UNITED STATES OF AMERICA

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

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ANTIVIRAL DRUGS ADVISORY COMMITTEE
IMMUNOSUPPRESSIVE DRUGS SUBCOMMITTEE

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PUBLIC MEETING
RAPAMUNE™ (SIROLIMUS), WYETH-AYERST LABORATORIES

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Tuesday
July 27, 1999

The meeting was held in the Whetstone Room at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, at 8:30 a.m., Dr. Henry Masur, Acting Subcommittee Chair, presiding.

PRESENT:

HENRY MASUR, MD	Chair
JAMES J. LIPSKY, MD	Member
ROBERT F. WOOLSON, PhD	Member
DARRELL ABERNATHY, MD, PhD	Consultant
M. ROY FIRST, MD	Consultant
COURTNEY V. FLETCHER, PharmD	Consultant
LAWRENCE G. HUNSICKER, MD	Consultant
RICHARD MANN, MD	Consultant
SUZANNE McDIARMID, MD	Consultant
STEVEN PIANTADOSI, MD, PhD	Consultant
RON SHAPIRO, MD	Consultant
MANIKKAM SUTHANTHIRAN, MD	Consultant
RHONDA W. STOVER, RPh	Executive Secretary

ALSO PRESENT:

BLANCHE M. CHAVERS, MD	Guest
LYNT JOHNSON, MD	Guest
TERRY STROM, MD	Guest
MARK GOLDBERGER, MD, MPH	FDA
MARC CAVAILLE-COLL, PhD, MD	FDA
SANDRA L. KWEDER, MD	FDA
ROSEMARY TIERNAN, MD	FDA
CHERYL DIXON, PhD	FDA
MAUREEN D. SKOWRONEK	Wyeth-Ayerst
JOSEPH CAMARDO, MD	Wyeth-Ayerst
BARRY D. KAHAN, PhD, MD	Univ. of Texas

C O N T E N T S

P R O C E E D I N G S

(8:30 a.m.)

CHAIRMAN MASUR: I'd like to welcome you all. I'm Henry Masur. I'm the Acting Chairman for the day. We thank the committee members and the guests and advisors for coming. Since this is a little bit out of my field and I don't know all of the committee members and guests, perhaps we can start, Suthan, with you and go around. If each person could introduce himself or herself and their institutional affiliation.

DR. SUTHANTHIRAN: I'm Suthan Suthanthiran. I'm Chief of Transplantation Medicine at New York Hospital, Cornell Medical Center.

DR. SHAPIRO: I'm Ron Shapiro. Division of Transplantation, University of Pittsburgh.

DR. MANN: I'm Richard Mann. I'm in the Division of Nephrology at Robert Wood Johnson Medical School in New Brunswick, New Jersey.

DR. HUNSICKER: I'm Larry Hunsicker, the Medical Director of Transplantation at the University of Iowa; Nephrologist.

DR. FIRST: Roy First, University of

Cincinnati Medical Center; Nephrologist.

DR. PIANTADOSI: Thank you. My name is Steve Piantadosi. I'm Director of Biostatistics at the Johns Hopkins Oncology Center.

DR. WOOLSON: Robert Woolson, Biostatistician, University of Iowa.

DR. LIPSKY: Jim Lipsky, Director of Clinical Pharmacology, Mayo Clinic, Rochester, Minnesota.

MS. STOVER: Rhonda Stover, FDA.

DR. CHAVERS: Blanche Chavers, Pediatric Nephrologist, University of Minnesota.

DR. DIXON: I'm Cheryl Dixon, Biostatistician, FDA.

DR. TIERNAN: I'm Rosemary Tiernan, Medical Reviewer, RDA.

DR. CAVAILLE-COLL: Marc Cavaille-Coll, Medical Team Leader, FDA.

DR. GOLDBERGER: I'm Mark Goldberger, Director of the Division of Special Pathogens, FDA.

DR. KWEDER: And I'm Sandra Kweder. I'm the Acting Office Director of 004 at FDA.

CHAIRMAN MASUR: All right, thank you very much. Maybe we'll quickly introduce our last two members. Suzanne, we're just introducing all the panel members so maybe you could just tell us your name and affiliation.

DR. McDIARMID: Sue McDiarmid, Pediatric Hepatologist, UCLA.

CHAIRMAN MASUR: Okay, Terry, you can introduce yourself. We're just going around -- you can use the microphone.

DR. STROM: My name is Terry Strom. I'm a Transplant Nephrologist in Boston, Beth-Israel Deaconess Medical Center.

DR. ABERNATHY: Darrell Abernethy. National Institute on Aging Director.

CHAIRMAN MASUR: All right. Be ready to push the button so that everyone can hear and this is appropriately recorded.

All right, thank you very much. Now we'll have Rhonda Stover read the Conflict of Interest Statement.

MS. STOVER: The following announcement

addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude ever the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests and firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers have been granted to Drs. Richard Mann, Roy M. First, Ron Shapiro, Henry Masur, and Lawrence Hunsicker. In addition, a limited waiver has been granted to Dr. Suzanne McDiarmid. Under the terms of the limited waiver, Dr. McDiarmid will be permitted to participate in the subcommittee's discussions of Rapamune™ but she will be excluded from participating in any vote related to this product.

Copies of these voter statements may be obtained by submitting a written request to FDA's

Freedom of Information Office located in Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Suzanne McDiarmid has unrelated interests in Roche and Wyeth-Ayerst which do not constitute financial interests within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict.

The agency has determined, not withstanding these interests, that the interests of the government in her participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants we ask, in the interest of fairness, that they address any current or previous financial involvement with any

firm whose products they may wish to comment upon.

CHAIRMAN MASUR: Okay, thank you. We will now proceed to the open public hearing. There have been two requests to address the committee. If there is anyone else in the audience who is interested in addressing the committee they can come up during the first presentation and talk to Rhonda Stover.

I want to remind anyone who does address the committee that we do request that you indicate any financial conflicts at the onset of your comment.

The first requestor of this committee is Lisa Kory, Executive Director of Transplant Recipients International Organization. And she'll have ten minutes to address the committee. Thank you.

MS. KORY: Good morning. I'm Lisa Kory. I'm the Executive Director of the Transplant Recipients International Organization, TRIO. We're a non-profit organization representing transplant candidates, recipients, donors, and their families.

My background is, I'm a Nurse and I've been a Transplant Coordinator for ten years in San Francisco. The last five years I've been the

Executive Director with TRIO here in Washington.

Our organization and our mission is 4-pronged: awareness, education, support, and advocacy. Advocacy: we are there to advocate the concerns and needs of members for the national and local legislative efforts to benefit transplant candidates, recipients, and families, and donor family members.

Education: we educate our members with current information on developments in transplant medication and social issues and finances.

Awareness: to promote public awareness of the importance of organ and tissue donation and transplantation. Support: we provide support for the candidates, the recipients, their families, and donor family members. We do this through several programs: through our local chapter affiliates, and through a national peer-to-peer program.

There are significant unmet needs in transplantation today: donor shortage, long-term graft survival and toxicity associated with the long-term immunosuppressive therapies available. Overall, according to UNOS, the United Network for Organ

Sharing, there are more than 68,000 people today on waiting lists for a transplant in the U.S. alone.

Nearly 45,000 are waiting for a kidney. Nearly 2,000 are waiting for a kidney/pancreas transplant. Each day 10 to 12 people die; 4,000 die each year before receiving a new organ. Organ transplantation can be characterized as I often say, as a crisis with a cure.

All patients should have information about and access to, all therapeutic alternatives. We support any therapy that will improve transplant outcomes, specifically by protecting and extending the longevity of the transplant organ. Based on clinical studies we believe that Rapamune™ will fill that need within the transplant medicine as another effective immunosuppressive therapy.

It is our understanding that Rapamune™ has the potential to improve long-term outcomes by reducing the toxicity and rejection rates, thereby possibly increasing the longevity of the transplant organ. We are in favor of any medication that improves the quality of life for transplant recipients

and any therapy that will result in better outcomes, both for the graft and for the patient.

We are not scientists, we are not researchers, and we are not pharmacologists. Our organization, Transplant Recipients International Organization, TRIO, represent people, candidates; people who are waiting, recipients, people who have been given the gift of life, and their families.

We are in favor of anything and everything that provides recipients and candidates choices; informed choices. TRIO is pleased to have the opportunity to encourage favorable action on the drug Rapamune™ because it will provide a broader range of therapeutic choices for the recipient.

There are also two bills in Congress right now: H.R. 1115 and S-631, the Immunosuppressive Drug Coverage act of '99. These bills will extend the coverage of medications beyond the present 36-month limit for those patients who have received a transplant under Medicare.

On behalf of the people, we, TRIO, will support each and every new drug like Rapamune™ that

promises to improve transplant outcomes and provide choices, informed choices. Transplantation is a matter of life or death. Thank you.

CHAIRMAN MASUR: Thanks very much, Ms. Kory. The second request to address the committee is from F.W. Zylwitis who -- is F.W. Zylwitis here? Okay, we have the letter which will be inserted into the record, so we appreciate your submission of that letter, Mr. Zylwitis.

If there are no other requests to address the committee we'll then proceed to the FDA introduction by Mark Goldberger who is the Director of the Division of Special Pathogens.

DR. GOLDBERGER: I'd like to extend our welcome to Dr. Masur, the other committee members, members of Wyeth-Ayerst and their invited consultants. And particularly extend our thanks to Wyeth-Ayerst for all the efforts they have made to get us to today when we can discuss this product.

As everyone's well aware, the management of rejection in renal transplantation continues to be quite challenging. Although the number of therapeutic

options that are now available is increasing, there are certainly room for additional therapies and we're here to discuss one of those today, sirolimus.

As with all such therapies, there are interesting and complex features in the assessment of the safety and efficacy, and that's made even more complex by the complex nature of the patients who are receiving these therapies. And we look forward to the discussions of the committee and to the advice that you will be providing us about the safety and efficacy of this product.

Thank you.

MS. SKOWRONEK: Good morning. I'm Maureen Skowronek of the Regulatory Affairs Department at Wyeth-Ayerst. On behalf of our organization, including the Rapamune™ Project Team, we're pleased to have this opportunity to review the data supporting our NDA for Rapamune™ Oral Solution for use in renal transplant patients.

Our NDA was submitted on December 15th, 1998 and received a priority status designation by FDA reflective of the seriousness of the medical condition

and the therapeutic potential of Rapamune™ in this setting.

We have the following agenda for today's Advisory Committee meeting. Upon completion of my brief introductory remarks Dr. Joseph Camardo, Senior Vice President of Clinical Research at Wyeth, will review the salient, non-clinical data, the mechanism of action, the results of early clinical and pharmacokinetic studies, and the design of two, double-blind, Phase III efficacy studies that form the basis of our NDA.

Dr. Barry Kahan of the University of Texas and a longstanding investigator involved with the Rapamune™ Project Team, will review the efficacy results from those Phase III studies.

Following the efficacy presentation Dr. Camardo will return to summarize the collective safety experience and state the conclusions of our presentation.

To facilitate these proceedings I have a few remarks about our products and the development history. As depicted on this slide, Rapamune™ is

known in the transplant community by a variety of names, including its trade name, Rapamune™, its generic name, sirolimus, a common name, rapamycin, and a common abbreviation, RAPA.

For the purposes of today's meeting we'll primarily refer to our product as Rapamune™. Rapamune™ is a macrocyclic lactone isolated from an organism, Streptomyces hygroscopicus. Shown on the left of this slide is the structure of Rapamune™.

The domain, highlighted in yellow, is identical to a corresponding domain of tacrolimus. Dr. Camardo in his upcoming presentation, will relate structure and mechanism of action, distinguishing Rapamune™ from other immunosuppressive drugs.

Over the course of development we've collected a sizable volume of non-clinical data pertaining to Rapamune™. The following results of pharmacology studies are key to today's presentation. Animal models have shown Rapamune™ to be a potent immunosuppressive agent when evaluated alone, and it acts synergistically with cyclosporine. Moreover, Rapamune™ has a mechanism of action distinct from

approved immunosuppressive drugs.

With regard to formulation, our product is an oral solution supplied as a one mg/mL concentrate. Once daily administration requires the dilution of the prescribed dose in a small volume of orange juice or water for which the patient drinks the entire dose.

From the onset of our activities we've had a highly interactive relationship with FDA on all aspects of the development program. This is noteworthy as we had the opportunity to study Rapamune™ pre-clinically and clinically in many different ways. With FDA consultation we've chosen a specific pathway culminating in the submission of our NDA and today's meeting.

Paramount in our negotiations with FDA are the following. Rapamune™ was evaluated with cyclosporine and corticosteroids in early clinical trials and in the Phase III efficacy studies. Key agreements regarding design of those Phase III efficacy studies include the selection of the primary efficacy endpoint. That is, the first occurrence of acute rejection, graft loss, or death at six months.

Patient and graft survival at 12 months were also key.

We also agreed with regard to the selection of the comparators. In the U.S. trial Rapamune™ is compared to azathioprine; in the Global study Rapamune™ is compared to placebo. Wyeth and FDA also collaborated on the analyses of the Phase III studies, and at this time we'd like to thank FDA for their contributions made over the course of development.

Finally, as stated in our NDA in the Advisory Committee briefing package, we seek approval of the following indication and dose recommendations.

Rapamune™ is to be used for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune™ be used in a regimen with cyclosporine and corticosteroids.

For most patients a Rapamune™ dose of 2 mg once daily is recommended. For patients at high risk of rejection a Rapamune™ dose of 5 mg once daily is recommended.

These conclude my introductory remarks and

at this time I'd like to introduce Dr. Joseph Camardo, Senior Vice President, Clinical Research, Wyeth-Ayerst.

DR. CAMARDO: Thank you, Maureen. Good morning. I'd like to begin today by acknowledging my colleagues at Wyeth who worked on the Rapamune™ project. There are literally hundreds of them and I can't name them all but for many of them the development of Rapamune™ was a major part of their career, and for one individual it was literally his life's work.

I'd also like to acknowledge the more than 100 transplants teams and the thousands of patients and their families who participated in the clinical trials. It's really my good fortune to represent all of the people who worked on the Rapamune™ project.

Most important message of our presentation is that Rapamune™ Oral Solution, as part of a combination regimen with cyclosporine and corticosteroids, provinces the clinical benefit of a low rate of acute rejection, excellent graft and patient survival, and manageable side effects.

Safety and efficacy for Rapamune™ were demonstrated in two well-controlled clinical trials in recipients of mismatched renal allografts. The Doltrane Study characterizes the product at doses sufficient for nearly all patients who will be treated in clinical practice.

All of you know that this decrease has seen significant progress in the management of patients with renal, heart, and liver failure. Transplantation offers a definitive, immediate benefit with good short-term graft survival and function. Although there are many new drugs and the risk of acute rejection episodes has decreased, acute rejection is still a clinical problem for patients and transplant teams.

This decade has also seen numerous, well-controlled trials that support improvements in clinical practice, and these have also set the standards for development of new drugs.

However, there remain significant challenges to have optimal combination regimens for individual patients that will prevent rejection with

minimal toxicity, to find optimal regimens for high-risk patients such as African-Americans, and to improve long-term graft survival by preventing or treating chronic rejection and chronic allograft failure.

My colleagues and I submitted this NDA because the data demonstrated that Rapamune™ provides an immediate, tangible benefit to patients and that it will meet the challenges of transplantation in the future.

Today we have two goals. First, to demonstrate that Rapamune™ should be a key component of clinical transplantation immediately in 1999 on the basis of the results of the Phase III clinical trials. And second, demonstrate that the unique, biologic activity of Rapamune™ endows it with a great potential to improve the practice of transplantation in the future.

The biologic activity of Rapamune™ has been the subject of hundreds of scientific papers over the last 20 years so it is certainly not possible to review this in any depth today. I will limit my

comments to the key properties of Rapamune™ that distinguish it from other drugs and make it attractive for transplantation.

Ms. Skowronek told you that Rapamune™ shares structural homology with tacrolimus. However, Rapamune™ is substantially different from tacrolimus and from other immunosuppressants. It is a novel drug -- neither a calcineurin inhibitor nor an anti-metabolite -- and it has a unique cellular target called mTOR, the mammalian target of rapamycin.

Rapamune™ blocks mTOR and this blocks cytokine-mediated cell proliferation in T cells, B cells, and mesenchymal cells, including vascular smooth muscle cells.

The important differences between Rapamune™ and the calcineurin inhibitor drugs that are the mainstay of therapy, are shown here. Cyclosporin and tacrolimus bind to the intracellular protein, cyclophillin or FBKP12, respectively, block the activity of the effective protein, calcineurin.

Calcineurin blockage reduces transcription of IL-2 message, blocks activation of T cells at the

G_0 stage of the cell cycle. Rapamune™ also binds to FKBP12 but inhibits neither calcineurin nor transcription of IL-2 message; rather, Rapamune™ blocks mTOR and this inhibits the response to IL-2. This interrupts the intracellular response blocking the signal transduction pathway required for cell cycle progression from G_1 to S phase.

Data from several laboratories indicate that all known biochemical effects of Rapamune™ that inhibit cellular proliferation result from inhibitation from the cell cycle kinase mTOR. The pathways to illustrate this important point, that the target of Rapamune™ mTOR is a key regulatory protein that coordinates many different enzyme pathways to control cell division.

Pathways are notoriously complex and I simplified them to make this one point. These data are published and easily available. Cell surface stimulation by antigen-induced cytokines and co-stimulation converge at mTOR and initiate biochemical events that commit the cells to proliferate.

Acting through intermediary proteins mTOR

activation induces activation of p70 S6 kinase and phosphorylation of the S6 ribosomal sub-unit, which increases synthesis of specific ribosomal proteins required for cell cycle progression.

Translation of specific messenger RNAs that code for cell cycle proteins by phosphorylation and disassociation of phase-1, the inhibitor of the initiation factor for these proteins, and activation of cycline-dependant kinases of disassociation and degradation of P27 cdk, a regulatory protein that controls sequential activation of these kinases required for coordinated DNA synthesis.

The Rapamune™ FKBP12 complex blocks all of these at mTOR, the action of Rapamune™ is specific and reversible, and Rapamune™ is not cytotoxic. Moreover, this activity as an inhibitor of cell cycle progression is the basis of the immunosuppressive, anti-proliferative activity of the molecule. These properties and the fact that Rapamune™ acts differently from calcineurin inhibitors make it an attractive new agent.

In animal models, Rapamune™ has three

important activities relevant to transplantation. First, in rats, pigs, and primates, Rapamune™ prolongs allograft survival when used alone in safe and tolerated doses. Second, Rapamune™ is synergistic with cyclosporine for prevention of rejection.

And third, Rapamune™ inhibits rapid, smooth muscle proliferation after immune or mechanical vascular injury and prevents graft vessel disease. This is important because many studies have shown that vascular proliferation is a distinct characteristic of the pathology of chronic rejection.

I'd like to review the core experiments which illustrates two of the three activities just mentioned: immunosuppression and synergy with cyclosporine.

First, Rapamune™ prolongs graft survival in pig orthotopic renal allografts. This is a well-studied and stringent model to test new immunosuppressants, and in this model survival of the recipient is dependent upon function of the allograft. The bars represent mean survival, shown on the left

ordinant. The blue line represents blood levels of Rapamune™, shown on the right ordinant.

Cyclosporine, azathioprine and prednisone shown in orange at appropriate therapeutic doses for this model prolong survival over placebo, shown here. Rapamune™ alone prolonged survival significantly. And this is dose and blood concentration-related, proving that it's a clear pharmacologic effect.

Second, in a heart transplant model in the rat, both Rapamune™ and cyclosporine alone each prolonged graft survival. And this is dose-related. Survival time is shown on this axis from zero to 120 days. Shown here are survival times for the untreated controls. Cyclosporine treatment is shown in orange; Rapamune™ here is shown in blue.

Note that dose-related improvements in graft survival for each drug alone are modest, and the lowest doses have no effect over placebo. However, combinations of these same doses of Rapamune™ and cyclosporine are shown in green. The graphical display shows that these combinations increase survival much more than the same doses of either drug

alone.

These are more than simply additive; they are synergistic. For example, survival at the highest dose of cyclosporine, 2 mg/kg, is about 14 days. The same for the highest dose of Rapamune™; 0.04 mg/kg, 14 days. But for the combination shown here, the mean survival time is nearly 100 days.

The development of Rapamune™ included extensive toxicologic evaluation, and the toxicity has been fully described in the application. For the purposes of this clinical discussion I want to emphasize only that Rapamune™ appears to be free of an important toxicity of calcineurin inhibitors.

Specifically, in pre-clinical toxicity studies there were no effects of Rapamune™ on glomerular filtration rate, BUN/creatinine, or anatomical renal morphology in any species. The results indicate there was no nephrotoxicity associated with Rapamune™ in short-term or long-term animal studies.

Our pre-clinical studies demonstrated that Rapamune™ is a potent, novel immunosuppressant. Its

activity is independent of calcineurin, it is synergistic with cyclosporine, it prevents proliferation of smooth muscle cells, and the safety profile is free of some important side effects of the calcineurin inhibitor such as renal toxicity.

Moreover, the pre-clinical program provided a rational basis for the clinical program. First, the biochemical and cellular studies the animal pharmacology and the toxicity studies showed that Rapamune™ is compatible and can be combined with cyclosporine-based therapy.

Second, the synergy between Rapamune™ and cyclosporine suggests the possibility that combinations of cyclosporine and Rapamune™ would be better than cyclosporine alone or Rapamune™ alone to achieve a therapeutic benefit, and that this combination might allow for the use of lower doses of cyclosporine to avoid some toxicities. These data convinced us to begin clinical studies of Rapamune™ in transplantation.

Turning now to the clinical program, I'd like to review the key results of the Phase II renal

transplant studies, then discuss the pharmacokinetics of Rapamune™, then the design of the Phase III studies.

There is a large database to support the safety and efficacy of Rapamune™. Of the more than 3000 patients in 55 studies, more than 2,600 received at least one dose of Rapamune™, and at the time the NDA was submitted in December of 1998, over 700 had been treated for at least one year and many continuing studies.

I will begin with the Phase I and Phase II. Phase I studies were performed in stable renal transplant patients, in patients with chronic rejection and renal compromise, in patients with refractory psoriasis, in healthy volunteers, and in children.

Phase II studies in de novo renal transplant recipients included a study of recipients of living, related donor allografts at a single center, a multi-center study of full and reduced-dose Sandimmune™ with low doses of Rapamune™, and recipients of cadaver kidneys, and a study of steroid

withdrawal. And finally, a study of higher doses of Rapamune™ as primary therapy without cyclosporine.

The Phase II multi-center study supported the design of the Phase III program, and this is the only study I will discuss in detail. In this dose-ranging study, 151 de novo, mismatched renal allograft recipients were randomized to one of six groups of 25 each.

Three groups received standard dose cyclosporine administered in the original Sandimmune™ formulation, three groups received reduced-dose Sandimmune™. All patients received prednisone. In the standard groups, placebo, 1 or 3 mg Rapamune™ per meter squared was added to the regimen. In the reduced dose Sandimmune™ group, 1, 3, or 5 mg/m^2 Rapamune™ was added to the regime.

The trough levels in the reduced-dose Sandimmune™ groups were about 60 percent of the trough cyclosporine levels in the standard dose groups. In this study, Rapamune™ as you can see, was adjusted by body surface area. The length of the trial was six months but many patients continued into

follow-up for up to two years.

To simplify the presentation, outcomes for the groups that received Rapamune™ have been combined to illustrate the most important conclusions. The numbers of patients included in each analysis are shown here. Acute rejection in the cyclosporine group, the control group, was 32 percent.

This panel shows the rejection rate of 16 percent for the five Rapamune™ groups combined. This panel shows the rejection rate of less than ten percent for the two groups who received standard dose Sandimmune™ and Rapamune™ at 1 or 3 mg/m^2. The last panel shows the rejection rate of 20 percent for the three reduced-dose Sandimmune™ groups who received 1, 3, or 5 mg/m^2 Rapamune™.

The key result is that all the groups who received Rapamune™ had a lower rate of acute rejection than cyclosporine, prednisone alone, and statistical significance was achieved for standard dose Sandimmune™ combined with 1 or 3 mg/m^2 Rapamune™.

A subgroup analysis showed a difference in the rate of acute rejection in the reduced-dose

Sandimmune™ recipients depending upon the ethnic origin of the recipient. Black patients are shown here in purple, non-Black patients here in blue.

In the standard dose cyclosporine groups, both Black and non-Black recipients achieved a low rate of acute rejection. However, in contrast in the reduced-dose Sandimmune™ groups, non-Black recipients had a lower rate of acute rejection but Black recipients with reduced-dose cyclosporine and Rapamune™ at any dose had a higher rate of rejection no different from standard dose cyclosporine or prednisone.

These data suggested that reduced-dose cyclosporine with Rapamune™ may not provide sufficient immunosuppression for Black recipients.

We concluded from Phase II that Rapamune™ is a potent clinical immunosuppressant. The main side effects were dose-related, reversible hyperlipidemia and a reduction in platelet count that is also reversible.

A site-specific epidemic of pneumocystis in the Phase II combination study in patients who were

not receiving PCP prophylaxis indicated that given the additional immunosuppression of the Rapamune™ cyclosporine combination, pneumocystis prophylaxis should be continued in all patients for at least one year.

These results were the basis for the design and dose selection for the Phase III clinical trials. Before we discuss these studies I want to review the most critical aspects of the clinical program that were guided by the Phase II results.

As you saw, acute rejection is a key component of the endpoint for Phase III studies and has been so for other studies of new drugs and biologics. Acute rejection rates were significantly lower than standard therapy when 1 mg/m^2 or 3 mg/m^2 Rapamune™ was combined with standard dose Sandimmune™ for both Black and non-Black recipients.

A complete analysis of the dose and blood concentration data for Rapamune™ indicated that adjustment of dose for body surface area had no impact on drug exposure and was thus an unnecessary inconvenience to the patient and the transplant teams.

The dose of 1 mg/m^2 provides exposure nearly identical to a 2 mg fixed dose. The dose of 3 mg/m^2 is nearly identical to a 5.5 mg fixed dose. For Phase III, the next lower integer dose, 5 mg, was employed.

This range of exposure from 2 to 5 mg provides a comprehensive description of a therapeutic window for Rapamune™. The absolute requirement for blinded studies for efficacy, for acute rejection, was a key factor in the decision to use combination Rapamune™ and standard dose rather than reduced-dose cyclosporine.

A one-year blinded study with reduced-dose cyclosporine would not be feasible. This would not be acceptable control therapy and was clearly sub-optimal for Black recipients. Thus, this program satisfied the need for well-controlled, Phase III trials. We deferred other studies suggested by the Phase II data to pursue in Phase III-B.

Before we discuss the Phase III in detail I want to review the clinical pharmacokinetics of Rapamune™. An extensive program was performed to characterize the pharmacokinetic behavior and this

provides practical dosing guidance for physicians as well.

As is customary in dealing with pharmacokinetics, I will refer to the drug as sirolimus when speaking about the blood levels as opposed to Rapamune™ when speaking about the medication.

Sirolimus is rapidly absorbed. The medium t_{max} is less than one hour. Sirolimus is 14 percent bioavailable and the AUC and C_{max} are linear and dose proportional over a range of 1 to 12 mg/m^2. The slide from Phase I shows the profile over time. Note there is a long half-life for sirolimus. The insert shows the short t_{max}.

This slide demonstrates that steady-state concentrations and terminal half-life of sirolimus are consistent with ascending oral doses. Steady-state is achieved within about one week after multiple, oral doses twice daily. The terminal half-life remained constant over a 13-fold dose range from .5 mg/m^2 twice a day to 6.5 mg/m^2 twice a day.

PK modeling indicating that steady-state

sirolimus levels could be achieved more efficiently with a loading dose of three times the maintenance dose. Loading doses were used in Phase II and Phase III, and are recommended for clinical practice. Given the long half-life, Rapamune™ was administered once per day in all subsequent studies.

Data from formal crossover design dose proportionality studies in Phase I confirmed that the C_{max} and the AUC are linear with dose. This particular example shows data for 3 to 12 mg/m^2. Sirolimus is highly partitioned into blood elements. The blood-to-plasma ratio was 36, thus the plasma fraction is small and what remains in the plasma is highly protein-bound.

The volume of distribution is 1.6 L/kg. sirolimus is a substrate for cytochrome P3A4, and there are seven major metabolites, both hydroxylated and de-methylated. These metabolites have no significant immunosuppressive activity. Elimination is predominantly through the GI tract. There is almost no renal elimination of sirolimus. As shown previously, the terminal half-life is long; a mean of

about 62 hours.

Demographic factors have no significant clinical impact. Clearance decreased somewhat with age, however, around the median age for the Phase III patients clearance is relatively constant. This change with age is skewed by a higher clearance in children younger than 12 years of age.

There was a small, detectable difference in half-life and clearance by gender. Ethnic origin -- that is, Black or non-Black -- has no effect on the pharmacokinetics of sirolimus.

A high-fat meal decreases sirolimus C_{max} and increases AUC. Hepatic impairment decreases oral dose clearance. Based on nine drug interaction studies in healthy volunteers sirolimus clearance was significantly affected by only four of the drugs studied.

After co-administration, a Rapamune™ with diltiazen, keteconazole and neoral, sirolimus exposure was increased significantly -- shown here. As to rifampin, exposure was decreased significantly -- shown here. The five remaining drugs had no effect.

This slide shows that sirolimus exposure is also sensitive to the timing of administration to neoral. The Y-axis is the exposure relative to Rapamune™ administered alone, which would be a value of one. Simultaneous administration of Rapamune™ and neoral increased sirolimus exposure more than threefold. Staggered administration -- that is, Rapamune™ four hours separated from neoral, increased exposure less than twofold.

This observation led us to separate the doses of Rapamune™ and neoral in Phase III to minimize the interaction. Note also the simultaneous administration of Sandimmune™, the original cyclosporine formulation that was used in Phase II, has only a modest effect to increase sirolimus exposure, therefore the pharmacokinetic interaction between sirolimus and cyclosporine appears to be formulation-dependent.

Most important to the discussion today is the behavior of Rapamune™ in de novo renal transplant recipients. These pharmacokinetic data are derived from the Phase III program in which Rapamune™ was

administered with neoral. In this section I want to discuss some of the cyclosporine data from Phase III studies as well.

A key point is the Rapamune™ behaves similarly in de novo allograft recipients as it does in other populations. This shows data from a subset of patients from Phase III in whom full pharmacokinetic profiles were obtained in months 1, 3, and 6. This is a total of 42 patients.

Blood level monitoring was not performed in Phase III to adjust the Rapamune™ doses. Note that the C_{max}, the AUC, and the C_{min} are roughly dose proposal. The t_{max} is relatively constant from 2 to 5 mg, and the clearance is unchanged as the dose is increased. Analysis of variance showed no significant differences by treatment, race, or time, for the data from these studies.

The next slide shows that whole blood sirolimus C_{min} is strongly correlated with AUC in de novo renal transplant recipients. The same data from the previous slide for the 42 patients with full profiles of 1, 3, and 6 months was used for this

analysis.

Correlation is clear from the graph. Most of the points fall within the 95 percent prediction interval, and the r^2 value is .96, thus it is reasonable to conclude that C_{min} predicts exposure.

Continuing, exposure was identical for Black and non-Black recipients at both the 2 and 5 mg treatment groups in the Phase III studies. These data represent trough levels from nearly 500 patients over the first six months. The mean trough levels were 8.5 ng/mL for the 2 mg dose; 17 ng/mL for the 5 mg dose. And these are the same for both Black and non-Black recipients.

Our formal analysis of variance showed no effect of race. The inter-subject coefficient of variation is about 45 percent. The intra-subject coefficient of variation is less than 40 percent. But note that it is the same for Black and non-Black recipients.

Sirolimus pharmacokinetics from Phase III were stable over time. The left figure in this slide shows that the mean sirolimus trough levels for

Rapamune™ 2 mg were constant from month-1 through month-6. The figure on the right shows the trough levels for the 5 mg group.

The actual values are shown in blue; dose normalized; 2 mg are shown in yellow. These are also constant over the first six months and moreover, the dose normalized values are barely distinguishable for the values for the 2 mg group shown on the left.

Moving to the cyclosporine dosing in Phase III, cyclosporine was trough concentration controlled. We will discuss this in more detail when I review the design of the Phase III studies.

These data illustrate a pharmacokinetic interaction that was not seen in early Phase I studies in volunteers but was observed in Phase III studies of renal transplant recipients receiving cyclosporine as neoral.

The point is that not only will neoral affect clearance of sirolimus but sirolimus will affect the clearance of cyclosporine. The interaction is in both directions. In one of the Phase III studies patients received Rapamune™ 2 mg, Rapamune™

5 mg, or azathioprine as a control treatment.

Average cyclosporine trough concentrations shown here on the left ordinant and shown again at the top of the panel, are nearly identical for the 2 mg, 5 mg, and the azathioprine control groups. Thus, patients in the Rapamune™-treated and azathioprine control groups had equal cyclosporine exposure in this study.

The protocol design required reduction in cyclosporine target levels at specific intervals over the first six months. This was accomplished, thus the protocol was followed.

This slide illustrates how these results were achieved: by concentration monitoring and cyclosporine dosing at the clinical site. Presented here are the cyclosporine levels for each treatment group at month-1. This is exactly what you saw for month-1 on the previous slide.

Here are the actual doses in mg/day required to achieve these target levels. In the control group the mean dose was 601 mg/day; for Rapamune™ 2 mg the dose requirement was 568 mg/day;

for the 5 mg dose it was 528 mg/day. And these are statistically significant.

The data suggests that when neoral is used in combination with Rapamune™ lower doses of neoral are required to achieve the same target cyclosporine levels. As expected, Black patients required higher doses of neoral to achieve cyclosporine target levels, but there was a proportionate decrease in the dose requirement for Black patients on Rapamune™ as well.

This observation has important implications for dosing of cyclosporine. Based purely on the pharmacokinetic considerations the data indicate that physicians will have to anticipate a downward adjustment of cyclosporine doses to achieve any given target range when used in combination with Rapamune™.

In conclusion, pharmacokinetic behavior of sirolimus has been well characterized. It's rapidly absorbed and dose proportional over a range of 1 to 12 mg/m^2. The C_{min} predicts the exposure by AUC, sirolimus is partitioned into formed blood elements, what remains in the plasma is highly protein-bound.

Sirolimus is a substrate for cytochrome P3A4 and P-glycoprotein. There is extensive first-pass metabolism. There are multiple metabolites but these contribute very little to the immunosuppressant activity. The oral dose clearance is variable.

The effect of demography is not clinically significant with regard to drug interactions. There are significant interactions with ketoconazole, rifampin, diltiazem, and cyclosporine. There are no interactions with digoxin, acyclovir, nifedipine, Lo/Ovral, and glyburide.

Finally, most important, in de novo renal transplant recipients key pharmacokinetic characteristics include the absence of any significant difference in the behavior of sirolimus for Black and non-Black patients; a continued strong correlation between C_{min} and AUC; stability of the trough concentrations over time. Finally, the trough variabilities: 45 percent inter-subject, 38 percent intra-subject. But the same for both Black and non-Black recipients.

This concludes my discussion of the

pharmacokinetics of Rapamune™. I want to move now to a discussion of the Phase III study design.

The Phase III program was designed to support the indication for Rapamune™ in combination with cyclosporine and corticosteroids for prophylaxis of organ rejection in patients receiving renal transplants.

The two Phase III studies were double-blind, controlled, randomized, stratified, multi-center, large-scale studies. A key point of the studies was that all sites were obligated to follow the participates for the full duration of the study for acute rejection, graft survival, patient survival, and serious adverse events, even if discontinued from study medication.

Two critical time points for these studies are the 6-month endpoint for efficacy, the 12-month endpoint for patient and graft survival. For the 6-month endpoint very few patients had missing data for acute rejection. You'll see this. Most important, the transplant teams achieved 100 percent follow-up for patient and graft survival for all 1,295 patients,

for both 6 and 12 months.

In both studies patients are continuing to be followed for longer-term endpoints. In these studies, called US(301) and Global(302), all patients were treated with neoral and steroids. In the US study patients were randomized then to 2 mg Rapamune™, 5 mg Rapamune™ or azathioprine. This required a double-dummy design.

In the Global study patients were randomized to 2 mg Rapamune™, 5 mg Rapamune™, or placebo. Doses were not adjusted by therapeutic drug level monitoring.

This slide shows some of the key similarities and differences between the studies. In the US study patients were randomized within 48 hours after surgery; in the Global study randomization occurred before surgery. Stratification was by center and race in the US and by center and donor origin in the Global study.

Antibody induction therapy was prohibited in both studies. Prophylaxis was required for PCP for all patients, and for CMV for patients who met

criteria for higher risk for CMV infection.

The rational for stratification by ethnic origin or race in the US study is as follows. Graft survival and acute rejection rates remain higher in African-American renal transplant recipients. That is, graft survival is not as good and acute rejection rates are higher.

Black patients appear to require higher doses of immunosuppressants and this was observed in the Phase II dose ranging study where rejection was clearly higher in Black patients treated with reduced dose cyclosporine and Rapamune™. The US Phase III study was prospectively stratified to ensure the Black patients were represented equally in all the study groups to allow for the assessment of safety and to determine the optimal dose of Rapamune™ for African-American recipients.

The US Phase III study included 38 centers and 719 patients. The Global study included 34 centers, 576 patients in Canada, Australia, France, Spain, Italy, Norway, and the United States. The randomization scheme was 2:2:1; two patients in each

Rapamune™ group for every one patient on control therapy.

The number of patients in each treatment group are shown in the pie charts, and these colors to identify the groups will be used in most of the slides throughout the presentation: pink for azathioprine, blue for placebo, 2 mg Rapamune™ in yellow, 5 mg Rapamune™ in green.

Enrollment occurred between June of 1996 to September of 1997. These dates are relevant to the choice of the control groups and that it was a time when combination therapy was clearly changing in favor of newer immunosuppressants. However, no new standard was yet in place in all the centers of the world that were needed to perform these studies.

Thus, we chose in favor of combination regimens with which there was substantial present and past experience, namely: double therapy with cyclosporine and prednisone; and triple therapy -- cyclosporine, prednisone, and azathioprine.

These studies included recipients of a first transplant, either cadaveric or living donor at

least 13 years old. Patients who received HLA-identical living donors were excluded. All patients received cyclosporine in steroids. These patients were treated with neoral, not Sandimmune™, since neoral became available just prior to the Phase III program.

Within 24 to 48 hours of transplantation patients received a single loading dose of Rapamune™, 6 or 15 mg orally, or azathioprine in the US or placebo in the Global study. Then from day-2 onward, Rapamune™ 2 or 5 mg, azathioprine or a placebo.

Guidelines were included in the protocol to decrease the dose of blinded medication, to manage specific side effects, and to avoid serious toxicity. These guidelines included adjustment for elevated lipids, decreased platelets, and decreased leukocytes.

I want to review now the cyclosporine concentration guidelines and the blood levels. At the time we began the Phase III studies the optimal dose of cyclosporine for use in combination with Rapamune™ was not known. This slide shows the rationale for cyclosporine dosing. I told you earlier the reasons

for the decision to use standard rather than reduced cyclosporine.

The specific target levels for cyclosporine concentrations represented agreement among the investigators to provide standardization across the centers and to assure adequate immunosuppression for the control group.

For month-1 the target trough cyclosporine concentrations in the US study were 200 to 350 ng/mL; in the Global study, 200 to 400 ng/mL. For months-2 and -3 the targets in both studies were 200 to 300 ng/mL; for months-4 to -6 the targets were 150 to 250 ng/mL.

The mean cyclosporine trough levels in the US study were equal in the groups and decreased as mandated by protocol. You've seen this slide previously in the pharmacokinetic section. The mean levels are shown at the top for azathioprine, Rapamune™ 2 and Rapamune™ 5 mg group for the US study.

I want to call your attention to the fact that these mean trough levels were slightly above the

protocol-mandated target range, thus patients were more than adequately treated with cyclosporine in all the groups. But the key is that the mean concentrations were the same in the three groups for the first six months of the study.

The primary endpoint of these studies was the same in both these studies: a composite comprised of the first occurrence within six months of biopsy proven acute rejection, graft loss, or death. The primary analysis was intention-to-treat using Cochran-Mantel-Haenszel statistic stratified by center, the Breslow-Day test for consistency of treatment across the pre-defined strata.

To compare the results for patient and graph survival, point estimates and confidence limits for patient and graft survival, and confidence limits for the differences between the Rapamune™ and the control groups were determined. The sample size was estimated to assure 90 percent power to detect a 50 decrease in the efficacy failure rate with a 2-tailed test and P less than .025.

For the US study a 36 percent failure rate

for azathioprine was assumed; for the Global study a 40 percent failure rate for the placebo group was assumed. The sample size was not determined to demonstrate statistically significant differences among the predefined strata nor among the various sub-groups that were analyzed.

Finally, the sample size was not determined in anticipation of showing an improvement in patient or graft survival. However, there are sufficient patients in the studies to demonstrate that within reasonable limits patient and graft survival were equivalent for the Rapamune™ and the control patients.

This concludes my discussion of the Phase III study design. It is my pleasure now to introduce Dr. Barry Kahan from the University of Texas who will review with you the efficacy results from Phase III.

DR. KAHAN: Thank you, Joe. Good morning. It gives me great pleasure to present the data on the benefits of the addition of Rapamune™ versus azathioprine or placebo to a cyclosporine/prednisone regimen in de novo renal transplant recipients.

The two Phase III pivotal trials that I will describe represent the seamless transition from three previous studies of the addition of Rapamune™ to a cyclosporine/prednisone regimen.

First, a Phase I study in quiescent renal transplant patients. Second, this same combination used de novo in mismatched, living donor transplants. And third, as Dr. Camardo described, a Phase II multi-center trial in cadaveric donor renal transplants.

In the Phase I/II study we found that addition of Rapamune™ markably reduced the incidence of acute rejection episodes and facilitated steroid withdrawal. The later, multi-center study confirmed the efficacy of Rapamune™ cyclosporine/prednisone combination for acute rejection prophylaxis and showed that reduced doses of cyclosporine were effective for non-Black patients compared with Black patients.

As previously described by Dr. Camardo, the Phase III trial was prospectively stratified by ethnic origin -- Black versus non-Black patients -- while the Global trial was prospectively stratified by donor source; that is, cadaveric versus mismatched

living donors.

This slide shows the distribution of some demographic variables among patients in the US trial. I'd like to call your attention to the fact that 22 to 25 percent of the patients were of Black ethnic origin and that there were more female patients randomized to the azathioprine group than to the other two Rapamune™ groups.

In the Global trial there was no statistically significant difference in the distribution of donor origin, the primary stratification variable, of ethnic background or of gender of the patients.

As summarized here, the patients in both trials showed distributions across treatment groups for the demographic features of age, etiology of renal failure, pre-transplant PRA status -- although the majority of patients have low PRA detectable in serum -- degree of HLA mismatch, and graft ischemia time.

I'd now like to share with you the intention-to-treat analysis of the primary efficacy endpoint; namely a composite index of the first

occurrence of a biopsy-confirmed acute rejection episode, graft loss, or death within the first six months after transplantation.

The US trial is shown on your left and the Global trial is shown on your right. I'd first like to call your attention to the color scheme utilized throughout this presentation. Azathioprine is shown in pink; placebo is shown in blue; Rapamune™ 2 mg/day group is shown in yellow; and Rapamune™ 5 mg/day group is shown in green.

The numbers at the top of the bars give the actual result in percent. The numbers at the bottom of the bar show the number of patients in that cohort, the P-values of Rapamune™ for each comparison. Please note that in the US trial the rate of efficacy failure was reduced from 32.3 percent to 18.7 percent in the Rapamune™ 2 mg/day group, and to 16.8 percent in the Rapamune™ 5 mg/day group.

As you will note, each of these comparisons was highly statistically significant at P=0.002 or less. In the Global trial there was a reduction in the incidence of composite failure from

47.7 percent to 30 percent among the patients receiving Rapamune™ 2 mg/day and 25.6 percent among the patients receiving Rapamune™ 5 mg/day. Again, each of these comparisons was highly statistically significant.

These bars show the rates of occurrence of each of the individual components of the primary endpoint. That was biopsy-confirmed acute rejection indicated by the solid color.

Next, the distribution of four patients for whom the information on whether they had an acute rejection episode was not known. Next, the graft losses indicated by the vertical fill; and finally, the patient deaths indicated by the cross-hatches.

Patients lost to follow-up were considered as efficacy failures in this analysis. As you will note, biopsy-confirmed acute rejections shown in the solid color, were the major component of the primary endpoint. Note that the efficacy failure rate is lower in the US trial then in the Global trial.

We attribute the lower rate of efficacy failure in the US trial compared with the Global trial

to at least four possible factors. First, randomization in the Global trial occurred prior to transplantation. In the US trial patients were randomized after transplantation but the rate graft function was slightly higher in the Global trial with the expected increased risk of an acute rejection episode.

Second, the Global trial showed higher rates of death and graft loss. Third, more patients in the Global study received less than five doses of study medication. Fourth, you will recall that the US trial had an active comparator, azathioprine, and the Global trial had a placebo comparator.

Multiple, secondary efficacy measures were also evaluated at the 6-month endpoint. These included the incidence of first biopsy-confirmed acute rejection episode, the histologic grade of the first acute rejection episode, and the use of anti-lymphocyte antibody.

Preparations to treat the first episode of acute rejection -- one where patient and graft survival will be reviewed -- and I'll then present an

analysis of efficacy failures across demographic variables.

This graph shows that Rapamune™ decreases the incidence of biopsy-confirmed acute rejection episodes for all randomized patients. Again, the US trial is shown on your left and the global trial is shown on your right.

For this analysis the four patients walked to follow-up in the US trial were considered as having had an acute rejection episode. The Cochran-Mantel-Haenszel analysis of the US trial shows that the incidence of acute rejection was decreased from 29.8 percent in the azathioprine group to 17 percent in the Rapamune™ 2 mg/day group and 12 percent in the Rapamune™ 5 mg/day group, respectively.

In the Global trial the incidence of biopsy-confirmed acute rejection episodes was reduced from 41.5 percent in the placebo group to 24.7 percent in the Rapamune™ 2 mg/day group, and 19.2 percent in the Rapamune™ 5 mg/day cohorts. Once again, each of these comparisons was highly statistically significant with all P-values being equal to or less than 0.003.

Our first episodes of biopsy-confirmed acute rejection were scored using the 1993 Banff classification for histologic grade by the local pathologist who was blinded to the treatment assignments. Shown here in the solid colors is the percent of patients with either a moderate, Grade II or a severe, Grade III, rejection episode.

As you can see, Rapamune™-treated patients in both trials have significantly fewer episodes scored as moderate or severe acute rejection episodes when compared to control therapies. Our P-values were less than 0.01 for Rapamune™ versus comparators.

Mild, Grade 1 acute rejection episodes are shown in the hatched areas. There were fewer of these episodes among Rapamune™-treated patients as well. Consistent with the reduced incidence of moderate and severe Grades of rejection episodes, there was a reduced use of anti-lymphocyte antibody therapies to treat the first episode of biopsy-confirmed acute rejection.

In the US trial shown on the left, this

difference was statistically significant for both Rapamune™-treated groups; namely a decrease from 12.4 percent in the azathioprine group, to 5.6 percent in the Rapamune™ 2 mg/day group, to 2.9 percent for the Rapamune™ 5 mg/day group.

In the Global study there was a low percentage of patients treated with antibody therapies; only 8.5 percent in the placebo group and four percent and 3.2 percent in the Rapamune™ 2 mg and 5 mg/day groups, respectively.

However, both Rapamune™ groups show less than half the percent of patients requiring antibody therapy, and there was a significant difference for the use of antibody therapy in the Rapamune™ 5 mg/day cohort.

These benefits were obtained with no penalty in patient or graft survival. Shown here is the one-year patient survival, including the 95 percent confidence limits. I would like to point out that there was 100 percent follow-up for this endpoint.

As you will note, the one-year patient

survival rates among all groups were high, ranging from 94.6 percent to 98.1 percent. Both Rapamune™ dose groups were associated with greater than 95 percent, one-year patient survival.

Similarly, one year graft survival rates ranged from 87.7 percent to 93.8 percent with both Rapamune™-treated cohorts shown greater than 90 percent graft survival. Again, there was 100 percent follow-up for this endpoint. Since the confidence intervals overlap none of the differences among either patient or graft survival rates were significant.

In the next three slides the rates of efficacy failure and acute rejection episodes across the prospectively defined strata, will be presented. I would like to point out that the sample size was not powered to demonstrate statistical significance across each stratum.

The US trial was the first to ever be effectively stratified upon ethnic origin. Efficacy failure for non-Black patients is shown on your left and confirms the benefit of both doses of Rapamune™ in this population with a P-value of 0.0003.

For Black patients shown on your right, there was a lower rate of efficacy failure in the 5 mg/day Rapamune™ cohort than in the 2 mg/day Rapamune™ group or the azathioprine group. The overall P-value for Black patients was 0.077.

Please recall that although the number of Black patients in each group is different, the proportion of Black patients is similar among the groups. The low rates of efficacy failure were similar for Black versus non-Black patients treated with 5 mg/day Rapamune™.

A similar pattern is observed among the rates of acute rejection episodes when stratified by ethnic origin. The overall P-value is 0.094 for Black patients. The 14.8 percent of incidence acute rejection for Black patients was similar to the 11.3 percent incidence observed among non-Black patients treated with 5 mg/day Rapamune™.

Parenthetically, these results are similar to those described after analyses of randomized trials with tacrolimus or with mycophenolate cyclosporine, both of which require higher drug doses to demonstrate

a benefit in Black patients.

As you will recall, in the Global trial patients were prospectively stratified by donor source; that is, either cadaveric or mismatched living donor. Efficacy failure at six months after transplantation for patients receiving cadaveric donor organs in the Global trial is shown on your left and demonstrates a significant difference for the 5 mg/day Rapamune™-treated cohort and an improvement with the 2 mg/day Rapamune™ treatment.

Shown on your right for patients receiving mismatched living donor organs there was a statistically significant reduction in the rates of efficacy failure for both Rapamune™-treated groups; namely from 61.3 percent to 24.5 percent with 2 mg/day Rapamune™ and 17.8 percent for 5 mg/day Rapamune™ when compared to the placebo comparator.

It should be noted that this analysis represents a conservative intention-to-treat analysis. One recipient of a living, mismatched donor organ was mistakenly stratified by the study center into the cadaveric group of the 2 mg/day cohort. When

accounting for the stratification error a supplemental analysis reveals that the efficacy failure rate between placebo and 2 mg/day Rapamune™ meets statistical significance with a P-value less than 0.05.

The rates of efficacy failure based upon the degree of HLA mismatch are shown here for the US and Global trials combined. Patients with zero to three mismatches were grouped as shown on your left, revealing a beneficial effect of both doses of Rapamune™ compared to placebo, and up to 5 mg dose of Rapamune™ when compared to azathioprine.

The pattern observed among patients with four to six HLA mismatches shown on your right, also reveals statistical significance for the Rapamune™ groups when compared to placebo but not when compared to azathioprine.

As a summary to the overall efficacy presentation, when compared to either azathioprine or placebo in combination with cyclosporine and prednisone, the pivotal studies demonstrated that the 2 mg/day and 5 mg/day doses of Rapamune™ were highly

effective to significantly reduce the rate of the primary endpoint efficacy failure during the first six months after transplantation.

Both studies demonstrated that the Rapamune™ 2 mg/day and 5 mg/day treatments significantly reduced the rates of biopsy-confirmed acute rejection episodes and biopsy-confirmed Grade II and Grade III acute rejection episodes.

Furthermore, the overall use of anti-lymphocyte antibody preparations to treat acute rejection episodes was significantly reduced in both Rapamune™-treated groups in the US trial and in the 5 mg/day Rapamune™ group in the Global trial.

Rapamune™ therapy was associated with excellent, one-year patient and graft survival. In patients of Black ethnic origin, the 5 mg/day dose of Rapamune™ but not the 2 mg/day dose reduced the incidences of both efficacy failure and acute rejection episodes.

Therefore, it seems reasonable that the 5 mg/day dose of Rapamune™ is as appropriate for Black and possibly other high-risk patient populations.

The Phase III efficacy results support the use of Rapamune™ for the proposed indication of prophylaxis of acute rejection episodes in renal allograft recipients.

I would like to thank you for the opportunity to present these interesting data and for your kind attention. Dr. Camardo will now present the safety data.

DR. CAMARDO: I'm going to complete our presentation now with safety data for Rapamune™. The majority of our data for safety come from the Phase III studies and I'm going to discuss these in the greatest detail. Additional information from other of our smaller studies will be reviewed as needed to support the interpretation of safety. Most of the analyses present data integrated from the two Phase III studies.

We combined these data since the doses of Rapamune™ were the same in the studies, the study design were similar, and in general the results were consistent between the studies, but I will point out some of the important exceptions.

You'll see data from patients followed for up to 24 months for adverse events with a median follow-up of about 15 months. I'm presenting one-year data for patients and graft survival, for infection, malignancy and laboratory parameters.

Recall that the primary endpoint of this study was six months so the safety data are additional beyond the primary endpoint. Recall that over 2500 patients received at least one dose of Rapamune™. In the Phase III trials alone, 976 patients were treated. Of the 700 patients followed for up to one year, 500 of them came from the Phase III studies.

I will review safety in this order: first, patient and graft survival; the discontinuation of blinded medication as an assessment of tolerability; the adverse events specifically related to immunosuppression; the laboratory parameters; other treatment-emergent adverse events; and finally, the safety profile in Black recipients.

The data I will show you demonstrate that with regard to the key safety parameters, the 2 mg dose presents minimal additional risk to the recipient

when compared with the control regimens used in each study. Graft and patient survival, infections, and malignancy do not differ significantly from the double and triple therapy control groups.

The side effects that do occur can be managed. The 5 mg dose is tolerated but the incidence of adverse events is higher, management of the side effects may be more of a challenge, and as Dr. Kahan has indicated, this dose should be reserved at patients for higher risk of rejection.

As you've seen in the Phase III studies already, patient survival was greater than 95 percent for the Rapamune™-treated patients for both studies combined, and graft survival was greater than 90 percent.

I want to review in some detail now, the analyses that support the conclusion that Rapamune™ has no adverse impact on graft or patient survival. Then I will review the causes of death and graft loss in each group. I remind you again, these analyses represent 100 percent follow-up for all patients at one year.

For the US study, patient survival was 98.1 percent in the azathioprine group, versus 97.2 in the 2 mg group and 96 in the 5 mg group. The differences in survival are -1 percent for Rapamune™ 2 versus azathioprine; -2.2 percent for Rapamune™ 5 mg versus azathioprine.

Both the 95 percent and 97.5 percent confidence limits include zero for both doses: range from -4.2 to +2.3 for the 2 mg dose; -5.7 to +1.4 for the 5 mg dose.

For the Global study patient survival, 94.6 percent for placebo; 96.5 percent for the 2 mg; and 95 percent for the 5 mg group. The difference in survival favors the 2 mg group by 1.9 percent and the Rapamune™ 5 mg group over placebo by 0.4 percent. Again, the 95 percent and 97.5 percent confidence limits include zero, and here range from -3.4 to 7.1 for the 2 mg group; -5.2 to 5.9 for the 5 mg group.

I believe it's reasonable to consider that equivalent survival will be demonstrated with assurance if the confidence intervals for the difference fall between 2 and -5. This is true for

both studies for the 2 mg group. For the 5 mg group some determinations of the confidence limits are just beyond this boundary condition.

The mortality rate and the causes of death for each group and for the Rapamune™ groups combined now for both studies are shown here. There is no statistically significant difference in the mortality rate or the causes of death. Vascular disease, including cardiovascular and cerebrovascular events were the most common cause of death. These are highest in the placebo group from the Global study but there is no significant difference.

There is a slightly higher mortality from infection in the Rapamune™ groups but this is not statistically significant either. There was a very low rate of death for malignancy and it is the same for all the groups.

Graft survival is shown here in the same format as I just showed you the patient survival. In the US study, 93.8 percent graft survival versus 94.7 in the 2 mg group and 92.7 in the 5 mg group. Differences favor the 2 mg group by .9 percent; favor

the azathioprine group over Rapamune™ by -1.1 percent.

The confidence limits again, include zero -- both the 95 percent and 97 percent. Range from -4.3 to 6.1 for the Rapamune™ 2 mg group; -6.6 to 4.5 for the 5 mg group. That's one lower limit here; falls outside the boundary condition.

For the Global study the rates are 87.7 percent versus 89.9 for the 2 mg group and 90.9 for the 5 mg group. Again, the difference is 2.2 percent favoring Rapamune™ over placebo at 2 mg; 3.2 percent favoring Rapamune™ 5 mg over placebo for the 5 mg group.

Confidence limits again, range here from -5.7 to +11; thus these lower limits here are just beyond the boundary condition of -5, although as you will note, graft survival was actually higher in the 2 mg group than in the placebo group from this study.

The causes of graft loss again, now combined from both studies are shown here. This illustrates that there was no unexpected, single cause of graft loss in the Rapamune™ group. The rate for

each group were comparable to one another. Death with the functioning graft was numerically highest in the placebo group from the Global study.

Acute rejection as a cause of graft loss was higher in the placebo and azathioprine groups compared with the two Rapamune™ groups. Delayed graft function or ATN as a cause of graft loss are numerically lower in the Rapamune™ group. Thrombosis as a cause of graft loss was the same for all the groups.

I want to point out that none of the differences from any of the causes of graft loss are statistically significant.

I want to review now the next category, safety information discontinuation. This slide shows patient withdrawal for efficacy failure in the solid color, for protocol violation here, and for adverse event in this striped color up here. This is from the cumulative database with a median follow-up of up to 15 months.

I want to make three points here. First, the rate for discontinuation for any cause is lowest

in the Rapamune™ 2 mg group. This is 44 percent. Second, the reasons for discontinuation are clearly different. The rate for efficacy failure is highest in the placebo and the azathioprine groups and lowest in the Rapamune™ groups.

Third, discontinuation for adverse events is highest in the Rapamune™ 5 mg group but it's about the same for the Rapamune™ 2 mg group as compared with azathioprine and placebo. In fact, when this is stratified by ethnic origin the rate for the 5 mg group is not really different for Black recipients.

But it looks as though the higher dose is somewhat less tolerated. Later I'll review the individual causes of discontinuation but I want to move on now to the next category of safety information; that's the side effects of Rapamune™ related to immunosuppression, malignancy, and infection.

All patients were followed for serious infections in this study; meaning those requiring hospitalization, whether or not they were discontinued from study medication. Furthermore, the protocol

mandated specific guidelines for the confirmation and reporting of infections in these patients.

I remind you again, anti-microbial prophylaxis for PCP was mandated by protocol for all patients and for CMV for patients at high risk for CMV infection. The results at one year show no difference in the clinically important infections for the Rapamune™ 2 mg group compared with the control therapy.

The only difference that was observed in these studies that is significant is a reported higher rate of mucosal Herpes simplex in the 5 mg group; and I'll discuss this further in a moment.

The specific opportunistic infections from these studies are listed here. There is no difference in the incidence of CMV; either generalized CMV or tissue-invasive CMV. Note that the incidence of tissue-invasive disease was in fact, very low.

Herpes zoster, Epstein-Barr virus, and Pneumocystis occurred equally in all the groups. There were three cases of PCP. These are carried in patients in whom prophylaxis had been discontinued.

As previously mentioned, Herpes simplex was reported more frequently in the 5 mg group.

Some of these were confirmed by culture but the majority were clinically diagnosed mucosal infections. These were not in general serious infections and there were no cases of Herpes esophagitis in the first year.

There was no difference among the groups in the incidence of sepsis, death from sepsis, pyelonephritis or urinary tract infection, wound infections, or pneumonia. Wound infections and pneumonia were numerically higher in the 5 mg group but the difference was not statistically significant.

The individual causes of pneumonia shown here confirm the low incidence of pneumocystis pneumonia, CMV pneumonia, and confirmed viral pneumonia. There are no statistically significant differences in bacterial pneumonia, which is a little bit higher than the other causes. No statistically significant differences for fungal pneumonia, which was very rare. And there's no difference in the incidence of microbacterial pneumonia among the four

dose groups.

Moving on to malignancy, this occurred at the same rate for all groups up to one year. I'm showing you the rates here on the top line for total malignancy. Post-transplant lymphoproliferative disorder and lymphoma were combined for this analysis.

These were somewhat more common in the 5 mg group after one year but the difference was not statistically significant from the other groups, nor were the rate and the confidence intervals around the rate inconsistent with numerous other studies in transplant recipients who received similar levels of immunosuppression.

Also this analysis includes patients who had been discontinued from Rapamune™ and were treated with other medications. The incidence of skin cancer was highest in the placebo group.

I want to show you now that the higher rate of PTLD that was observed in the combined 5 mg groups from both studies is due solely to a higher rate in the Global study: 2.3 percent in this study versus .7 percent in the US study in which the rate of

PTLD was not different among the groups. There was no increase in mortality from lymphoma or PTLD in these studies.

I want to move now to the laboratory parameters, beginning with renal function. In contrast with what I've just shown you, the data I will show you now is limited to patients who remained on therapy at each time point analyzed. Patients who discontinued from blinded medication are not included in the analyses after they discontinued.

In order to understand the effect of Rapamune™ on renal function I've included some data from pre-clinical studies, Phase II studies and renal transplant recipients treated without cyclosporine, and patients with psoriasis treated with Rapamune™.

The data from Phase III demonstrate that the mean serum creatinine for patients on therapy at one month, six months, and one year with international units shown on the left in micromoles and U.S. units shown on the right in mg/dL.

Groups are placebo, azathioprine, Rapamune™ 2 mg and Rapamune™ 5 mg combined from both

studies. The numbers in each group in the analysis at each time point are shown here. Note that all groups improved from month-1 to month-6. Second, note that mean creatinine was slightly higher in the Rapamune™-treated patients, and the differences were statistically significant.

At six months the highest mean in the 5 mg group was 160 micromole, which is about 1.8 mg/dL in US units. Third, at 12 months the mean creatinine was less than 2 mg/dL in all the groups, but there remains a statistically significant difference in the mean creatinine for the Rapamune™ groups versus the control groups.

As part of the pharmacodynamic analysis we evaluated the correlation of creatinine with sirolimus blood level drawn nearest to the measured creatinine. The lines represent data from the various time points. This is from month-1; these are from months-2 through 12. This is the creatinine on the left ordinant.

Note that there appear to be no steep change in creatinine levels even though sirolimus concentration is increased over a nearly 30-fold

range, from 1.5 ng/mL to 30 ng/mL, with the exception of the highest range at month-1.

This lack of a steep correlation suggests the possibility that the alteration of renal function may not be a direct effect of Rapamune™. And I want to show you now some additional data to support that statement.

First, Rapamune™ exerts no hemodynamically mediated effects on renal function in animal models. In this study, cyclosporine, tacrolimus, Rapamune™, or a placebo vehicle were administered to cell-depleted rats and glomerular filtration rate and renal blood flow were measured after 14 dates of treatment.

The data show that Rapamune™ is identical to vehicle and has no effect on glomerular filtration. in contrast, both cyclosporine and tacrolimus in this model clearly reduce filtration.

The same is observed for renal blood flow in blue. There was no effect of Rapamune™ by comparison with the placebo vehicle but there is a significant effect of the calcineurin inhibitors.

This study suggests that Rapamune™ does not decrease glomerular filtration or renal blood flow in this model.

Second, Rapamune™ was studied in de novo renal transplant recipients without co-administered cyclosporine in two Phase II studies. I mentioned these earlier when I was discussing the early Phase programs. These were comparative studies in which patients were randomized to receive either Rapamune™ or cyclosporine.

In one study patients received Rapamune™ or cyclosporine in combination with azathioprine and corticosteroids. In a second study patients received Rapamune™ or cyclosporine in combination with corticosteroids and mycophenolate mofetil.

In these two studies the Rapamune™ and cyclosporine groups had similar one-year graft survival. The doses of Rapamune™ that were used in this study were higher than those used in the Phase III trials. This is about 30 mg or so for the first week, then tapered over the next three months to a mean of between 6 and 9 mg/day for up to one year.

This shows the creatinine levels at months 1, 6, and 12; international units here, US units on the right, for the Rapamune™ in green and cyclosporine in red, recipients combined from both studies.

The number of patients with data at each time point are shown here at the bottom. The important observation is that the creatinine levels shown here for the combined Rapamune™ groups are lower than the combined cyclosporine groups for months 6 and 12 for patients who were maintained on the therapy with Rapamune™.

The lower value for creatinine at month-12, less than 1.5 mg/dL is statistically significant. One can compute the value for cyclosporine-treated patients at month-12.

And third, the absence of renal toxicity for Rapamune™ was confirmed in a study performed in 118 psoriasis patients randomized to Rapamune™ 1, 3 or 5 mg/m^2 per day, or a placebo for 12 weeks. This is approximately 2, 5, or 10 mg/day. Renal function in these patients was absolutely normal. Mean

creatinine was less than one mg/dL in the patients treated for 12 weeks at doses equal to or higher than those used in the Phase III studies.

Thus a Rapamune™ clinical trial database shows different effects on renal function depending on whether or not cyclosporine is co-administered. We observed normal renal function in patients with psoriasis and normal kidneys at baseline who are treated with Rapamune™ alone at up to 10 mg/day for 12 weeks.

We observed lower creatinine in transplant recipients treated with up to 10 mg/day of Rapamune™ for one year compared with cyclosporine-treated de novo recipients.

We observed higher creatinine levels in recipients of Rapamune™ in combination with cyclosporine in the Phase III program when compared with azathioprine and placebo.

I want to remind you first there was a limitation in the Phase III studies by comparison with clinical practice in transplantation. This is important because it may affect the results of the

Phase III study, specifically with regard to the renal function.

In order to contribute meaningful data by following the protocol, some of the adjustments in cyclosporine levels that would occur in actual practice could not be instituted. There were constraints on cyclosporine dose reduction in this study. Moreover, as I showed you previously, cyclosporine levels were actually at or above the upper limit of the target range so the doses were relatively high.

The data from a variety of studies -- I've shown you some examples -- indicate that Rapamune™ preserves renal blood flow and glomerular function. We have prophesied therefore, that higher creatinine in Rapamune™-treated patients in Phase III may be related to cyclosporine, not to Rapamune™ itself, unless one might reason that this could be managed by cyclosporine reduction or elimination.

I want to emphasize that this is a hypothesis. However, the hypothesis is being tested in two large studies in which 750 patients have been

enrolled.

I want to turn now to other laboratory parameters starting with the lipid effects of Rapamune™. An observation made very early in the clinical program was the effect of Rapamune™ on cholesterol and triglycerides. This is of course, not unique to Rapamune™.

Hyperlipidemia is a common program for transplant recipients related to the diseases such as diabetes that cause renal failure. It is worsened by renal insufficiency itself, by diet, obesity, lack of exercise, and it's further complicated by the lipid elevating effects of cyclosporine, corticosteroids, diuretics, and beta-blockers.

The analysis I will show you now represent mean values for patients on therapy at the specific time points. This will include all patients who did not discontinue up to that time point but it is not the same cohort for each analysis point.

The prevalence of patients with triglyceride elevation above 400 mg/dL or cholesterol above 240 mg/dL will also be presented along with the

response to therapy and the clinical consequences.

The key results of these analyses show a dose-related increase in cholesterol and triglycerides that improves with time after transplantation and can be managed with currently available therapy. The improvement is not related to the disappearance of the activity of Rapamune™ on lipids; on the contrary. The effect of Rapamune™ persists.

The most likely explanation for this is the elimination of exacerbating factors, reduction in the dose of Rapamune™ for some patients, and improved management of lipids in these patients once the complex acute post-transplant period has passed.

There were protocol guidelines for dose reduction of blinded medication, for specific lipid abnormalities, but the initiation of lipid-lowering therapy was the choice of the transplant teams. There were no guidelines for this in the protocol.

This graph shows that mean cholesterol for the population -- the units millimole here, ng/dL here -- are elevated from baseline to month-2, then decline in both the control groups, the Rapamune™ 2,

and the Rapamune™ 5 mg groups. At many of these time points the differences between Rapamune™ and the control groups are statistically significant.

By month-12, although mean cholesterol had declined in all the groups, it remained elevated above baseline for all the patients. This is not so unexpected since all the background medications have lipid side effects.

I want to show you more clearly what happens over time. This shows the mean cholesterol for the populations at months-3 and month 12; again, millimolar here, mg/dL here. These are the millimolar units. For the placebo, azathioprine and combined 2 and 5 Rapamune™ groups from both studies, to numbers of patients in the analyses are shown here.

What I want to show you is that by month-12 the means for the Rapamune™ groups had decreased from month-3. The mean cholesterol for the 2 mg group by this time point was only about .54 millimolar higher than the respective control groups. And .54 millimolar is about 20 mg/dL.

The results from the two studies

individually show improvement over the first year. In the US study by one year there were no longer any statistically significant differences between Rapamune™ and the azathioprine group. In the Global study by one year the only statistically significant difference was for the 5 mg group versus placebo.

The prevalence of elevated cholesterol was compared as well. This shows you the percent of patients with cholesterol over 240 mg/dL at months-3 in the solid and at month-12 in the hatched panel. Note that it is high in all the groups at all the time points, but the Rapamune™ groups clearly had a higher prevalence of cholesterol above 240.

Again, this decreases over time in the Rapamune™ 2 and in the Rapamune™ 5 mg group, so that by one year there is an excess of only about 10 to 15 percent of patients with elevated cholesterol in the Rapamune™ 2 mg group versus the azathioprine and placebo groups by one year.

I want to point out this is not an artifact of discontinuation. It was confirmed by our cohort analyses and as you will see, lipid elevation

in and of itself was a rare cause for discontinuation, especially in the 2 mg group.

Patients in all the groups respond to cholesterol lowering therapy. This shows the mean cholesterol in a subset of patients: 25 from the two control groups, 84 from the Rapamune™ 2 mg group, 99 from the Rapamune™ 5 mg group. Cholesterol levels were available both before initiation of therapy here in magenta, and during cholesterol therapy, shown here in blue.

Point out, this is not the total of patients treated; it's just those patients with complete lipid data, both before and during treatment. And as I mentioned, these treatments were initiated by the transplant teams, not mandated by the protocol.

The reductions are statistically significant in each group. The magnitudes are similar as shown here at the bottom. This data make it reasonable for us to conclude that Rapamune™ in and of itself does not interfere with the treatment of cholesterol with statins.

All these patients were taking

cyclosporine. Buffer statin were most likely used with the usual cautions at the lower doses to be used for people taking cyclosporine. It's not surprising that serious side effects of these drugs were avoided.

I want to move on to the triglycerides. Mean triglycerides were elevated over baseline in both the Rapamune™ and the control groups but there is only a small elevation in the control patients. There are significant differences for both the 5 and the 2 mg dose compared with the control groups, but the mean triglyceride improves somewhat over time.

To show this more clearly here are the mean values at month-3 and month-12. Again, for placebo, azathioprine, Rapamune™ 2 mg, Rapamune™ 5 mg, millimolars here, mg/dL here, for month-3 and month-12. The number of patients in the analyses are shown here.

By month-12 the mean for the Rapamune™ groups had decreased somewhat. The difference between the control groups and the Rapamune™-treated 2 mg group at month-12 had narrowed to about .75 millimolar. This is about 60 mg/dL. The difference

was clearly greater for the 5 mg group. Just remind you again, this effect is dose-related.

The results of the two studies were consistent in the US study by 12 months. There was no statistically significant difference between the Rapamune™ and azathioprine groups for mean triglycerides. In the Global study only the 5 mg group was significantly higher than placebo.

Triglyceride elevation above 400 mg/dL was more common in the Rapamune™ groups. It was around 20 percent to 30 percent as compared with ten percent or less for the control groups in these studies at months-3 and month-12.

The percentage of patients with elevated triglycerides decreased over time in the Rapamune™ groups as shown here for the comparison for 3 to 12 months. For the 2 mg group at one year there was in excess of about 5 percent of patients with triglycerides over 400 mg/dL. The percentage is higher from the 5 mg group, both month-3 and month-12.

Fibrate therapy will lower triglycerides in the control and Rapamune™ groups. This shows the

triglycerides in a subset of patients for whom complete data are available; before treatment was initiated in magenta and during fibrate treatment in blue; millimoles here, mg/dL here.

The numbers are six from the control groups, 25 patients from the Rapamune™ 2 mg group, and 31 patients from the Rapamune™ 5 mg group. This is the mean triglyceride level. Fibrates, lower triglycerides in these populations in both the control and the Rapamune™-treated patients. The decrease is somewhat more substantial for the 5 mg dose.

This is not a surprise these triglycerides were higher. However, I should point out that the mean probably represents the population here because some patients don't respond to fibrates at all.

However, as shown in the next slide, many individual patients, shown in yellow, do respond to fibrates dramatically and rapidly: 23 of the 31 patients on the 5 mg dose responded to fibrate therapy but others show in here in blue may be refractory to fibrate therapy; may require some additional interventions, may require a decrease in the dose of

Rapamune™, or may not tolerate Rapamune™ at all.

There were very few discontinuations for hyperlipidemia. In the 2 mg group, 0.4 percent; 2.5 percent in the Rapamune™ 5 mg group. It's consistent with the dose dependence of this effect. There was a low incidence of pancreatitis in all the treatment groups. I believe this is in the briefing document.

In this database no patient with high triglycerides developed pancreatitis that would be attributed to the high triglycerides. That is, that acute and unexpected complication in these patients related to triglyceride elevation appears to be small. After one year of follow-up there was no increase in the incidence of cardiovascular events in the Rapamune™-treated patients versus the control patients.

In summary, there is a dose-related, reversible increase in cholesterol in the majority of patients treated with cyclosporine and steroids. Rapamune™ has additional effects on cholesterol. Triglyceride elevation is less common in transplant recipients, thus the effect of Rapamune™ on

triglycerides is more obvious. The elevations of lipids are manageable.

Cholesterol and triglycerides improve with time possibly due to the decrease in cyclosporine and steroid doses, the use of lipid-lowering drugs, improvement in diet and exercise, and the use of standard lipid treatments with are effective and tolerated.

Specifically, there were no cases of rhabdomyolysis in the Rapamune™-treated patients. One case was observed in the trials. This occurred in the patient in the azathioprine group. Ongoing metabolite studies indicate that the effect of Rapamune™ includes elevation of both LDL and VLDL. HDL is not changed. The mechanism may be related to inhibition of lipoprotein lipase activity and delayed clearance of lipoprotein remnants.

I want to discuss the hematology parameters now. With regard to hematology the effects of Rapamune™ on bone marrow-derived cells are consistent with the biological activity of Rapamune™. Small decreases in platelets, red cells in leukocytes

are observed, but most important, there is no evidence of chronic or irreversible marrow dysfunction.

Frank thrombocytopenia was rare, Rapamune™ has a smaller effect on leukocytes than azathioprine. As an example, discontinuation for leukopenia was 4.4 percent for azathioprine versus less than one percent for patients on Rapamune™. Mean hemoglobin for the groups was greater than 13 g/dL by month-12.

In the interests of time I will show you only the mean values for the populations and the main conclusions. If there are specific questions we can address them later. The on therapy platelet counts are shown here for placebo, azathioprine, and the combined Rapamune™ 2 and 5 mg groups.

Here are the actual platelet counts for each group, the means. Here are the number of patients in the analysis at these time points. Keep in mind what follows: first, the counts are lower at all time points for the Rapamune™-treated patients compared with placebo. These are dose-related and statistically significant.

Second, the decrease from the control groups is actually very modest. The actual platelet counts are shown here and even though there are statistically significant differences the mean values stay within a clinically acceptable range for the population.

Third, there is no progressive decrease over time; rather the counts are stable if patients continued on Rapamune™ up to one year. We observed also that in patients with low platelet counts in whom the dose of Rapamune™ was reduced or the drug discontinued, the platelet counts improved.

For most patients, based on the results of these trials, no intervention is required to manage platelet count abnormalities. If the counts are low enough to pose a risk the dose of Rapamune™ can be reduced; the platelets will return to normal.

The mean leukocytes for all treatment groups were within clinically acceptable ranges. This slide uses the same cclors in the same order. Shows that the lowest leukocyte counts were observed in the patients treated with azathioprine. This difference

is statistically significant at month-6 and month-12.

More important, for the entire database no patient presented with a neutrophil count of less than 1000, thus there was not a single case of severe neutropenia. As with platelets, this side effect appears to require no specific intervention, is not likely to be a cause of discontinuation of Rapamune™ in clinical practice.

Finally, hemoglobin was similar among the treatment groups and improved in all the groups from month-1 to month-6. The mean values were highest in the placebo group, lowest for the 5 mg group, consistent with the dose-related effect of Rapamune™ on red cells. But the decrease is limited to about one g/dL for the population or 10 g/L.

Note also that at months-12 the mean hemoglobin in all the groups was greater than 13. Furthermore, anemia rarely required discontinuation. No patients were discontinued for anemia in the control or 2 mg Rapamune™ groups; 3 patients in the 5 mg group were discontinued for anemia.

I want to turn now to other events not

considered to be related to immunosuppression but nevertheless considered to be adverse events. These again, represent combined data from both studies. I'll show you the rates, emphasize the statistically significant differences resulting from the combined analyses, then show specific events for which the outcome was different between the two studies.

I should emphasize, these represent cumulative data with a median follow-up of 15 months; thus again, these are data beyond the primary endpoint as submitted in the NDA in December.

Adverse events other than infection that occurred in greater than 20 percent of patients are shown in these slides. There are no differences for abdominal pain, chest pain, dyspnea, headache, tremor, or elevated creatinine. There was a higher incidence of reported hypercholesterolemia and hyperlipemia in the 2 and 5 mg groups compared with control.

Hypertension was significantly less frequent in the azathioprine group as compared with placebo or RAPA 2 and RAPA 5 mg. There is a somewhat higher incidence of arthralgia, peripheral edema,

diarrhea, and thrombocytopenia in the 5 mg group alone.

I want to point out there was no particular definition of thrombocytopenia here. This term includes reports of reduced platelets; likely would not meet criteria for actual thrombocytopenia.

There was more dyspepsia in the placebo group, more leukopenia and vomiting in the azathioprine group, more hyperkalemia in the placebo and azathioprine groups compared with the Rapamune™.

This slide shows adverse events that occurred in more than five percent of patients but more than 20 percent. Note there are no statistically significant differences for diabetes, liver function test abnormalities, abnormal healing.

There is a slightly increased occurrence of hypokalemia, hirsutism, an increased LDH in the 5 mg group compared to the control groups. Epistaxis, rash, tachycardia, and lymphocele are also more common in the Rapamune™ 2 and Rapamune™ 5 mg groups, and there is a slight dose relationship here.

These are the adverse events for which one

or both doses of Rapamune™ were significantly higher than the control patients in both studies; that is, the studies are consistent. This includes hyperlipemia, tachycardia, lymphocele, rash, epistaxis, hyperkalemia, and pharmacytopenia. Note for these two only the 5 mg group was significantly higher than the control groups.

These are adverse events for which the two studies are inconsistent. Only one study showing a significant increase in the Rapamune™ versus the respective control. In the US study, hypertension, hirsutism and diarrhea were more common in control but not in the Global study.

In the Global study, hypercholesterolemia, anemia and arthralgia were more frequent than in the control. This didn't occur in the US study. Note also that four of these -- hirsutism, diarrhea, anemia, and arthralgia -- were more frequent only in the higher dose group, the 5 mg group.

The discontinuations for adverse events for which there is a statistically significant difference between the groups are shown here. The

rate of withdrawal for adverse events is the same for the placebo group, the azathioprine and the Rapamune™ 2 mg groups.

There is a statistically significant increase in discontinuation for the 5 mg group for which hemolytic uremia syndrome, hyperlipemia, and hypercholesterolemia were the reasons for withdrawal in four, three, and two percent of patients.

Transplant rejection caused significantly higher withdrawal in five percent of patients on placebo, as did increased AST on placebo.

Leukopenia, nausea, and vomiting caused significantly higher rates of discontinuation in the azathioprine group compared with the other groups. I want to point out finally, that there was no single cause of discontinuation that was significantly highest in the Rapamune™ 2 mg group.

My final section addresses the particular issues related to the use of the 5 mg dose. As shown in this slide from Dr. Kahan's presentation of efficacy, the 5 mg dose but not the 2 mg dose appears to lower the rate of efficacy failure and acute