
9 survival of 2.9 years versus 1.5 years for patients
10 receiving chemotherapy alone. Notably, the hazard ratio of
11 1.66 indicates that the relative risk of progressing was 66
12 percent greater for patients who did not receive INTRON A.

13 One can also utilize the Kaplan-Meier curves to
14 estimate progression-free survival rates at both 18 months
15 and 3 years, and the important thing to stress from this
16 slide is that the improvement in progression-free survival
17 rates at 18 months is maintained at 3 years as the curves
18 remain parallel.

19 With a median duration, again, of follow-up of
20 6.1 years, the median overall survival for patients
21 receiving CHVP plus INTRON was significantly better than
22 for patients receiving CHVP alone. Again, the median has
23 not yet been reached for patients receiving the combination
24 therapy and is at 5.6 years for those receiving

1 chemotherapy alone. The P value for this difference is
2 statistically significant, at a value of .0084. Again, the
3 hazard ratio can be used, notably 1.63, or indicating that
4 the relative risk of dying is about 63 percent greater for
5 those patients who did not receive INTRON A.

6 One can also use, again, the Kaplan-Meier
7 estimates from the survival curves, as shown on this slide,
8 to calculate the overall survival rates at 3 and 5 years,
9 and, again, the point to be made here is that at 3 years
10 after randomization, there is a survival difference, and
11 that this absolute increase of 14 percent is maintained at
12 5 years.

13 In order to assess the potential influence of
14 baseline patient variables on progression-free and overall
15 survival, a Cox multivariate analysis was performed using
16 all baseline characteristics as additive terms in the
17 model. The results of this step-wise regression analysis
18 indicate that for both progression-free survival as well as
19 for overall survival, the beneficial treatment effect of
20 INTRON A remained statistically significant, even after
21 correcting for other prognostic factors. In addition, a
22 number of the prognostic factors which were identified on
23 this study are very similar, if not identical, to other
24 studies looking at similar patient populations, and those

1 have identified the same prognostic factors as this study.

2 In summary, the efficacy results of the GELF
3 study demonstrate that treatment with INTRON A in
4 conjunction with the doxorubicin-containing, but modified
5 CHOP chemotherapy regimen, the CHVP regimen, which was
6 utilized in the GELF study, significantly increased both
7 progression-free survival from 1.5 to 2.9 years, as well as
8 overall survival past the 5.6 years seen with chemotherapy
9 alone.

10 Now I'd like to move on to a discussion of
11 safety from the study. I think we all recognize that the
12 therapeutic gain from the addition of interferon to a
13 doxorubicin-containing chemotherapy regimen must be weighed
14 against the potential toxicity, the additive toxicity over
15 the use of chemotherapy alone. On this slide, one sees
16 those adverse events which occurred with a greater than 10
17 percent difference in incidence between the two treatment
18 groups.

19 As you can see, the greatest difference in
20 incidence for these adverse events occurred for asthenia or
21 fatigue, fever, neutropenia, and elevated liver
22 transaminases. All of these events are all known to be
23 associated with interferon toxicity and currently appear in
24 our present interferon label. With the exception of

1 asthenia, neutropenia, and elevated liver enzymes, the
2 greatest bulk of this difference in incidence between the
3 two treatment arms are comprised mainly of adverse events
4 of mild to moderate severity.

5 Other events which are identified by the FDA as
6 occurring more frequently in the CHVP-plus-INTRON group
7 include the following adverse events: dyspnea,
8 paresthesias, and polyuria. I think one can see for
9 paresthesias as well as polyuria, again, the difference in
10 incidence between the two treatment arms are made up
11 entirely of mild to moderate adverse events and not Grade 3
12 and 4 adverse events. Although there was a 4 percent
13 incidence of Grade 3 or 4 dyspnea for patients receiving
14 CHVP plus INTRON, in all cases it was reversible, and as
15 I'll show you later, it did not result in interferon
16 discontinuation.

17 Here are the most common Grade 3 or 4 adverse
18 events in each treatment group, as described on this slide.
19 Again, I'd like to emphasize that this pattern is rather
20 typical for interferon-treated patients. Only two of the
21 events, neutropenia and asthenia, occurred with a
22 difference in incidence of greater than 5 percent between
23 the two treatment arms. Although the patients who were
24 treated with CHVP plus INTRON had a 34 percent versus 6

1 percent incidence of Grade 3 and 4 neutropenia, this
2 difference was not associated with a substantially
3 different incidence in neutropenic infections.

4 In fact, the incidence was low in both
5 treatment arms, 2 percent versus 6 percent of incidence of
6 neutropenic infections. In these cases of neutropenic
7 infections, these were mostly viral syndromes, otitis
8 media, other kinds of mild bacterial infections that did
9 not require hospitalization. In no case of neutropenic
10 infection was there sepsis or permanent sequelae.

11 Of the six patients who developed Grade 3 and 4
12 hepatotoxicity, three of these events occurred in
13 individuals who would be considered at high risk for
14 developing hepatotoxicity by virtue of the fact that they
15 had active viral hepatitis B infections or alcoholic liver
16 cirrhosis.

17 Of the 136 patients in the intent-to-treat
18 population randomized to CHVP plus INTRON, two of the
19 patients never received INTRON, and for the purposes of
20 this analysis of discontinuations for toxicity, we have
21 excluded them from this analysis. Again, as expected,
22 asthenia or fatigue, a well-described interferon-associated
23 toxicity, was the most common reason for discontinuation of
24 INTRON on this study. Other reasons for stoppage included,

1 again, typical described adverse events which have been
2 associated with interferon toxicity. Overall a total of 13
3 patients, or 10 percent of the interferon-treated patients,
4 discontinued interferon for toxicity.

5 This slide provides a summary analysis of
6 chemotherapy dose intensity during cycles 1 through 6 as
7 compared to cycles 7 through 12. Again, this analysis was
8 done for the efficacy population, the reason being because
9 we're evaluating compliance here with a protocol-specified
10 chemotherapy regimen and in follicular lymphoma patients.
11 So this analysis is really most relevant to the efficacy
12 population.

13 One can see from the analysis that in general
14 at least 90 percent of the patients in both treatment arms
15 received nearly full doses of chemotherapy, as defined by a
16 greater than/equal to 80 percent of the prescribed
17 chemotherapy doses. Furthermore, the dose intensity
18 between cycles 1 through 6 and 7 through 12 were comparable
19 between the treatment arms. Thus, the addition of
20 interferon to this doxorubicin-containing chemotherapy
21 regimen did not interfere with the ability to deliver the
22 protocol-specified target doses of the respective
23 chemotherapy agents. Likewise, if one looks at interferon
24 compliance, one can see that 91 percent of the patients

1 received greater than 80 percent of the prescribed dose of
2 interferon on the study.

3 So to summarize the safety results from the
4 study, there was an increased incidence of Grade 3 or 4
5 neutropenia, 34 percent versus 6 percent, as well as Grade
6 3 or 4 asthenia, 10 percent versus 3 percent, for patients
7 receiving concomitant interferon therapy. However, as I've
8 showed you, the incidence of neutropenic infection between
9 the treatment arms is low and numerically similar between
10 the two treatment arms, 6 percent versus 2 percent.

11 Twenty-eight percent of the patients who
12 received interferon did require dose adjustments, usually
13 temporary interruptions of the drug or dose reductions. In
14 addition, as mentioned before, 10 percent of the
15 interferon-treated patients required permanent
16 discontinuation, again, for reversible toxicity.

17 There were a total of four deaths on study
18 treatment or within 30 days of last treatment dose, two in
19 both treatment arms, and in all four cases, as per the
20 investigator's assessment, these deaths were not felt to be
21 related.

22 You've seen this slide before. It's important
23 to emphasize again that all the study patients in the GELF
24 ~~study had follicular lymphoma and were in clinical need of~~

1 treatment due to the presence of high tumor burden. CHOP,
2 as you've heard, is one of many anthracycline-containing
3 regimens that are utilized as initial therapy for such
4 patients. The anthracycline-containing regimen utilized in
5 the GELF study was known as CHVP, which, as we've said
6 before, is a variation of CHOP, which will deliver similar
7 cumulative doses, but obviously with less dose intensity
8 for doxorubicin and cyclophosphamide.

9 It's important to emphasize that in this study,
10 treatment with CHVP alone, again, a modified CHOP regimen,
11 resulted in a 5-year survival rate of 56 percent. Although
12 it might be difficult to directly compare the heterogeneous
13 patient populations, as shown on this slide, there is a
14 common theme here of patients treated with a clinically
15 aggressive disease or high tumor burden, and one can see
16 very similar 5-year survival rates when one uses other
17 modified CHOP chemotherapy regimens, like COPA, CHOP-Bleo,
18 M-BACOD, and here is the full-dose CHOP as utilized by the
19 Swedish lymphoma group.

20 So I think one can take away from this slide
21 the results, which are that the clinical efficacy in terms
22 of 5-year survival rates is really quite comparable when
23 one uses CHOP or CHOP-modified regimens like COPA, as the
24 Eastern College Oncology Group did, or like GELF did with

1 CHVP.

2 Now I'd like to put the results of the GELF
3 trial in perspective with some of the other randomized
4 trials which are described on this slide and appear on page
5 44 of your briefing book. As shown on this slide, a total
6 of seven prospective randomized trials were conducted with
7 interferon in follicular lymphoma, most of these studies
8 utilizing INTRON A. As you can see from this slide, the
9 studies differed in a number of ways. In one case here, as
10 described on the slide, interferon given either in
11 conjunction with an anthracycline-containing regimen or in
12 conjunction with single agent or non-anthracycline-
13 containing regimens is one way in which the studies differ.
14 The studies also differ in terms of the dose of interferon
15 utilized and the duration of interferon.

16 In addition, the studies differ in terms of the
17 patient populations either having clinically aggressive
18 disease or in some cases, as in the CALGB study, which I'll
19 talk about in a little bit, including patients with low
20 tumor burden or indolent follicular lymphoma.

21 In four of the studies, interferon was given in
22 conjunction with an anthracycline-containing regimen. The
23 remaining three studies evaluated the interferon in these
24 studies with single agent or non-anthracycline containing

1 regimens. For the four studies in which interferon was
2 used in conjunction with an anthracycline-containing
3 chemotherapy regimen and given at a dose of at least 5
4 million units, a significant prolongation of progression-
5 free survival was consistently demonstrated across all four
6 of these studies. In addition, in two of the studies --
7 namely, the GELF study and the Mexican study -- significant
8 improvement in overall survival was also demonstrated with
9 the addition of interferon treatment. The reason for the
10 question mark there for the German lymphoma study is the
11 fact that the study is not mature yet and has not reached
12 median survival.

13 I'd like to spend a few minutes describing the
14 Eastern College Oncology Group study. This was a study
15 that was conducted in 249 patients, of which 70 percent had
16 follicular lymphoma with clinically aggressive disease.
17 The treatment consisted of an anthracycline-containing
18 regimen known as COPA, which delivers virtually identical
19 doses of doxorubicin and cyclophosphamide as CHOP, but over
20 a 4-week period instead of a 3-week period. The patients
21 were randomized to receive COPA or interferon plus COPA,
22 and the interferon was given at 6 million units per meter
23 squared every day, 5 days per month. The total monthly
24 amount of interferon delivered in this study is virtually

1 identical to the monthly amount of interferon delivered on
2 the GELF study.

3 The results of this study indicated that for
4 patients who received interferon in conjunction with COPA,
5 there was a significant prolongation of median progression-
6 free survival. However, there was no significant
7 difference in overall survival, and the patients in the I-
8 COPA group were noted to require approximately a 25 percent
9 dose reduction in the main myelotoxic agents,
10 cyclophosphamide and doxorubicin.

11 On this slide, one can see that if one looks at
12 the 3-year progression-free survival rate between the ECOG
13 study and the GELF study, there is a virtually identical
14 absolute 20 percent increase in the 3-year progression-free
15 survival rate for patients receiving concomitant interferon
16 with chemotherapy as compared to those receiving
17 chemotherapy alone.

18 Again, to try to delineate what kind of safety
19 profile one might anticipate if one gives interferon with
20 chemotherapy regimens that more approximate the full-dose
21 CHOP, one can see that in the ECOG study, again, utilizing
22 interferon concomitantly with a modified CHOP regimen known
23 as COPA, there was an identical incidence of Grade 3 and 4
24 neutropenia. Again, very similar or identical to the GELF

1 study, this neutropenia was not associated with an
2 increased incidence of neutropenic infection, and there was
3 comparability in some of the other hematologic toxicities,
4 as shown on this slide, and some of the other interferon-
5 associated toxicities.

6 One notices this difference of 1 percent
7 incidence of Grade 3/4 fever on the GELF study as compared
8 to 12 percent on the ECOG study, and it's been speculated
9 that this difference may be due to the intermittent
10 interferon dosing on the ECOG study, which may not allow
11 for tolerance to the interferon.

12 This is the third study that was put in the
13 overview slide, which, again, is another study that looks
14 at delivering interferon in a slightly different approach.
15 This is the German lymphoma group study, 247 patients,
16 again, a large follicular lymphoma patient population.
17 Eighty-one percent of the patients had follicular lymphoma.
18 Again, all of these patients had clinically aggressive
19 disease and required treatment.

20 What the German lymphoma group did was they
21 treated a patient either with an anthracycline-containing
22 induction chemotherapy called prednimustine-minus-anthrone,
23 or CVP, which is a non-anthracycline-containing regimen,
24 and for all patients responding to the initial

1 chemotherapy, they were randomized to receive INTRON A, 5
2 million units three times a week, the identical GELF
3 interferon regimen, until progression versus just
4 observation alone. And the results, again, reveal a
5 significant prolongation of median progression-free
6 survival in the interferon-treated patients, 3.1 years
7 versus 1.7 years, with a P value of 0.003.

8 This study was also very interesting because it
9 clearly demonstrated that an enhanced interferon-mediated
10 effect in terms of improved progression-free survival is
11 more often seen when the interferon is given in association
12 with the anthracycline-containing regimen prednimustine-
13 minus-anthrone than with the CVP regimen, which is a non-
14 anthracycline-containing regimen. And, again, the median
15 survival for this study has not yet been reached in either
16 treatment arm, and so the study is still immature in terms
17 of the survival data.

18 One can compare across these three trials which
19 I've described, the GELF trial, the ECOG trial, and the
20 German lymphoma study, and when one looks at the median
21 progression-free survival across all three trials, one sees
22 a marked similarity of about 1.5 years of median
23 progression-free survival for patients receiving
24 anthracycline containing chemotherapy regimens. Moreover,

1 in all three trials, the addition of interferon therapy
2 either as concomitant therapy, as done in the GELF study or
3 in the ECOG study, or as maintenance therapy, as done in
4 the German lymphoma study group, significantly prolonged
5 progression-free survival in a very comparable way across
6 all three trials.

7 As I mentioned before, three of the studies on
8 the overview slide utilized interferon in conjunction with
9 single agent chemotherapy or non-anthracycline
10 chemotherapy. Updated results of all three trials have
11 recently been presented in medical meetings and have
12 demonstrated no significant difference in progression-free
13 survival. There's a questionable minor difference here in
14 the EORTC regarding subset analysis, but for the entire
15 patient populations on all three studies, looking at
16 relatively low doses of interferon in conjunction with non-
17 anthracycline-containing regimens, there is no significant
18 improvement in either progression-free or overall survival.

19 The CALGB study was a large study which looked
20 at interferon in conjunction with single agent
21 cyclophosphamide. It should be noted that the dose of
22 interferon on this study was, again, lower than what was
23 utilized in the GELF study, 2 million units per meter
24 squared, and in addition, the study enrolled patients whom

1 would be characterized as having indolent disease in about
2 70 percent of the patients and were not in clinical need of
3 treatment at the time of study entry. By today's
4 standards, many of these patients might be managed by a
5 watch-and-wait approach.

6 So, in summary, in reviewing these randomized
7 interferon trials in the literature, I think there is a
8 consistent benefit which is demonstrated when interferon is
9 given in conjunction with an anthracycline-containing
10 chemotherapy regimen, and this benefit is seen across a
11 number of trials, validating a therapeutic benefit for
12 interferon in this setting.

13 In addition, the benefit is seen most often and
14 most consistently in patients who have high tumor burden
15 follicular lymphoma with clinically aggressive disease, and
16 I think the studies help one identify the exact patient
17 population most likely to benefit from interferon
18 treatment.

19 Finally, review of the GELF study, as well as
20 other studies in the literature really begins to elucidate
21 or delineate a variety of approaches in which interferon
22 therapy may be integrated with chemotherapy for the
23 treatment of clinically aggressive follicular lymphoma.

24 ~~So, in conclusion, the GELF study results~~

1 demonstrated that for patients who had clinically
2 aggressive follicular lymphoma, the addition of INTRON A
3 significantly improved both median progression-free
4 survival and median overall survival, and these results are
5 now clinically meaningful because they are maintained
6 during long duration of follow-up. Moreover, the clinical
7 benefit that is demonstrated in the GELF study is
8 positively balanced against additive, but manageable
9 incremental toxicity.

10 Finally, the INTRON-mediated improvement in
11 progression-free survival that's seen in the GELF study is
12 really quite consistent with a number of other studies in
13 the literature showing virtually identical improvement in
14 progression-free survival when similar patients are studied
15 in combination with anthracycline-containing chemotherapy
16 regimens.

17 So the data from the GELF study, as well as
18 from the studies that were reviewed today in the
19 literature, we believe support the proposed indication on
20 this slide -- namely, that INTRON A is indicated in
21 previously untreated patients with clinically aggressive
22 follicular non-Hodgkin's lymphoma, in conjunction with an
23 anthracycline-containing regimen only.

24 ~~The studies, I think, also clearly demonstrate~~

1 efficacy and safety established with modified CHOP
2 regimens, such as the CHVP regimen, which was utilized in
3 the GELF study, or the COPA regimen, another modified CHOP
4 regimen which was utilized in the ECOG study. The clinical
5 experience, though, is limited to modified CHOP regimens
6 and does not include any experience with concomitant
7 interferon use with full-dose CHOP, and thus we would not
8 recommend that that be done at this time.

9 In addition, there is other clinical experience
10 highlighting a benefit for maintenance therapy after
11 response to induction chemotherapy, as shown in the German
12 lymphoma study.

13 Thank you very much for your attention.

14 DR. BROUDY: Thank you.

15 Are there any questions from the committee for
16 the speakers from Schering-Plough? Dr. Gabrilove?

17 DR. GABRILOVE: That was a very nice
18 presentation of all the data. Just one clarification
19 perhaps. In our briefing booklet, on page 23 there is a
20 Table 5, a comparison of the different characteristics
21 between the CHVP alone versus CHVP and INTRON A, and I was
22 just curious, in terms of the follicular pathology, whether
23 there was any difference in the large-cell component
24 between the two groups. There is a comment here about the

1 cell type, but I wasn't sure if that refers to cytological
2 diagnosis or actually pathologic diagnosis between the two
3 arms.

4 DR. TENDLER: It refers to the histology at the
5 time of diagnosis, and I think what you'll see there is
6 about 70 percent of patients had follicular mixed-cell
7 lymphoma. That's if you add up the two categories 5 to 15
8 percent and 15 percent to 50 percent large cells. The GELF
9 study utilized a slightly different definition of mixed
10 cell than we do in the States. We usually cut it off at
11 about 30 percent, so in fact there were few patients who
12 had from 30 to 50 percent large cells, and we would
13 probably consider those diffuse large-cell follicular --

14 DR. GABRILOVE: But this refers to all
15 histologies, that they were quite comparable between the
16 groups.

17 DR. TENDLER: Correct.

18 DR. GABRILOVE: Okay. Not just ones that were
19 done cytologically.

20 DR. TENDLER: My understanding -- and we can
21 check with Phillipe -- was that at the time of diagnosis,
22 the diagnosis was established by biopsy and not by
23 cytological examination.

24 ~~DR. SOLAL CELIGNY: Nodal biopsy was required~~

1 for all patients.

2 DR. GABRILOVE: Okay. That's very helpful.

3 The second question is just a point of
4 interest. In the patients who have relapsed, was there any
5 difference in the pathology seen in the two groups?

6 DR. TENDLER: There was no difference in the
7 incidence of, let's say, transformation between the two
8 groups, but that always has to be qualified by how
9 frequently one rebiopsies a patient at the time of relapse.
10 But for those patients who were biopsied, there didn't seem
11 to be a treatment effect which was associated with a
12 decreased transformation rate, let's say.

13 DR. GABRILOVE: And just out of curiosity,
14 again, a downgrading? Any change from -- I mean, realizing
15 that there is a random -- when you biopsy, you can see
16 variable results, have you seen any difference in the
17 predominance going from a patient who might have a large
18 diffused component to follicular in the relapse patients?

19 DR. SOLAL-CELIGNY: No, we didn't see any
20 difference in the pathological aspects at relapse between
21 the two groups, and about 70 percent of the patients are
22 biopsied at relapse, and there was no difference in the
23 incidence of pathological transformation between the two
24 groups.

1 DR. GABRILOVE: Thank you very much.

2 DR. BROUDY: Are there other questions? Dr.
3 O'Fallon?

4 DR. O'FALLON: I'm going to ask some questions
5 and probably make some observations about the fact that the
6 GELF study was terminated after the first interim analysis.
7 There were some statements in the material that we had
8 received prior to the meeting that left me a little bit
9 confused, so let me state what I understand, and then you
10 can certainly correct me.

11 Interim analyses were scheduled with the
12 understanding that you would use the Pocock rule, which
13 distributes the overall level of significance of the test
14 uniformly. That's one of a number of different stopping
15 rules that are available and has a different sort of
16 emphasis. So one of the questions that I may ask the
17 investigators is why that particular rule. Many others
18 favor a more conservative rule that would have required a
19 much higher level of significance.

20 Let me just continue. If I read it correctly,
21 there were going to be potentially five interim analyses at
22 the .02 level each, which would have meant that they were
23 willing to settle for a final level of significance of .10,
24 ~~which strikes me as also somewhat unusual.~~

1 Third point. The first interim analysis
2 resulted in the study being terminated. I read that the
3 first interim analysis was scheduled after 200 patients
4 were randomized into the study. Obviously, you couldn't
5 perform the analysis at least for 18 months after that,
6 because the therapeutic process required the conclusion of
7 18 months. We obviously were being shown here in the
8 briefing booklet the analyses of more than 200 patients.
9 We were being shown the analyses of 273 or something like
10 that. So presumably the other 73 were not part of the
11 analysis that led to the conclusion to terminate the study.
12 Question mark in there.

13 Another point is, what happened when the
14 conclusion was finally reached to the treatment that was
15 currently under -- the patients who had been randomized in
16 between the time that the 200 was obtained and the time
17 that the decision was made to terminate the study? What
18 was the decision that was made about the treatment of the
19 patients who had already been randomized in that interim
20 period? I understand once the study was terminated, no
21 additional patients were randomized, but it seems like we
22 catch maybe as many as 70 patients in a kind of a never-
23 never land, and I'm just asking you what happened to those
24 patients. Did their therapy continue, or was their therapy

1 discontinued on the same ethical grounds that you used to
2 terminate the study?

3 And then all of the results that we've been
4 exposed to here today, I think, are results of a much
5 longer term of follow-up than would have been available
6 when the analysis was performed, so I was just wondering if
7 we have seen or could see the actual results on which the
8 interim decision was made.

9 And then, finally, were any of the other
10 clinical trials that you offered here in support -- the
11 ECOG, the German, the Mexican, any of the others -- did any
12 of them result in an early study stoppage? Were there
13 interim analyses scheduled, and did they terminate early?

14 An awful lot of questions there, most of them
15 having to do with the interim analysis.

16 DR. TENDLER: I think I'd like to ask Dr.
17 Solal-Celigny to address the study conduct questions about
18 the timing and how it affected the total study population,
19 and then will ask Dr. Tio to just review the statistical
20 analyses with regard to the interim analysis.

21 Phillipe?

22 DR. SOLAL-CELIGNY: I am not the statistician
23 of this study, so it will be difficult for me to answer. I
24 can answer some of the questions. First, concerning the

1 patients between the interim analysis decision and the
2 treatment, we decided to treat the patients with the same
3 regimen and no crossover, because we were doing formation
4 on the overall survival at that time. So all the patients
5 in the chemotherapy-only arm received only chemotherapy and
6 were not changed to any other treatment.

7 DR. TENDLER: Let me just clarify, too, that
8 the interim analysis was done in January 1992 and included
9 6 months of treatment for patients that were randomized up
10 to June 1991. So you're right, there is that period of
11 time of 6 months in which patients were continued to be on
12 study treatment, but the randomization for the cutoff for
13 the study and for the interim analysis was as of June 1991,
14 but the results for the interim analysis were available in
15 January 1992. Actually, the analysis was performed in
16 January 1992.

17 DR. O'FALLON: You two are answering my
18 question in a little different way, so let me make certain
19 I understood. So anybody who had been randomized to let's
20 call it the control arm, you continued them on the control
21 regimen for the full 18 months of therapy that was
22 originally called for on that regimen. That's the way I
23 interpreted your answer.

24 ~~And what you're saying is that at the time of~~

1 the interim analysis, you had more than the 200 that were
2 supposedly complete, and you used some others who were only
3 halfway or even a third of the way through their treatment
4 regimen in the analysis.

5 DR. TENDLER: They were actually through the 6-
6 month time point, where the chemotherapy changed from
7 monthly to every other month. So that was a --

8 DR. O'FALLON: Okay. They had completed,
9 though, only one-third of the originally indicated therapy.

10 DR. TENDLER: Correct.

11 DR. O'FALLON: Okay. Why was the Pocock rule
12 chosen? It's not anywhere near as conservative as many
13 people feel you should be.

14 DR. TENDLER: I'll let our statistician handle
15 that one.

16 DR. TIO: Nick Tio. I understand that -- I
17 mean, I agree with you that there are other, more
18 conservative statistical rules, such as the O'Brien-Fleming
19 rule, which we ourselves use very often. That is if we are
20 planning a new trial. But this trial was conducted by
21 GELF, and at that point in time, I think Pocock's rule is
22 not an unreasonable rule. It still does ensure that the
23 overall significance level is still limited to the .05
24 level.

1 Actually, it might be useful for us to review
2 the statistical considerations. We do have a slide here,
3 Number 94.

4 DR. JAY SIEGEL: May I interrupt to ask a
5 question that might clarify the significance of some of
6 these issues? At the time of the first interim analysis in
7 January of 1992, was this trial still accruing patients?
8 And if so, how far short of its target was it? Or had it
9 in fact stopped accruing in June of 1991?

10 DR. TENDLER: Do you want to answer that,
11 Phillipe?

12 DR. SOLAL-CELIGNY: We stopped the accrual in
13 June 1991, and before analysis we waited 6 months so that
14 we had the results of the treatment of the patients who had
15 been registered just before June 1991.

16 DR. JAY SIEGEL: There was a plan, then, to
17 reopen accrual if you didn't meet stopping rules?

18 DR. SOLAL-CELIGNY: The trial was stopped, but
19 all the patients were registered and all were treated with
20 what we considered was the most active association of CHVP
21 plus interferon until 1994, when we began another trial
22 comparing what is our standard treatment to autologous bone
23 marrow transplantation. So from June 1991 to January 1994
24 all the patients were treated with CHVP plus interferon.

1 DR. MILLER: Off this protocol, though.

2 DR. SOLAL-CELIGNY: Yes.

3 DR. O'FALLON: The protocol stopped when that
4 interim analysis was --

5 DR. JAY SIEGEL: No, the protocol had already
6 completed accrual 6 months before the post-interim
7 analysis. That's the point I was trying to clarify.

8 DR. O'FALLON: Had already completed the
9 projected total accrual?

10 DR. JAY SIEGEL: I understand that's what we're
11 being told, which makes it a bit unclear what the meaning
12 of the interim analysis was.

13 DR. O'FALLON: Well, they said in the protocol
14 that I read that they had five interim analyses scheduled,
15 and this was only the very first one. What were they going
16 to --

17 DR. JAY SIEGEL: That's why I was trying to get
18 this clarified. Was there any finding on the interim
19 analysis that, by protocol, would have led to further
20 accrual of patients, or was full and total accrual
21 complete?

22 DR. SOLAL-CELIGNY: It was full and total
23 accrual complete. The problem was that we wanted to study
24 only the efficacy population, and at that time all the

1 pathology review had not been done, so we did not know
2 exactly how many patients would belong to the efficacy
3 population, and we wanted more than 200 patients in the
4 efficacy population.

5 DR. TENDLER: I think that's an important
6 point. In order to -- it was sort of one would have to
7 estimate how many patients one would need to have 200
8 evaluable patients. So it could be anticipated that one
9 would clearly go beyond the projection of 200 patients
10 before the interim analysis was performed, knowing that in
11 fact in most of the lymphoma studies to date, there was on
12 average a 10 percent misdiagnosis rate.

13 DR. TIO: If I may walk through the stat
14 section here and see if we can find out what they were
15 supposed to do, I think we all agree what the primary
16 efficacy variable is, which is progression-free survival.
17 The secondary efficacy variables would be the response rate
18 and the overall survival. And what methods are going to be
19 used would be the log rank test and the Cox regression, and
20 in terms of the response rate, we'll use the Fisher's Exact
21 Test. I think we can all agree with that.

22 Now let's get on to the interim analysis. In
23 the protocol, it is standard that five analyses were
24 ~~planned based on Pocock's method using a constant nominal~~

1 level of .016. These are the assumptions that went into
2 it: the usual significance level of .05, power is 90
3 percent, progression-free survival in the CHVP arm is 30
4 months. Now, that's something that you might want to focus
5 on as to why things are occurring so much faster. Twenty
6 percent improvement in progression-free survival in the
7 INTRON-plus-CHVP arm. And the enrollment period of 3 years
8 at 100 patients per year.

9 DR. O'FALLON: So if I see a protocol that says
10 I'm going to perform five interim analyses -- that's the
11 way that previous slide read -- during the course of the 3
12 years of accrual, I wouldn't have been anywhere near having
13 200 patients in when I did that first interim analysis. So
14 what happened? Why weren't the interim analyses performed?
15 I presume they would have been planned on an equal sort of
16 a -- uniformly distributed over the recruitment period
17 here.

18 DR. TIO: Well, I think the enrollment rate was
19 not uniform, and that was one of the reasons. The other
20 thing was, the actual progression-free survival is coming
21 in faster than 30 months. So you have compensating
22 factors, and also they planned the interim analysis using
23 actual calendar time. Every 18 months you're supposed to
24 do an interim analysis. In the original protocol, that's

1 what it was stated as. So some of the assumptions did not
2 turn out to be true, and they had more patients and more
3 events at the first interim analysis.

4 DR. O'FALLON: Well, that's one of the reasons
5 they terminated the trial, is because they had more events
6 than the first interim analysis, but hopefully they didn't
7 schedule that interim analysis because they had more
8 events. The schedule should have been according to the
9 protocol. So it wasn't quite a .02.

10 Let me ask one more kind of technical question.
11 It said on the last one there would be five interim
12 analyses. May I interpret that to mean that then there
13 would be one more analysis, which would have been the final
14 analysis had it all worked?

15 DR. TIO: If we want to be strict about it.
16 Considering that it was performed at close to 230 patients,
17 and right now we have 273. But still, I mean, given that
18 you already had so many patients, it would have been
19 impossible to do five interim analyses. So we're adjusting
20 for five when we, in all practicality, could not have done
21 more than two.

22 DR. TENDLER: I think Dr. Tiwari wanted to
23 comment from the FDA.

24 DR. TIWARI: Jawar Tiwari, biostatistics at

1 CBER. If we go back to the previous slide, the GELF
2 original protocol was very, very vague. None of these
3 details or very little of these details were presented in
4 there. It said the Pocock's analysis would be done at .02.
5 It did not specify the Cox regression analysis, it did not
6 specify the Fisher's Exact Test. Very, very vague
7 protocol. So all of this is a retrospective interpretation
8 of what the investigator wanted to do.

9 DR. TIO: May I comment on that? You're right
10 that Cox regression was not mentioned in there, but in
11 terms of the straight log rank test without adjusting for
12 covariates, it is in there. You agree?

13 DR. TIWARI: Most of the details that we see
14 here are not presented in the original protocol that was
15 given to us.

16 DR. O'FALLON: I don't want to get the two of
17 you involved in a debate over it. Let me just ask one
18 question here.

19 DR. BROUDY: One more question, and then I'm
20 going to ask the statisticians to take it outside.

21 (Laughter.)

22 DR. O'FALLON: The overall level of
23 significance somehow was not the normal .05 level. With
24 what I'm hearing here, it would have been closer to a .10

1 level. Am I wrong? Your own statement said the Pocock
2 rule applies equal probabilities to each of the interim
3 analyses. Admittedly, they didn't happen, but that's the
4 way the protocol read anyway. So you would have had a
5 protocol with an overall level of significance of .10,
6 which is kind of a surprisingly large level of significance
7 to establish for such an important study.

8 DR. TIO: I'm a little bit puzzled by that
9 comment, because it is preplanned for an overall level of
10 .05.

11 DR. O'FALLON: How can it be, when the
12 individual levels are .016 and you have five or maybe six
13 of them? So we can take that one outside.

14 Were any of the other studies that you're
15 reporting stopped early as a consequence of --

16 DR. TENDLER: Yes. I can answer that. The
17 German lymphoma study was terminated early, I believe in
18 June 1996, again, on the basis of a boundary being crossed
19 -- I don't know if it was Pocock's or if it was O'Brien-
20 Fleming, but a boundary that was crossed for a significant
21 difference in progression-free survival. And the same, I
22 guess, was true of the ECOG study as well, a boundary
23 crossed for progression-free survival. Similar number of
24 evaluable patients, about 250, in both of those studies.

1 Any other questions?

2 DR. BROUDY: Yes. I'd like to ask a brief
3 question about the quality of life data that you have on
4 page 41 of the material that we received. I don't
5 understand how this TWIST analysis was done and what it
6 means.

7 DR. TENDLER: I'm going to turn to our resident
8 expert, Dr. Cigano, to discuss Q-TWIST.

9 DR. CIGANO: Let me assure you, you're not the
10 only person in the room who feels that way. Just about
11 everybody on this side of the room feels the same way, so
12 you're not alone.

13 Let me just say, we did believe that quality of
14 life was an important issue here in this study, but since
15 it wasn't collected prospectively as a part of the trial,
16 we tried to do what we call a quality-adjusted survival
17 analysis technique. The specific methodology we used is
18 called Q-TWIST, and it was originally developed by Rich
19 Gelber at Harvard and Aaron Goldhirsch for breast cancer
20 trials, and it's subsequently been applied to other kinds
21 of cancer studies and studies in HIV also.

22 A quality-adjusted survival analysis differs
23 fundamentally from a typical survival analysis in that it
24 tries to account not only for the quantity of time of

1 survival, but also for the quality of that survival time in
2 some distinct ways. So that instead, for example, on this
3 graph, of just looking linearly at the survival time from
4 study randomization to death, we also are trying to
5 partition that time into three distinct health states, and
6 this is what Q-TWIST is all about.

7 These health states are defined as periods of
8 toxicity. Typically the Q-TWIST definition of toxicity is
9 a Grade 3 or Grade 4, so the duration of Grade 3 or Grade 4
10 toxicity is accounted for for each patient. Also, the time
11 in progression from progression to death is measured and
12 accounted for. And the good survival time or the
13 relatively good survival time, called TWIST, is that area
14 that is between those two time points, when they're not in
15 severe toxicity and prior to progression.

16 So what you're trying to do in a Q-TWIST type
17 of analysis is to measure that this is a two-dimensional
18 problem, where instead of, again, just linearly accounting
19 the amount of survival time, you're looking at also this
20 dimension of the utility or the quality of life value of
21 that time and saying, "I want to measure the total area in
22 these three boxes as sort of a quality-adjusted survival
23 time for that one patient."

24 ~~The way you look at this when you try to~~

1 accumulate the total covert experience of all the patients
2 in the two arms is, when you accumulate all the experience
3 of the patients in the two randomized arms, you can see
4 here we have the same Kaplan-Meier plots for survival and
5 progression that Dr. Tendler presented before, but they're
6 presented in a different way, and this fundamentally
7 different way says, okay, if you look at those people in
8 the INTRON A arm and you look at the time between the time
9 they progress to the time this cohort dies, this yellow
10 area is called the time in progression, and that mean time
11 in progression is essentially the covert's experience time
12 in that health state. You can compare, then, that mean
13 time in progression to the mean time in progression for the
14 other treatment arm.

15 In the same way, you can accumulate the time in
16 toxicity -- severe toxicity, as we defined it originally,
17 Grade 3 or Grade 4 -- the percent of patients that were
18 experiencing that kind of toxicity at each time point
19 during the treatment period, and you can accumulate, again,
20 these periods of time for both treatment arms, so you can
21 compare these two amounts of quality-adjusted survival time
22 in those two health states.

23 What you really want to look at, though, is the
24 white period, which is the relatively good survival time or

1 the best that can be expected from the two treatment arms,
2 and what you see here -- and it's not totally apparent. I
3 didn't put the data table, actually, in your briefing book,
4 but if you look at the two treatment groups, the amount of
5 time in toxicity, the mean survival time in toxicity for
6 this group is about 2 months longer than it is for the CHVP
7 arm. The time in progression is about 4 months shorter,
8 actually, and the good survival time is about 10 months
9 greater in the CHVP plus interferon. And it's really this
10 good quality time that drives the quality-adjusted survival
11 analysis, the attempt to sum this up in some way that makes
12 sense for a quality-adjusted survival analysis, albeit
13 retrospective.

14 But what you see here is, regardless of how one
15 might value time in toxicity, at least the way we define it
16 currently, one can argue that it would seem relatively
17 inconceivable that this group would have a poorer overall
18 quality-adjusted survival time than this group just because
19 of the sheer volume or benefit in terms of the good
20 survival time that's shown here.

21 This is, again, really more an exercise in
22 plausibility, and I really don't want to confuse people,
23 but what this is really saying is, if you look at this in
24 terms of a two dimensional problem, where we know from the

1 Kaplan-Meier plots what the quality-adjusted survival time
2 is just in terms of the partitioned amount of time, what we
3 don't know is the value of that time that a patient might
4 give to being in toxicity as opposed to being in
5 progression compared to TWIST, which would say we give a
6 value of 1.

7 You can do a kind of sensitivity analysis,
8 where you vary all the values of 0 to 1 for being in
9 progression or being in toxicity, and look for the areas or
10 those sorts of cases where being in the CHVP arm might have
11 been better than being in the CHVP-plus-interferon arm. If
12 you run all these different cases, you see there is really
13 no place where you would prefer to be in the alternative
14 group. And only in this little corner would you be in an
15 area where it would be better to be in the CHVP-plus-
16 interferon arm, but this would not be significant.

17 Now, since one can argue -- and we've certainly
18 debated this internally -- that perhaps the Grade 3/Grade 4
19 toxicity may be too high a standard, that there are other
20 types of toxicities associated with interferon that are not
21 reflected in Grade 3 or Grade 4, we took this analysis and
22 ran it all the way down to any grade of toxicity. So we
23 looked at all the time in toxicity for any grade of
24 toxicity and accounted for all that value of time, ran the

1 same kind of analysis, and you see essentially the same
2 results.

3 So, in summary, our summary basically was that
4 regardless of how you value or take down the definitions of
5 toxicity, the incremental toxicity or the time in that
6 toxicity for the interferon group was certainly more than
7 balanced by the good survival time that was a benefit by
8 that cohort.

9 DR. BROUDY: Thank you. That clarifies it
10 substantially.

11 Are there other questions for the company?

12 MS. HEINEMANN: I just wanted to ask one more
13 question. So what you mean by the last sentence on page 40
14 is that some patients might favor CHVP alone?

15 DR. TIO: Yes, some patients may.

16 DR. BROUDY: Okay. If there are no more
17 questions, I think we'll take maybe a 5-minute break and
18 then move forward very efficiently.

19 (Recess.)

20 DR. BROUDY: All right, I think we're ready to
21 hear the FDA perspective.

22 Dr. Cardinali?

23 DR. CARDINALI: Good afternoon. My name is

24 Massimo Cardinali. I'm a reviewer with the Oncology Branch

1 at CBER and I'm going to present the analysis of the
2 agency. As is customary, I will briefly summarize the data
3 that's already been extensively presented by the company
4 and focus on the points of interest for the FDA.

5 This is the panel of reviewers that
6 participated in this review.

7 This slide summarizes the approved indications
8 for the product. As you can see, the INTRON has been
9 approved approximately 10 years ago for a variety of viral
10 and neoplastic diseases. These different diseases were
11 treated with different concentrations of the drug, with
12 different routes of administration. I will come back to
13 this later on.

14 So this is the proposed new indication that the
15 company is seeking, the treatment of follicular lymphoma
16 with a combination chemotherapy containing doxorubicin in
17 patients with high tumor burden, intermediate grade, and
18 clinically aggressive disease.

19 The pivotal study conducted by the Group
20 d'Etude des Lymphomes Folliculaires was, as you heard,
21 conducted in France and Belgium, and this is the accrual
22 time.

23 I have summarized in this scheme the two parts
24 of the study, in orange here the part that's submitted with

1 the application. Also, low tumor burden patients were
2 evaluated and randomized to single-agent prednimustine or
3 INTRON or observation alone. The accrual with this part of
4 the study was slower than with the high tumor burden, and
5 the data was published earlier this year in the Journal of
6 Clinical Oncology. There was a very small difference in
7 those groups.

8 The eligibility for the high tumor burden, as
9 you heard before, follicular small-cleaved and mixed
10 lymphoma which had not been treated previously with
11 chemotherapy or corticosteroid at Stage 3 and 4 in
12 clinically aggressive disease.

13 So the patients were randomized to the
14 combination chemotherapy and combination chemotherapy plus
15 Interferon at 5 million units three times a week for the
16 duration of the study. The patients were randomized to
17 receive six cycles in what they call the induction phase,
18 which was delivered for 28 days. The patients who
19 responded or had stable disease were further treated in a
20 so-called maintenance -- further six cycles, where the
21 cycle duration was 56 days.

22 So the primary endpoint here is disease-free
23 survival, also overall survival, and response rate and
24 toxicity profiles were analyzed.

1 A few comments on the GELF study. This was an
2 open-label study, like all the other studies using
3 interferon. However, it's our feeling that the possible
4 bias of the open-label approach still plays a role in the
5 evaluation of this one. The tumor response assessment was
6 different in the GELF study to what is commonly employed in
7 the United States and in Europe. The protocol allowed for
8 a 1 diameter measurement of lesion, where in the United
9 States, commonly, two dimensions are measures for each
10 lesion. Also, there was no requirement for a consistent
11 radiologic assessment of the patient response in the
12 protocol. However, analysis of the data show that there
13 was a pretty consistent use of the same method for
14 evaluation and staging of the patients.

15 We were concerned with the possibility of loss
16 of information in the translation process, as usually
17 happens when studies are conducted in non-English-speaking
18 countries, but we have to say that the translation that was
19 provided by the company was fair.

20 The last point here, probably the most
21 important, is the chemotherapy regimen used in the GELF
22 study differed consistently from what is commonly employed
23 in the United States, namely the CHOP. In the next slide I
24 have made a summary of the chemotherapy, and I want to

1 point out that the dosage of doxorubicin is 50 percent of
2 those that are commonly used in the CHOP, and
3 cyclophosphamide is 600, slightly lower than CHOP.
4 Vincristine was replaced altogether with Teniposide, and
5 prednisone was less than half the amount that's normally
6 used in CHOP.

7 Also of importance to note is the cycle length.
8 The CHVP was delivered over a 28-day period, versus the
9 normal 21 days that CHOP is delivered.

10 I also put on this slide the composition of
11 COPA since the ECOG study that we're going to look at in a
12 moment employed this combination chemotherapy. Again,
13 here, the COPA was delivered in that study over a 28-day
14 period after a pivotal trial that determined that the
15 normal 21 days that is commonly used was too toxic with the
16 combination with interferon.

17 The field inspection of the study site showed
18 good compliance with the protocol. There was only one
19 instance of a minor violation in a single center. All the
20 patients were included in this survival analysis except one
21 -- again, a good point for the study.

22 I'm going now to again briefly summarize the
23 results of the GELF study, the patient subset disposition.

24 ~~We have five patients in the CHVP and three in the~~

1 interferon who did not receive drug. Therefore, we use
2 this modified intent-to-treat population of 135 patients.

3 The efficacy endpoint, again just repeating
4 what has already been described, is 48 percent, the three-
5 year progression-free survival, versus 29 percent in the
6 chemotherapy alone, and the number of patients alive and
7 progression-free as of May 15, 1996 was 26 percent in the
8 interferon arm versus 14 percent.

9 The median progression-free survival is 2.9
10 years and 1.5 years. The median overall survival is not
11 reached for the interferon arm, versus 5.5 years. As I
12 describe in the next two slides, which show the Kaplan-
13 Meier curves, the progression-free survival is 2.9 and 1.5
14 years, and for the overall survival again.

15 One point to note is that most patients were
16 followed for three years, and also at five years. So,
17 again, a good follow-up.

18 The clinical response rate was 90 percent in
19 the interferon versus 74 percent, and 56 percent for the
20 overall response, and for the complete response 32 percent.

21 Now I'm going to compare the GELF study with
22 the other study present in the literature that's been
23 conducted over the last 10 years. I have subdivided this
24 study in a slightly different way from what the company

1 did. In this first slide I have the study that had
2 interferon given concurrently with the chemotherapy. We
3 have two studies with the combination chemotherapy, the
4 ECOG study with COPA and the GELF study with CHVP. These
5 are the two studies conducted at St. Bartholomew in the
6 U.K. and the CALGB cyclophosphamide.

7 The alfa-interferon used in this study was
8 INTRON for the last three studies, and Roferon for the
9 ECOG. I have put the overall survival and progression-free
10 survival data here, highlighting in yellow the data that
11 showed significant difference. Again, the GELF shows
12 overall survival, where the CALGB, St. Bartholomew, and
13 ECOG groups do not show a significance for that parameter,
14 where the progression-free survival is supported by the
15 ECOG study and the St. Bartholomew study but not by the
16 CALGB study.

17 In the next slide, perhaps less important for
18 comparison with the GELF study is the delivery of
19 interferon as maintenance, not concurrently with the
20 chemotherapy regimen. Again, for the Mexican study group
21 used for induction, a variety of different combination
22 chemotherapy was INTRON, and for the EORTC was Roferon, and
23 the German low-grade lymphoma group didn't specify which
24 kind of alfa interferon in an abstract publication that we

1 reviewed.

2 Again, the overall survival is not supported by
3 the German low-grade lymphoma group or the EORTC, but the
4 Mexican study group shows an advantage in the survival.
5 The progression-free survival is supported by all three
6 studies described here. Perhaps of note is that the
7 Mexican study group is a smaller study, with about 45
8 patients per group, as opposed to the GELF, a much larger
9 group.

10 Now I'm going to describe the toxicity and
11 adverse events results. I've put in the first two slides
12 of this section the profile of the interferon adverse
13 events that is described in the label, and this is derived
14 from the hairy cell leukemia and the chronic hepatitis
15 study which used the same route of administration and
16 approximately the same amount of interferon that is being
17 considered for the GELF study. I listed here the most
18 prevalent, roughly, in decreasing order, and in the next
19 slide the less frequent adverse events profile.

20 In the next slide, in this table I have listed
21 the symptoms that were expected to be present in the study
22 based on the experience with the previous experience, and
23 they're pretty much all at the significant level, except
24 perhaps for flu. But again, flu is more widely described

1 by headache, fever, and asthenia, so I don't know what that
2 exactly means. But there was a significantly higher
3 incidence of this adverse event in the interferon arm.

4 By associated adverse events, I've described
5 the not expected adverse events that show a P value less
6 than .05, with one exception at .01 for the skin adverse
7 events. The skin adverse events mostly were due to this
8 difference we can see here, the local injection of the
9 drug, which, of course, was not done in the control group.
10 But in one case there was an exacerbation of psoriasis,
11 perhaps suggesting that interferon may flare up autoimmune
12 disease.

13 Elevation of liver enzyme was present, a
14 consistently higher level in the interferon arm, and in two
15 cases actually determined the interruption of treatment
16 with interferon, and those patients were subsequently
17 diagnosed with hepatitis B.

18 Anorexia was one of the expected adverse
19 events. However, in some cases it determined
20 discontinuation of the therapy.

21 Dyspnea was not expected, perhaps suggesting
22 some pulmonary effect of the drug.

23 I've summarized in this slide the neurologic
24 and psychiatric adverse events. There is no statistical

1 difference between the two groups, except perhaps for
2 paresthesia, where we had .06 level. But I want to make a
3 point that there was one episode of severe psychosis on the
4 interferon arm and two suicides in the interferon arm.
5 This was expected as an adverse event. The label already
6 reported the possibility of suicidal ideation, and the
7 label was approximately two years ago after the study on
8 hepatitis.

9 The hematologic toxicity, an expected one:
10 neutropenia 36 percent versus 8 percent. When all grades
11 are considered, 13 percent versus 2 percent for
12 thrombocytopenia, and it's likely less incidence of anemia,
13 at 8 percent in the interferon arm. For the 3 and 4 grade
14 in the next slide, again neutropenia is higher than in the
15 interferon arm in the chemotherapy alone, with infection
16 associated in some cases with this.

17 So the conclusion of our review is that we can
18 conclude that the results of the GELF study and other
19 randomized clinical trials show a progression-free survival
20 advantage when interferon was used in conjunction with
21 chemotherapy. However, the improved overall survival in
22 the GELF study is not supported by other publications.

23 The toxicity that interferon adds to this is
24 considerable, and one should closely monitor

1 myelosuppression, hepatic function, and perhaps neurologic
2 and psychiatric effects.

3 The combination regimen in the GELF study is
4 substantially different from the one used in the United
5 States, namely CHOP. The other point to note is that the
6 optimal duration of the interferon administration is
7 difficult to evaluate. In the comparison of different
8 studies, the range of interferon administration varies
9 between four months and 24 months. So we conclude that the
10 most appropriate and safe manner of addition of interferon
11 to chemotherapy has not been clearly addressed.

12 Thank you very much.

13 DR. BROUDY: Thank you.

14 Are there questions for Dr. Cardinali?

15 Ms. Meyers?

16 MS. MEYERS: Can I just confirm that there are
17 no children infected by this disease, so there was no
18 reason to do pediatric studies?

19 DR. CARDINALI: No, as far as I know.

20 DR. BROUDY: This is a very rare disorder in
21 children. They mostly have more aggressive high-grade
22 lymphomas, not low-grade lymphomas such as the ones being
23 addressed here. It would be very, very rare.

24 DR. CARDINALI: Yes. As you see, the

1 representative of the company already elaborated on that
2 aspect.

3 DR. MILLER: Just a comment, or a question I
4 guess it would be. Did either of your analyses look at the
5 late effects of the two arms, including secondary
6 myelodysplasias or AML in the one group versus the other?

7 DR. CARDINALI: Perhaps Dr. Keegan will address
8 that.

9 DR. WEISS: I'm actually wondering if Schering
10 could respond to that. We do not have any data provided to
11 us.

12 DR. SOLAL-CELIGNY: I can answer to the
13 question. We did not observe any case of myelodysplasia,
14 and the incidence of solid tumors was the same in both
15 groups, at least concerning the patient dying from solid
16 tumors.

17 DR. BROUDY: Dr. Berman?

18 DR. BERMAN: I just had a general comment, and
19 that is that I think we have to put these studies, the GELF
20 study in context with the other studies. Five of them have
21 not even been fully reported yet. They're in abstract
22 form. Some of the abstracts are as old as six years. So
23 you have to wonder whether there's something about these
24 ~~studies that hasn't been published, number one. Number~~

1 two, they certainly haven't been peer reviewed. As many of
2 us know, what goes into the abstract is sometimes different
3 than what goes into the final paper. So I would add that
4 as a note of caution when looking at the GELF study in the
5 context of these other studies. I would not hold these
6 other studies up as being hard data quite yet.

7 DR. BROUDY: Dr. O'Fallon, a comment?

8 DR. O'FALLON: That raises another question,
9 that the original New England Journal publication from the
10 GELF study is quite a few years ago and the data have
11 matured further. Have there been any more publications?
12 These are updated results, I know that. I was just
13 wondering if you've published any --

14 DR. SOLAL-CELIGNY: The final analysis of this
15 study has been submitted for publication to the Journal of
16 Clinical Oncology.

17 DR. BROUDY: All right. If that concludes the
18 questions, let's move on, then, to the questions for
19 discussion. Let's move on to Question 1a.

20 "Please discuss the relative importance of the
21 differences between the CHVP regimen and those more
22 commonly used in the U.S., particularly with respect to the
23 duration of treatment, relative dose intensity as
24 manifested by the incidence and severity of Grade 3 or 4

1 myelosuppression, and the dose of doxorubicin utilized per
2 cycle."

3 Who would like to comment? Dr. Miller?

4 DR. MILLER: I think there's a big difference
5 between this trial and what's commonly being done in the
6 States at this time. The duration of therapy for low-grade
7 lymphomas are generally much less than 18 months at this
8 time. However, I think the CHVP, where it's very different
9 than CHOP, the dose intensity I don't think is that
10 significantly different. The doxorubicin dose is
11 significantly lower, but it's made up for by the fact that
12 VM26 is also in the same type of inhibitor. So compared to
13 what they left out, which was vincristine, which is not
14 myelotoxic -- VM26 plus a dose of doxorubicin is very
15 approximate to what I'd consider a CHOP.

16 The cytoxin dose is lower, not a gram in low-
17 grade lymphoma. So it's a little bit lower, but I don't
18 think that the dose intensity is that much different than
19 what you'd expect. But the duration of therapy is
20 definitely much longer. That's why I'm surprised that they
21 haven't seen any late myelodysplasias in this 18 months of
22 therapy.

23 DR. BROUDY: Dr. Gabrilove?

24 DR. GABRILOVE: I would agree with those

1 comments. I think it is something that will have to be
2 followed up on, but I would also make the argument that
3 just because we use CHOP here in the United States and CHVP
4 is used abroad more often doesn't mean that one is
5 necessarily better than the other. I think it's up to
6 further studies to really compare these two in terms of
7 overall responses and survival and ultimately secondary
8 complications. That's something for the future. I don't
9 think that's something we can really fairly assess today or
10 is fair to the results of the studies presented to us.

11 I think that's ultimately a physician decision
12 which will be based upon future clinical studies comparing
13 different regimens that are effective. The question is is
14 this an effective regimen, and I think we've been shown
15 that it is effective.

16 DR. BROUDY: I guess I would say that I think
17 the CHVP is less myelosuppressive than CHOP. The incidence
18 of neutropenia is just a few percent. The incidence is
19 significantly higher with CHOP. Also, if you look at
20 weekly dose intensity, CHVP is on a 28-day cycle and the
21 CHOP is on a 21-day cycle. So I think that this is less
22 myelosuppressive, but I would certainly agree with the data
23 presented by the company, that the interferon can be used
24 safely with the CHVP regimen. I don't have any concerns

1 about that issue.

2 Other comments about comparability to CHOP?

3 Let's move on to Question 1b.

4 "Do such differences raise concerns regarding
5 the relative safety and effectiveness of the CHVP regimen
6 versus anthracycline-containing regimens more commonly used
7 in the U.S.?"

8 I think Dr. Gabrilove has already touched on
9 this.

10 DR. GABRILOVE: I would just add to that, that
11 I would agree with the sponsor comments which they have in
12 their last slide that there should be caution. I'm not
13 sure how you handle anthracycline-containing chemotherapy
14 regimens because I wouldn't want this seen as immediately,
15 nor do I think the sponsor would, to immediately be
16 transferred to everyone getting CHOP also to be receiving
17 interferon. I think that's going to require further
18 comparative studies.

19 So I think in terms of the anthracycline-
20 containing chemotherapy regimen, that has to be carefully
21 worded.

22 DR. BROUDY: Dr. Berman?

23 DR. BERMAN: A question for the sponsor. In
24 ~~your last slide you said that your recommendation would be~~

1 not with full-dose CHOP. Do you have specific
2 recommendations in terms of 75 percent dose reduction of
3 doxorubicin?

4 Dr. TENDLER: Again, if we can extrapolate from
5 the ECOG study, in which COPA is given, COPA is essentially
6 full-dose CHOP, which is given over four weeks. In that
7 study one needed -- the average dose received for
8 doxorubicin cyclophosphamide was approximately 25 percent
9 less, and that was handled with appropriate dose
10 modification. So I think if we actually recommend, based
11 upon hematologic toxicity, appropriate dose modification,
12 and one would use interferon in conjunction with a modified
13 CHOP regimen or with COPA, one could anticipate actually
14 giving about 75 percent doses of full-dose doxorubicin
15 cyclophosphamide given in CHOP.

16 DR. BERMAN: Would the doxorubicin be the only
17 one modified?

18 DR. TENDLER: Yes, I would agree with that.

19 DR. BROUDY: Actually, in the COPA regimen,
20 they decrease both the cytoxin -- the cytoxin and the adria
21 dose were 25 percent less. The doses that the plus
22 interferon group was able to receive was 25 percent less in
23 both cytoxin and adria. I would just remind the audience
24 again that this is a Q 28 day regimen, whereas CHOP is

1 usually a Q 21. We usually calculate dose intensity based
2 upon per week. So I do think substantial dose reductions
3 will be needed in both cytoxin and adriamycin in the
4 presence of interferon.

5 DR. TENDLER: I agree.

6 DR. BROUDY: Dr. Gabrilove, you had another
7 comment?

8 DR. GABRILOVE: I was just going to say, just
9 commenting on that aspect again, when using full-dose CHOP,
10 there are, of course, other supportive measures that are
11 presently being used, and that complicates the application
12 of interferon in that setting. So again, I think leaning
13 on the very conservative side in terms of the anthracycline
14 dose and the regimen in which the anthracycline is used is
15 probably prudent at this point.

16 DR. BROUDY: Dr. Berman?

17 DR. BERMAN: Any studies with interferon and
18 GCSF?

19 DR. TENDLER: At the time of the GELF study,
20 GCSF was not available in France. So none of these
21 patients received GCSF either prophylactically or during
22 the course of the study. One would anticipate that with
23 GCSF use, that the frequency incidence of neutropenia would
24 be somewhat less than what was seen in this particular

1 study. But we don't have data in combination with GCSF and
2 interferon in this regimen.

3 DR. BERMAN: Maybe Dr. Ozer can answer this.
4 I'm not aware of any studies that have actually looked at
5 interferon and GCSF together in any clinical setting.

6 DR. OZER: There certainly are none that are
7 randomized. We now routinely use it as secondary
8 prophylaxis in patients that may be also receiving
9 interferon, but it's thrown into the pot. There haven't
10 been randomized trials.

11 DR. BROUDY: But is it fair to say that there
12 is every reason to expect that the GCSF would be effective
13 in the interferon-treated group?

14 DR. OZER: Yes, I would agree with that
15 statement. I think that most clinicians would probably
16 approach this, as Janice implies, on a very conservative
17 level. But one could quickly add GCSF and might even be
18 able to maintain full doses of CHOP on a 21-day schedule
19 with GCSF support.

20 DR. GABRILOVE: I would argue, though, that
21 that should be done in a formal study, because I think it
22 has real clinical implications that would make everyone
23 feel more comfortable with what we're actually doing.

24 DR. BROUDY: Other comments?

1 All right, let's move on to Question 1c.

2 "To what extent are data derived from the
3 INTRON A in combination with CHVP likely to be applicable
4 to the use of INTRON A in combination with CHOP and CHOP-
5 like regimens?"

6 Any additional comments that anyone would like
7 to make here that we haven't already touched on? I think
8 we've pretty much covered that issue.

9 Let's move on to Question 2, and this will be a
10 voting question.

11 "Do the data from the GELF study, along with
12 reports in peer-reviewed journals of additional studies,
13 establish the efficacy of INTRON A as an adjunct to
14 chemotherapy for the initial treatment of patients with
15 low-grade follicular non-Hodgkin's lymphoma with features
16 of high tumor burden?"

17 Who would like to tackle this question? Dr.
18 Miller, do you have an opinion on this?

19 DR. MILLER: I just want to make a comment
20 about the paragraph that goes above the question, that the
21 way that this advisory committee discussed this in October
22 of 1996, the time to failure was an appropriate endpoint in
23 therapies for non-Hodgkin's lymphoma. That actually should
24 be qualified to say indolent non-Hodgkin's survival, since

1 we do think that our treatment impacts survival in
2 aggressive non-Hodgkin's lymphoma where we can cure
3 patients.

4 In the treatment of low-grade lymphomas, we are
5 in fact palliating, not expecting to cure patients with
6 chemotherapy. So what we are doing is relieving symptoms,
7 and it's controversial where progression-free survival is
8 in fact a benefit. Again, that's why good quality of life,
9 actually prospective quality of life analysis in the use of
10 an agent such as interferon which has significant toxicity,
11 especially when given for 18 months, can really be
12 outweighed by a potential benefit. Given that this data
13 was collected retrospectively, I suspect that the quality
14 of life data is not very clean, because you can't collect
15 quality of life information retrospectively, I don't think.
16 Most people say you can't collect good quality of life
17 information retrospectively.

18 So with those caveats, I do think that we have
19 in the past in this committee said that we would use
20 progression-free survival or time to failure as a surrogate
21 endpoint, or an endpoint. I do think that based on that,
22 the GELF study does support the use of decreased or
23 improved failure to -- actually, in that one study, an
24 improved overall survival. So I do think that this study

1 has met the burden that we've established in low-grade
2 lymphomas as proof of efficacy.

3 DR. BROUDY: Thank you.

4 Would either Dr. Gabrilove or Dr. Berman like
5 to comment on this?

6 DR. BERMAN: Yes, I would agree with what Dr.
7 Miller said. I think the data are fairly straightforward.

8 DR. BROUDY: And I completely agree. This
9 study, together with the one by Dr. Smalley in the New
10 England Journal, the COPA study, convinced me that the
11 addition of interferon does prolong progression-free
12 survival. So I agree with the comments you've all made.

13 Dr. Gabrilove?

14 DR. GABRILOVE: I would echo that. I would
15 just again make a comment that I think in future studies,
16 which I'm sure there will be, looking at comparative
17 regimens with and without interferon, that prospective
18 quality of life measures, especially TWIST analyses, would
19 be quite helpful in delineating benefit.

20 DR. BROUDY: I agree, though it is informative
21 that I think only 10 percent of the patients, a relatively
22 small percent of the patients, discontinued interferon
23 therapy, suggesting it was reasonably well-tolerated, at
24 least in the context of already getting CHVP chemotherapy.

1 Any other comments before we proceed to a vote
2 on this question?

3 All right. "Do the data from the GELF study,
4 along with the reports in peer-reviewed journals, establish
5 the efficacy of INTRON A as an adjunct to chemotherapy for
6 the initial treatment of patients with low-grade follicular
7 non-Hodgkin's lymphoma with features of high tumor burden?"

8 All who agree with this, please raise your
9 hand.

10 (Show of hands.)

11 DR. BROUDY: All who disagree, please raise
12 your hands.

13 (No response.)

14 DR. BROUDY: So that's eight in favor and none
15 opposing this statement.

16 So let's move on to Question 2b.

17 "Are the data sufficient to support a claim
18 that INTRON A, when combined with chemotherapy, improves
19 survival in this disease?"

20 Who would like to comment on this issue?

21 Dr. Miller? I saw a brief movement there.

22 DR. MILLER: This one study does suggest
23 improvement in survival. I think that when you're looking
24 at a disease such as indolent lymphoma, that even this

1 follow-up is too short to say that you're improving
2 survival. I doubt that it's going to improve survival.
3 All the studies have suggested that it doesn't improve
4 survival. So I would say there's not enough information to
5 say that INTRON A improves survival in this disease.

6 DR. BROUDY: Other comments on this issue?

7 I would have to agree. I would have to say
8 that the Smalley article did not convince me. This was the
9 other article in the New England Journal of Medicine, the
10 COPA article, which did not convince me that, at least in
11 the way that interferon was added, the way it was studied
12 in the Smalley article, that the interferon really did
13 prolong survival. Although I'm quite convinced that it
14 prolongs progression-free survival, I'm not convinced that
15 it prolongs overall survival.

16 DR. BERMAN: I actually have a question for the
17 sponsor. If you look on the overall survival graphs again,
18 it looks like there is a fairly impressive difference in
19 overall survival until about eight years, and then it looks
20 like there's one or two patients who drop off the curve.
21 Are those lymphoma-related deaths or deaths from other
22 causes? Because I think if you don't have those late
23 deaths, your curves may actually show higher significance.

24 DR. TENDLER: I think at that portion at the

1 curve, there's a lot of censoring and it's difficult to
2 really interpret the implication of that portion of the
3 curve at this point. But certainly with further follow-up
4 we'll be able to more accurately determine if there is a
5 true curative benefit for a small subset of patients.

6 DR. BERMAN: Do you know if those were
7 lymphoma-related deaths?

8 DR. TENDLER: I don't have that information.
9 For those patients at the very end of the tail of the curve
10 who begin to fall off, Phillipe, are those lymphoma-
11 related? Yes.

12 DR. BROUDY: Other comments about this
13 question?

14 Let's move on to Question 3. "Given that
15 patients in the GELF study received INTRON A for 18 months,
16 that the use of interferon for maintenance in published
17 reports has been for a minimum of one year, and that the
18 use of interferon in the ECOG and St. Bartholomew's trials
19 were for a minimum of eight months and 18 weeks
20 respectively, what recommendations should be made in
21 labeling regarding the duration of treatment with INTRON A
22 in conjunction with chemotherapy?"

23 Yes, Dr. Berman.

24 ~~DR. BERMAN: This reminds me of the initial~~

1 questions that were raised when interferon was licensed for
2 use in hairy cell leukemia and that the studies were all
3 over the map, from six months to two years. I think the
4 correct answer to that is that it is not known what the
5 correct length of time is, and anywhere from eight months
6 to 18 months has been shown to be safe, and in some early
7 reports effective. Certainly this is the one that has the
8 most mature data and it does show a probable significance,
9 use of the interferon for 18 months.

10 DR. GABRILOVE: I would just say that although
11 the ECOG trial might have some comparability, I think the
12 other trial is really irrelevant in terms of the
13 chemotherapy regimen used. I'm not sure the St.
14 Bartholomew's study is even relevant to this discussion.
15 So I think we have to go with the data that we have in hand
16 and the safety profile that we see here, and allow that to
17 be utilized.

18 DR. BROUDY: One option would be to recommend
19 its use up to 18 months and just have the details of the
20 two studies that were published in the New England Journal
21 available. The two studies have, of course, very different
22 schedules in the use of interferon, and then the physician
23 can make a choice as to how precisely to use it in his or
24 her individual patient.

1 DR. MILLER: We didn't answer 2b, did we?

2 DR. BROUDY: I think we did discuss the issue
3 of whether it improves survival in this disease. Do you
4 have another comment to make about that?

5 DR. MILLER: That was 2a. 2b I thought was for
6 products intended as an add-on to chemotherapy.

7 DR. BROUDY: There's a new question list.

8 DR. MILLER: Oh, I'm sorry. I apologize.

9 DR. BROUDY: Okay. Any other comments on the
10 duration of therapy with interferon that should be
11 recommended? No?

12 Now we're going to move on to Question 3b.
13 "Should the sponsor be encouraged to conduct a
14 postmarketing study comparing CHOP alone to CHOP plus
15 INTRON A? If so, should CHOP be given at standard doses or
16 reduced doses?"

17 Dr. Gabrilove, do you want to comment on this?

18 DR. GABRILOVE: I'm not sure that we should
19 dictate that they should do CHOP alone versus CHOP plus
20 INTRON A. I think what this does suggest is that there are
21 different regimens that have activity in patients with
22 aggressive forms of follicular lymphoma and that those
23 different regimens ought to be compared side by side with
24 ~~up to date, present supportive care modalities that are~~

1 used routinely. I think that's probably something that the
2 sponsor should be encouraged to pursue, and I would think
3 that they would be interested in pursuing it, especially
4 since at the present time the regimen that we're approving
5 today is not as commonly used in the United States.

6 So I think that type of study would be in
7 everyone's interest. But to dictate a CHOP versus CHOP
8 plus interferon, I'm not sure that's really the right
9 question.

10 DR. BROUDY: Dr. Berman, do you want to
11 comment?

12 DR. BERMAN: Well, I think that most would use
13 a CHOP-like regimen. So given that CHOP is considered
14 standard therapy for this degree of advanced disease, I
15 think that for the labeling in this country it's fine to
16 say that CHOP should be given but at reduced doses. I
17 think that was obvious from the data. It's pretty
18 straightforward, just CHOP at reduced doses.

19 DR. BROUDY: Yes, I think we should encourage
20 the company to go ahead, but I agree that we should not
21 dictate which specific regimen to use. I would encourage
22 them to do studies that would include GCSF because I'm
23 convinced that -- I use interferon a fair amount with GCSF
24 and it very effectively ameliorates the interferon induced

1 bone marrow suppression. I think one could increase the
2 dose intensity of the chemotherapy regimen plus interferon
3 by adding GCSF. I would just add one more time, though,
4 that the COPA regimen plus interferon, which was published
5 in the New England Journal of Medicine, that the COPA doses
6 had to be reduced by 25 percent, and it's already quite
7 dose-reduced from CHOP.

8 DR. KEEGAN: A study looking at standard doses
9 of CHOP might be a comparison of the additive value of
10 INTRON whether or not it was something more than just more
11 myelosuppressive and hopefully a more effective regimen in
12 comparison to standard doses. What actually is the value
13 being added by the INTRON as compared to a standard
14 regimen?

15 DR. GABRILOVE: I think it's substantially more
16 complicated than that, though, because there is in vitro
17 data to show that anthracyclines plus interferon enhance
18 apoptosis, and it may be the way in which the anthracycline
19 is given. So I think if you take two regimens -- let's
20 say, for argument's sake, CHOP versus CHVP plus interferon
21 -- and look at them side by side and see what progression-
22 free survival is, that would be one way. Another would be
23 to take advantage that this is a study, along with other
24 supportive studies, that there is potential synergism

1 between anthracyclines and interferon, which is a clinical
2 observation born out of laboratory observations, and try to
3 follow up on that.

4 But, a priori, you might want to do CHOP versus
5 CHOP plus interferon. That may be something that would be
6 interesting to study, but I don't think it should be
7 dictated. It's not the only question that could be looked
8 at. There are a number of questions that could be looked
9 at that might impact this population. I would be worried
10 about dictating that one because that actually could be the
11 study that doesn't show an added benefit because of the
12 myelosuppressive component.

13 DR. KEEGAN: Well, I guess it was a question of
14 would it be important to do additional studies that would
15 look for that synergistic effect over a simply additive --

16 DR. GABRILOVE: That I would say yes, but which
17 regimen should be chosen and how that should be structured
18 I think has to be left to the good sense of clinical
19 investigators working with the sponsor in a disease where
20 there are a number of regimens that look as if they're
21 active and we're all looking to improve the outcome of
22 these patients. Does that make sense? It's very generic
23 what I'm saying, but I wouldn't want to get stuck in a
24 specific avenue. I think that this is the springboard for

1 a number of studies that need to be done. I think it's in
2 everybody's interest to do them. This may be one type of
3 study that would be of interest, but I don't think it's the
4 only one and I don't think it's the one we should dictate
5 to be done.

6 DR. KEEGAN: So, therefore, not the most
7 important study and not necessarily a requirement that
8 should be imposed.

9 DR. GABRILOVE: I think what should be required
10 is that additional studies taking advantage of these
11 observations be performed in this disease entity.

12 DR. JAY SIEGEL: What I've been wondering about
13 I'd like to raise in this context. These results were
14 published three or four years ago. This is an approved
15 drug in this country. As a non-oncologist, I think it
16 would be fair to say that, in general, oncologists haven't
17 been too concerned about whether a particular use of a drug
18 is on the label or not on the label in terms of deciding
19 whether to put it into a combination regimen.

20 So you have a report in the New England Journal
21 saying that a drug improved survival, and you had a number
22 of reports saying it improved progression-free survival,
23 and yet I've heard several people today say that standard
24 regimen in this country is CHOP. It's not CHVP, it's not

1 I-CHOP or whatever you would call it.

2 So is the concern or the perception that adding
3 interferon to CHVP improves it, but it might not improve
4 CHOP? Is the concern that you'd have to reduce CHOP, and
5 maybe dose-reduced CHOP plus interferon isn't as good as
6 just standard CHOP? Is that something that is worrying
7 people? In which case, maybe that is the important
8 question to answer. What is the situation?

9 DR. GABRILOVE: I think these are interesting
10 points, but I think it's a little unfair. I think that the
11 way in which we design -- I mean, these are studies that
12 require large numbers of patients. They're planned many
13 years in advance, obviously, and you can't suddenly read
14 the New England Journal of Medicine and switch cooperative
15 group studies that have large numbers of patients to
16 suddenly look at a different question. I think CHOP has
17 been looked at because it was a regimen that people favored
18 in this country, and then there were other modalities to
19 add on to it -- dose-intensified CHOP and others. But that
20 doesn't mean that there wouldn't be an interest now in
21 asking new questions once those studies have been
22 completed.

23 I think there's always a time lag between
24 observations and new studies being done because of the

1 large number of patients required to do this kind of
2 investigation. So, in fact, if you look at the data now
3 that it's matured, this would be the time when you would
4 start to see whether people were actually interested in
5 this question and not a few years ago.

6 Would others agree with that assessment?

7 DR. BROUDY: A comment, Dr. Ozer?

8 DR. OZER: I would second what Janice says.

9 The results move very slowly in follicular lymphoma because
10 of the low numbers of patients and because of the long
11 survival time. In addition, the realization that
12 progression-free survival is a desirable endpoint is a
13 relatively new phenomenon both in the clinical community
14 and at the level of the FDA. Finally, the recognition that
15 synergy with anthracyclines to enhance apoptosis is a brand
16 new observation. We have historically not dose-intensified
17 therapy for these indolent lymphomas because we have failed
18 to recognize that a subset do very poorly with that
19 shortened median survival.

20 So I think what this does is open up a new
21 avenue of questions, as alluded to, about all of those
22 issues, and whether in fact we can identify a patient
23 population that would benefit from a novel combination.

24 DR. BROUDY: And I think probably the reason

1 the individual physicians haven't jumped on this
2 observation, Dr. Siegel, and started adding interferon to
3 their regimens is because it adds cost and some toxicity.
4 So I think I agree that there should be additional studies
5 to look at the synergism between the anthracycline and the
6 interferon plus or minus GCSF, but I think it will be some
7 time before the usual oncologist in practice adds
8 interferon to an adria-based regimen.

9 Any other comments?

10 Okay, let's move on to Question 4. "Given the
11 increased incidence of adverse events, most notably
12 myelosuppression observed in the interferon-containing
13 regimens, what specific information should the labeling
14 provide regarding the additive or synergistic toxic effects
15 of INTRON A when used in conjunction with chemotherapy?
16 What information or recommendations should be provided
17 regarding modifications of an already-established
18 combination chemotherapy regimen if INTRON A is to be
19 administered concurrently?"

20 Who would like to comment on this? Dr.
21 Gabrilove?

22 DR. GABRILOVE: Well, I think we've been
23 discussing this previously, but again, I guess the
24 ~~qualifications regarding side effects of myelosuppression~~

1 in particular need to be emphasized with regard to the dose
2 intensity, or rather the actual dose of drug delivered if
3 the labeling allows for a broader anthracycline-containing
4 regimen. If it specifies specific regimens that have been
5 studied and the doses are well understood, then one merely
6 needs to present the toxicity information for the physician
7 to evaluate.

8 DR. BROUDY: Other comments?

9 All right. Question 4b. "Should labeling
10 contain specific warnings regarding the potentiation or
11 increased incidence of parasthesias when INTRON A is used
12 in combination with vincristine or Teniposide?"

13 Comments on this?

14 I guess I can comment. I think the difference
15 was very small. I think it was 6 percent in the
16 Teniposide-alone group, and perhaps 13 percent in the
17 regimen plus INTRON A. So I'm not sure that an additional
18 specific warning needs to be added.

19 I'm not sure that there was any specific
20 difference in the incidence of parasthesias in the COPA
21 trial, which has vincristine, which is what we think of as
22 usually causing parasthesias. So I don't think I would add
23 a specific warning about parasthesias.

24 ~~Any other comments? Dr. Miller agrees.~~

1 Okay, let's move on to Question 4c. "The GELF
2 trial revealed a higher incidence of severe pulmonary
3 toxicity among patients receiving chemotherapy and INTRON
4 A. Please discuss the potential mechanisms for this
5 finding and to what extent these events should be
6 emphasized in the labeling."

7 Does anyone here have any insights into what
8 the mechanism of the shortness of breath in the INTRON A-
9 treated group was? Does anybody in the company have any
10 thoughts on what might have caused the pulmonary symptoms?

11 DR. MILLER: There's a question how much
12 semantic it was. The severe events never required anybody
13 to be discontinued from the study because of this. So I
14 guess I question calling it severe pulmonary toxicity when
15 all the patients continued on the drug. That's what it
16 would be interesting for them to comment on.

17 DR. BROUDY: Dr. Tendler?

18 DR. TENDLER: This slide will show the severe
19 pulmonary events in INTRON-treated patients that was
20 alluded to by the agency. A total of 11 patients
21 experienced what would be considered severe pulmonary
22 events. Again, I would just emphasize that the majority of
23 these were dyspnea, but in most cases this was a secondary
24 term. So there could have been some repetition here,

1 dyspnea patients with pleural effusion or dyspnea patients
2 with a pulmonary embolus. But in general, when one looks
3 at all these events among these 11 patients, all were
4 reversible without mechanical ventilation or any other
5 aggressive medical intervention.

6 There was one of these episodes of pulmonary
7 embolism that resulted in a permanent INTRON
8 discontinuation, but there was full recovery for the
9 patient. So that's the spectrum of pulmonary toxicity that
10 we're seeing on the GELF study for INTRON-treated patients.

11 DR. GABRILOVE: This is captured in different
12 ways, so some of the dyspnea may be redundant. Is that
13 what you're saying?

14 DR. TENDLER: Correct, but these are actual
15 patients who experienced these terms, 11 total patients of
16 134.

17 DR. BERMAN: In the patient with the pulmonary
18 embolus, are you directly relating the pulmonary embolus to
19 the INTRON?

20 DR. TENDLER: No. In terms of adverse event
21 reporting, we're not establishing causality here or
22 anything like that. We're just saying it was an event
23 described in a patient receiving interferon.

24 ~~DR. BERMAN: But the interferon was stopped.~~

1 DR. TENDLER: For the pulmonary embolus it was.

2 DR. GABRILOVE: For the pulmonary events, was
3 there a specific time course or were these seen variably
4 throughout the whole treatment program?

5 DR. TENDLER: I would have to honestly say I
6 don't know the answer to that question specifically with
7 regard to the occurrence of these events, where in the
8 course of the treatment they occurred. I can tell you that
9 for the interferon discontinuations, the 13 patients who
10 discontinued, 10 out of the 13 occurred within the first
11 seven months of treatment.

12 DR. MILLER: Are these 11 occurrences or 11
13 patients? It's hard to think that somebody with a
14 pulmonary embolism wouldn't also have dyspnea. Do you know
15 if that's --

16 DR. TENDLER: For this particular slide, the
17 way it's done, it's 11 patients. Eleven out of the 134
18 patients experienced these events that were described.

19 DR. MILLER: In the brochure it says "compared
20 to seven severe events, total number of subjects unclear."

21 DR. TENDLER: That was in the FDA's book.

22 DR. MILLER: But you're saying the number of
23 subjects is clear, it's 11. So people who had pulmonary
24 embolism without dyspnea

1 DR. TENDLER: No. In other words, let me see
2 if I can clarify what was done. We have these terms in our
3 database and when we search, we find patients who have
4 these terms, and in this case for dyspnea, there are five
5 patients that have Grade 3 or 4 dyspnea. There's one
6 patient that had Grade 3 or 4 respiratory insufficiency.

7 PARTICIPANT: But it's events, 11 events.

8 DR. TENDLER: Correct.

9 DR. MILLER: All right, 11 events.

10 DR. BROUDY: I'd remind all the speakers to
11 talk into the microphone, please.

12 DR. TIO: Some patients may have multiple
13 events. So it adds up to 11. That's why it's confusing to
14 most people.

15 DR. GABRILOVE: We're just trying to clarify.
16 So it wasn't 11 patients; it's 11 events.

17 DR. TIO: No, it is 11 patients. It is 11
18 patients. I know you are adding up the numbers and you
19 think the events is adding up to 11. It just so happens
20 that that is indeed the case, but there are some patients
21 with multiple events that can have dyspnea with some other
22 things.

23 DR. SOLAL-CELIGNY: For the patients who had
24 ~~dyspnea with any other cause well established of this~~

1 dyspnea. That is to say, dyspnea without established
2 cause. But patients with pulmonary embolism also had
3 dyspnea, but they were not included in the dyspnea.

4 DR. BROUDY: Thank you for clarifying that.

5 I think my take-home is that many of these
6 problems resolved without discontinuing the drug, and I
7 can't think of any real mechanism why interferon should
8 cause worrisome pulmonary events that we'd need to put a
9 particular warning in for. So even though there was a
10 difference in the pulmonary events in the plus and minus
11 interferon arm, it's not a major concern of mine at least.

12 Any other comments? Dr. Gabrilove.

13 DR. GABRILOVE: This may be very naive on my
14 part, but on the package insert you will have the list of
15 toxicities observed, the major toxicities observed in the
16 study, so the physician will be --

17 DR. JAY SIEGEL: This information is there.
18 The question we're asking is to what extent these events
19 should be emphasized in the labeling. As you know, we
20 could put numbers in there or we could put a boxed warning
21 saying "Caution," or potentially at the far other extreme
22 we could not mention them.

23 DR. BROUDY: But I think you have to mention
24 the important things, and clearly the important thing is

1 the myelosuppression. I think the dyspnea and the
2 parasthesias are much less important and not really
3 convincing to me that they were any different or due to the
4 interferon particularly.

5 DR. JAY SIEGEL: Right. Myelosuppression, of
6 course, is a known and label toxicity for this drug. We're
7 asking about these in particular because, in the case of
8 the drug toxicity, that is being used in combination with
9 known neurotoxic drugs. In the case of the pulmonary
10 toxicity, I believe that is not labeled for this drug. Is
11 that right? So the question is whether simply to put data
12 in there or whether, based on mechanisms or concerns, to
13 include a more prominent warning, or to write it off to the
14 play of chance. We're looking for some guidance.

15 DR. BROUDY: Well, I would favor just putting
16 the data in there and letting the physician make his or her
17 own decision about it. Otherwise, I think we'll be
18 emphasizing things that I think are so much less important
19 than the major toxicity, which is myelosuppression.

20 Other comments?

21 DR. GABRILOVE: I would agree with that.

22 DR. BROUDY: Okay. Let's move on to the last
23 question, Question 5. I think this will be a voting
24 question.

1 "The findings of this trial and in the
2 literature report the positive results in patients with
3 high tumor burden and no evidence of an advantage in
4 patients with more indolent disease features. Given the
5 additive and/or synergistic toxicity of INTRON A, should
6 labeling specifically state the concurrent use of
7 chemotherapy and INTRON A is not indicated in patients with
8 low-grade follicular lymphoma with a low tumor burden?"

9 Dr. Berman?

10 DR. BERMAN: Yes.

11 (Laughter.)

12 DR. BROUDY: Would you care to elaborate on
13 that?

14 (Laughter.)

15 DR. BERMAN: The labeling should state that
16 there are no conclusive data showing that interferon adds
17 anything to chemotherapy for low-grade low tumor burden.

18 DR. BROUDY: And I would completely agree with
19 that.

20 Dr. Miller, do you want to make a comment?

21 DR. MILLER: I agree.

22 DR. BROUDY: Dr. Gabrilove?

23 DR. GABRILOVE: I agree.

24 DR. BROUDY: Okay. Let's take a vote on

1 Question 5. All those who think that the label should
2 state that concurrent use of chemotherapy and INTRON A is
3 not indicated in patients with low-grade follicular
4 lymphoma and low tumor burden, please raise your hand.

5 (Show of hands.)

6 DR. BROUDY: And any opposed?

7 (No response.)

8 DR. BROUDY: That's seven in favor and no
9 opposed.

10 I believe that concludes the questions from the
11 FDA, so I'd like to thank the company for their
12 presentation, and I'd like to close this session.

13 Thank you.

14 (Whereupon, at 4:15 p.m., the meeting was
15 adjourned.)

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