DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# ANTIVIRAL DRUGS ADVISORY COMMITTEE

## IMMUNOSUPPRESSIVE DRUGS SUBCOMMITTEE MEETING

NDA 21-083 Rapamune (sirolimus) Oral Solution

Cyclosporine Withdrawal Maintenance Regimen

Thursday, January 24, 2002

8:30 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

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Tara P. Turner, Pharm.D., Executive Secretary

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Rosemary Tiernan, M.D., M.P.H.

C O N T E N T S

P R O C E E D I N G S

CALL TO ORDER

DR. ENGLUND: Good morning, everyone. Welcome to the Subcommittee for Immunosuppressants Meeting of the Antiviral Drugs Advisory Committee group. I hope you are all in the right place here.

My name is Janet Englund. I am the Acting Chairperson for this session. I am from the University of Chicago and am a member of the Antiviral Drugs Advisory Committee. We are very grateful to have such knowledgeable guests and voting members here to help us with the discussion today.

At this point in time, I think what we can do is ask everyone at the table to introduce themselves, their name and their affiliation. Perhaps, if we could start at the very back, to my left.

DR. MANNON: I am Dr. Roslyn Mannon. I am the transplant nephrologist at NIH and I am the Medical Director of Transplantation at the NIDDK Organ Transplant Program where we do kidney, kidney-pancreas, pancreas transplants and, for the past year and a half, have had extensive use in rapamycin.

DR. HUNSICKER: Larry Hunsicker from the University of Iowa. I am a transplant nephrologist also. I am a clinical trialist. I think that suffices.

MR. LAWRENCE: William Lawrence. I am an attorney. I am Director of Patient Affairs for the United Network for Organ Sharing. I am a liver recipient of some fourteen years.

DR. AUCHINCLOSS: My name is Hugh Auchincloss. I am a transplant surgeon at Harvard.

DR. ABERNETHY: Darrell Abernethy, National Institute on Aging. I am a clinical pharmacologist.

DR. DeGRUTTOLA: Victor DeGruttola, statistician at Harvard School of Public Health.

DR. TURNER: Tara Turner, Executive Secretary for the Committee.

DR. EBERT: Steven Ebert. I am an infectious diseases pharmacist at Meriter Hospital and Professor of Pharmacy at the University of Wisconsin.

DR. SUTHANTHIRAN: Mannikam Suthanthiran. I am Chief of Transplantation Medicine at New York Hospital, Cornell Medical Center.

DR. SHAPIRO: I am Ron Shapiro. I am

Director of Renal Transplantation at the Thomas E. Stassel Transplantation Institute at the University of Pittsburgh.

DR. TIERNAN: Rosemary Tiernan, medical reviewer, FDA.

DR. CAVAILLE-COLL: Marc Cavaille-Coll, medical team leader, Division of Special Pathogen and Immunologic Drug Products, FDA.

DR. ALBRECHT: I am Renata Albrecht, Acting Director, Division of Special Pathogen and Immunologic Drug Products.

DR. ENGLUND: Thank you. Welcome, everyone. I would like now to have Tara Turner, the Executive Secretary, read the conflict of interest statement.

Conflict of Interest Statement

DR. TURNER: Thank you. 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 even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for

Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. Ron Shapiro has been granted waivers under 18 USC 208(b)(3) and 21 USC 355(n)(4) amendment of Section 505 of the Food and Drug Administration Modernization Act for his lectures supported by a competitor on unrelated matters. He receives more than $10,000 a year.

Dr. Janet Englund has been granted a waiver under 18 USC 208(b)(3) for her consulting for a competitor on unrelated matters. She receives less than $10,000 a year.

Dr. Lawrence Hunsicker has been granted limited waivers allowing his participation without voting privileges under 18 USC 208(b)(3) and 21 USC 355(n)(4) amendment of Section 505 of the Food and Drug Modernization Act for three grants and contracts to his employer. The first is a grant from the federal government and a competitor involving competing products funded for less than $100,000 per year. The second is a contract from a competitor involving competing products and the product at issue. However, Dr. Hunsicker is

unaware of the details of this contract. The third is a grant from the federal government involving competing products which receives funding greater than $300,000 per year.

A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30, of the Parklawn Building. 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.

Thank you.

DR. ENGLUND: Thank you. I think we have Dr. Johnson here with us, if you want to introduce yourself.

DR. JOHNSON: I apologize for the tardiness. Sometimes, it is hard when you have a

meeting that is at home. I am Lynt Johnson. I am the Director of Transplantation at Georgetown University Medical Center here in Washington, D.C.

DR. ENGLUND: Thank you. Glad you're here.

At this point, I would like Dr. Renata Albrecht, who is Acting Director of the Division of Special Pathogens and Immunological Drug Products at the FDA, to give us some opening remarks.

FDA Introductory Remarks

DR. ALBRECHT: Thank you, Dr. Englund. On behalf of the Division, I would like to extend a welcome to you, Dr. Englund, to the members of the committee, our distinguished guests and representatives from Wyeth-Ayerst. We very much appreciate your being here today to discuss a new Rapamune regimen in the management of patients with renal transplants.

Specifically, this is the first time the agency and the committee has been asked to consider a regimen, a maintenance regimen, in which cyclosporine is withdrawn as the Rapamune dose is increased to target blood levels.

Many of you will recall the original application for Rapamune was brought before this

subcommittee in the summer of 1999 and resulted in the approval of Rapamune, the 2 milligram dose, in combination with cyclosporine and steroids for maintenance. Results were also presented for the 5 milligram dose which was interpreted as showing similar efficacy and increased toxicity.

One of the noteworthy findings from those original studies was the reduction in glomerular-filtration rate noted in the Rapamune, cyclosporine and corticosteroid arm relative to the other arm. This raised questions about long-term consequences of the regimen and also prompted the agency to ask the sponsor to conduct some phase IV studies.

Now the company has submitted to us a supplemental application containing studies in which many patients were randomized to the cyclosporine-withdrawal arm and had the Rapamune doses increased. Questions that arise are whether the cyclosporine withdrawal may have affected efficacy either favorably or unfavorably.

The other questions are regarding safety. Are there changes in the safety profile. Has the GFR been preserved? Are there other new toxicities that may be introduced with this new regimen?

These are some of the questions that we will be asking you to deliberate during the course of this meeting.

Finally, I would like to express our appreciation to Wyeth for putting forth a great effort in planning in bringing forth this application to the committee for discussion. I would also like to recognize some of my colleagues, Dr. Marc Cavaille-Coll, Rosemary Tiernan, Karen Higgins and Cheryl Dixon for the intense effort they have put forth into this project.

In the first part of the morning, Wyeth will present a number of talks on the clinical and pharmacokinetic findings from their studies. This will be followed by a presentation by Dr. Rosemary Tiernan. Finally, as I mentioned, we do have a number of questions that we would like the committee to deliberate and give us guidance on this application and on issues relative to clinical-study endpoints.

With that, thank you and I will return it to you, Dr. Englund.

DR. ENGLUND: Thank you. At this point, I think I would like to introduce Randall Brenner from Wyeth-Ayerst Research to start your

presentation.

Sponsor Presentation--Wyeth-Ayerst Research

Introduction

DR. BRENNER: Good morning, everyone.

[Slide.]

I am Randy Brenner from the Regulatory Affairs Department at Wyeth-Ayerst. On behalf of our organization, we are pleased to have this opportunity today to review the data supporting our supplemental NDA for the cyclosporine elimination indication for Rapamune for use in renal-transplant patients.

[Slide.]

Our presentation today has the following agenda. Upon completion of my brief introductory remarks, Dr. John Neylan will discuss the need for a calcineurin-inhibitor-free immunosuppressive regimen in renal-transplant patients. He will review in detail the designs of our pivotal-study Protocol 310 and a supportive phase II study Protocol 212 and provide a review of the collective efficacy and safety data from these studies.

Following Dr. Neylan, Dr. James Zimmerman will review the pharmacokinetics of Rapamune in concentration-controlled trials and therapeutic

drug monitoring in this patient population.

For a conclusion, Dr. Neylan will return and summarize the results presented today and address any questions you may have.

[Slide.]

The oral solution formulation of Rapamune was first approved in the United States in September of 1999. This application received a priority review from FDA and was presented to this advisory committee in July of 1999.

The approved package insert recommends fixed dosing of this product in combination with cyclosporine. Specifically, a 6 milligram loading dose followed by a 2 milligram fixed daily dose is recommended for most patients. A 5 milligram dose has also been approved.

Immediately following approval of the oral solution formulation, an application requesting approval of a tablet formulation was submitted to FDA. The 1 milligram tablet, which was approved in August of 2000, provided significant advantages over the oral solution in terms of patient convenience while not compromising safety or efficacy.

[Slide.]

The original advisory committee presentation was supported by two phase II pivotal studies, Protocols 301 and 302. These studies demonstrated that, when used in combination with cyclosporine, patients receiving fixed doses of Rapamune had significantly lower rates of acute rejection at less than 18 percent while maintaining excellent patient and graft survival at greater than 95 and 90 percent respectively.

As such, this committee voted unanimously that this product was safe and efficacious. One of the more important issues discussed in detail was the unexpected impact of the Rapamune-cyclosporine combination on renal function. As a result, this committee and the FDA recommended that Wyeth further evaluate this finding.

We were optimistic that we could demonstrate that the observed renal effects in Protocols 301 and 302 were due to the exacerbation of cyclosporine toxicity and were not directly related to Rapamune.

[Slide.]

To demonstrate this, we looked at the information we knew from our phase III pivotal studies, Protocols 310 and 302, which used fixed

dosing of Rapamune in combination with cyclosporine. We also looked at information we knew from additional phase II studies which used Rapamune as base therapy demonstrating a favorably safety profile with significant improvements in renal function.

This was further supported by animal data demonstrating Rapamune to be nonnephrotoxic and an effective immunosuppressive agent when evaluated alone. Rapamune's inherent absence of nephrotoxicity is what makes a calcineurin-inhibitor-free regimen with this product potentially so beneficial to renal-transplant patients.

As a result, we designed the current registration studies, Protocols 212 and 310. These studies evaluated the currently approved combination of Rapamune plus cyclosporine versus a group of patients that had cyclosporine eliminated from the immunosuppressive regimen two or three months after transplantation.

Additional details regarding the designs of these studies will be presented by Dr. Neylan in the design portion of this presentation.

[Slide.]

Protocols 212 and 310, the studies in the current application, demonstrate equivalent efficacy with excellent patient and graft survival with an improvement in safety specifically in regard to renal function and blood pressure. Importantly, despite a difference in the number of acute-rejection episodes immediately following cyclosporine elimination, by month 12, there were similar rates of acute-rejection episodes in both arms.

Dr. Neylan will relate the impact of acute rejection immediately following cyclosporine elimination as it relates to severity, long-term patient and graft survival and the impact on renal function.

[Slide.]

The application currently under review and in front of this committee today seeks approval of an indication that will allow for the elimination of cyclosporine from the immunosuppressive regimen. The Rapamune dosing for this new indication recommends fixed dosing for the initial post-transplant period.

At the time of cyclosporine withdrawal, at two to four months post-transplantation, Rapamune

dosing will be based on trough concentration levels within a recommended range. As this new dosing will require patient dosing utilizing trough concentration levels, therapeutic drug monitoring will now be required.

Dr. Zimmerman will discuss therapeutic drug monitoring in detail during his presentation.

[Slide.]

As a reminder, Rapamune is currently indicated in use in combination with cyclosporine. The currently approved indication is provided here. Rapamune is indicated for the prophylaxis of organ rejection in patients receiving rental transplants. It is recommended that Rapamune be used in a regimen with cyclosporine and corticosteroids.

You will see today that the results of Studies 212 and 310 provide physicians with an alternate dosing regimen for Rapamune which provides acceptable immunosuppressive while preserving renal function. As such, we seek approval of an indication provided here in which Rapamune is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids.

Cyclosporine withdrawal should be considered two to four months after transplantation.

This concludes my introduction. I would now like to introduce Dr. John Neylan, the Vice President of Clinical Research and Development for Wyeth-Ayerst.

Overview

DR. NEYLAN: Thank you Randy, and good morning.

[Slide.]

As Mr. Brenner told you, Rapamune was recommended for approval by this committee in 1999 in combination with cyclosporine for the prevention of rejection in renal-transplant patients. The registration of this product has provided new opportunities to advance immunosuppressive therapy and improve patient outcomes.

We are here today to provide additional data which will allow transplant physicians new opportunities to build upon this success, improve graft function and potentially extend the life of transplant kidneys.

[Slide.]

While the addition of new drugs has decreased the incidence of acute rejection and

improved graft survival in the short term, long-term outcomes remains suboptimal. Indeed, most patients must continue to expect that their transplants will fail within a decade.

In most cases, this graft failure will be secondary to a deterioration, progressive over time, in renal function.

[Slide.]

Calcineurin inhibition, while providing effective immunosuppressive, has long been associated with time and dosage-dependent toxicities that may lead to chronic allograft nephropathy. This nephrotoxic injury has been reported in up to 65 percent of renal, liver, heart and bone-marrow transplant recipients and has been directly implicated in causing end-stage renal disease in up to 10 percent of nonrenal solid-organ recipients.

It is not surprising, then, that, since 1983 and the introduction of cyclosporine, clinicians have continued in their quest to eliminate nephrotoxicity. Our goal today is to provide data to convince you that patients will benefit from withdrawal of cyclosporine and maintenance therapy with Rapamune. That is the

single objective of the current studies.

[Slide.]

Rapamune, through its distinct biologic activity and non nephrotoxic profile, offers the opportunity to provide a new cornerstone to immunosuppressive regimens. Although many of you are familiar with the mechanism of action, I will briefly review it now.

[Slide.]

Rapamune is a novel drug, neither a calcineurin inhibitor nor an antimetabolite. It has a unique cellular target, mTOR, the mammalian target of rapamycin. mTOR is a protein kinase which is critical for cell-cycle progression and cell proliferation. Rapamune blocks mTOR. This action blocks cytokine-mediated cell proliferation in T-cells, B-cells and mesenchymal cells including smooth-muscle cells.

[Slide.]

All known therapeutic effects of Rapamune result from inhibition of mTOR. Critical pathways affected by Rapamune include the following. One, activation of translation for specific messenger RNAs coding for cell-cycle proteins. Two, activation of cyclin-dependent kinases required for

coordinated DNA synthesis. Three, synthesis of specific ribosomal proteins required for cell-cycle progression.

The interaction of Rapamune with mTOR is specific and it is reversible and, importantly, Rapamune is not cytotoxic. In summary, the biologic activity of Rapamune as an inhibitor of cell-cycle progression is consistent with both the immunosuppressive and antiproliferative effects of the molecule.

[Slide.]

Next, we will review the data supporting the design of the current registration trials. This includes the utility and outcome seen when Rapamune is administered with cyclosporine to renal-transplant recipients. In addition, data will be presented from clinical studies in which Rapamune was utilized as a prophylactic agent in renal-transplant patients.

Finally, data will be presented in which Rapamune was utilized as primary therapy for recalcitrant psoriasis.

[Slide.]

In two phase III blinded trials comprising some 1300 patients, Rapamune at 2 milligrams per

day or 5 milligrams per day was coadministered with cyclosporine and corticosteroids and compared with either placebo or azathioprine controls.

The Rapamune treatment groups proved to have low rates of acute rejection and twelve-month patient and graft survival was excellent. However, an unanticipated finding in the unblinding of these studies was the somewhat higher mean serum creatinines in the Rapamune-treated patients.

Data from other trials with Rapamune had suggested that the drug was not inherently nephrotoxic. Thus, the change in renal function in these studies was considered to be secondary to an exacerbation of cyclosporine toxicity and not directly related to Rapamune.

[Slide.]

The absence of nephrotoxicity is supported by data obtained from two phase II trials in which Rapamune was utilized as primary therapy in the absence of cyclosporine. In one trial, study 207, patients were randomized to receive either Rapamune or cyclosporine in combination with azathioprine and corticosteroids.

In the second trial, study 210, patients received either Rapamune or cyclosporine with

concomitant mycophenolate mofetil and corticosteroids.

[Slide.]

Pooled data from these studies demonstrated that Rapamune and cyclosporine had similar benefits in the prevention of acute rejection and two-year patient and graft survival but were associated with very different effects on renal function.

Shown here are statistically significant improvements in both creatinine and calculated glomerular filtration rates in the Rapamune-treated patients. These improvements were seen early and were sustained over 24 months of follow up.

[Slide.]

In psoriatic patients, Rapamune as monotherapy similarly demonstrated no adverse effects on renal function. Patients with recalcitrant psoriasis were administered Rapamune monotherapy at doses of 1, 3 and 5 milligrams per meter squared per day and compared with placebo-treated patients. There were no differences seen in mean serum creatinines following twelve weeks of therapy in any of the treatment groups even when Rapamune was

administered at doses as high as 10 milligrams per day.

[Slide.]

In summary, when Rapamune was administered in two phase III trials with concomitant cyclosporine treatment, low rates of acute rejection but higher serum-creatinine concentrations were observed compared to control therapies. When Rapamune was administered to renal-transplant patients as primary therapy for up to 24 months in doses ranging from 6 to 9 milligrams per day, these patients enjoyed similar patient and graft survival but had lower serum creatinines and higher glomerular-filtration rates compared to cyclosporine-treated patients.

Rapamune administered as monotherapy to patients with recalcitrant psoriasis at doses of up to 10 milligrams per day had no adverse impact upon renal function. These collective data demonstrated the clinical utility of Rapamune in a variety of settings. While the combination of Rapamune plus cyclosporine resulted in improved rejection outcomes, the changes in renal function were in clear contrast to studies in which Rapamune was used without concomitant cyclosporine.

Design of Clinical Studies

DR. NEYLAN: These collective observations led us to conduct trials of Rapamune-based therapy to test the benefit of cyclosporine elimination.

[Slide.]

We worked closely with over 60 investigators worldwide to develop studies that would test the hypothesis that Rapamune-based therapy could replace long-term cyclosporine-based therapy.

[Slide.]

Since the introduction of cyclosporine, numerous trials have been conducted to examine whether this agent could be safely withdrawn from long-term maintenance regimens. Many such studies were based on a classic elimination strategy in which immunosuppression was maximized early on for its potential benefits in the prophylaxis of acute rejection with subsequent elimination of cyclosporine in the maintenance phase to decrease long-term toxicity.

[Slide.]

Studies 310 and 212 were modeled after designs tested in previous elimination trials. Specifically, all of the patients were treated for

the first two to three months with a regimen consisting of Rapamune plus cyclosporine and corticosteroids to maximize freedom from rejection during this period of greatest immunologic risk.

[Slide.]

As we previously demonstrated in two large pivotal trials, Rapamune, in combination with cyclosporine, provides one of the lowest rates of acute rejection in this early post-operative period when compared with other immunosuppressive regimens.

Following the period of initial risk, patients in the control groups continue to receive combination therapy with cyclosporine while patients in the treatment arms had cyclosporine withdrawn from regimen and concentration-control Rapamune continued during the maintenance phase. The comparison of these regimens allowed us to examine the incidence of acute rejection when cyclosporine was withdrawn and to identify differences in the safety profiles following the elimination of cyclosporine.

The pivotal phase III trial in this application is study 310. It is supported with data from Study 212, a smaller phase II trial.

Both trials were open label, controlled, randomized and multicenter. Study 310 was conducted in 57 centers in Australia, Canada and Europe and included a total of 525 patients.

These patients were either primary or secondary recipients of renal allografts and received donor organs from either cadaveric or HLA-mismatched living donors. Randomization in this trial occurred at Month 3.

In Study 212 conducted in 17 centers in the U.S. and Europe, 246 patients were enrolled. These patients were recipients of primary renal allografts from cadaveric donors with randomization occurring Days 2 through 7 following transplantation. It is important to note that, in both studies, all centers were required to follow the patients for the full duration of the study for the occurrence of acute rejection, graft survival, patient survival and serious adverse events even if these patients discontinued study medication.

[Slide.]

The primary endpoints of the two studies differed. study 310 was powered for equivalent graft survival at one year while study 212 was powered to demonstrate a significant difference in

renal function in a population of patients who remained rejection free and on therapy at six months following transplantation. For those studies, multiple secondary endpoints were examined.

[Slide.]

For study 310, major secondary endpoints included patient survival, the incidence of biopsy-confirmed acute rejection, renal function, efficacy failure and treatment failure. For study 212, major secondary endpoints included patient and graft survival, the incidence of biopsy-confirmed acute rejection, renal function beyond six months and treatment failure.

[Slide.]

Exclusion criteria for randomization were slightly different for the two studies. In study 310, all enrolled patients went on to randomization at month 3 with the following exceptions. Patients were excluded from randomization if they had a Banff grade III acute rejection or vascular rejection during the preceding four weeks.

Patients were excluded if they were dialysis-dependent at the time of randomization or had a serum creatinine in excess of 4.5 milligrams

per deciliter. Finally, patients were excluded if, in the opinion of the study investigator, they had the inadequate renal function to continue in the trial.

For study 212, all enrolled patients were randomized at days 2 through 7 with the following exceptions. Patients were not randomized if, in the opinion of the investigator, they had inadequate renal function within the first 48 hours following transplantation or had ongoing acute tubular necrosis or delayed graft function persisting at day 7 post transplant.

[Slide.]

In total, studies 310 and 212 included 771 patients. Of the 525 patients enrolled in study 310, 215 were randomized to the Rapamune plus cyclosporine group and 215 were randomized to the Rapamune group. 95 patients were not eligible for randomization. In study 212, 246 patients were enrolled and 97 were randomized to the cyclosporine plus Rapamune group and 100 were randomly assigned to the Rapamune group. 49 patients were not eligible for randomization. However, in study 212, the nonrandomized patients were permitted to receive Rapamune at a dose of up to 5 milligrams

per day along with cyclosporine. These patients continued to have follow up through month 12.

Note the color scheme used in this slide and throughout the remainder of the presentation. The Rapamune plus cyclosporine group is shown in red and the Rapamune group is depicted in purple.

[Slide.]

In study 310, a total of 525 patients were enrolled and were administered a regimen consisting of a single loading dose of 6 milligrams of Rapamune followed by a fixed dose of 2 milligrams per day. Cyclosporine was coadministered to maintain trough concentrations of 200 to 400 nanograms per ml for the first month followed by a gradual reduction through month 3.

At month 3, patients were randomly assigned to one of two treatment groups. 215 patients were randomly assigned to the Rapamune plus cyclosporine group. Patients in this group continued to receive fixed doses of Rapamune at 2 milligrams per day. Cyclosporine was gradually tapered for the specified ranges for the duration of the study period.

215 patients were also randomly assigned to the Rapamune group. This group of patients

received doses of Rapamune to maintain a sirolimus trough concentration range of 20 to 30 nanograms per ml from the time of randomization through the end of month 12. Thereafter, sirolimus trough concentrations remained at 15 to 25 nanograms per ml for the duration of the study.

After randomization, patients had the dose of cyclosporine tapered by 25 percent per week and cyclosporine was to be completely eliminated from the regimen within four weeks time. Patients in both randomized groups received standard tapering doses of corticosteroids.

[Slide.]

In study 212, 246 patients were randomly assigned to one of the two treatment groups. 97 were randomly assigned to the Rapamune plus cyclosporine group. Patients in this group were administered a regimen consisting of a single loading dose of Rapamune followed by a fixed dose of 2 milligrams per day.

Cyclosporine was coadministered to maintain trough concentration ranges of 200 to 400 nanograms per milligram for the first month and was gradually tapered to the specified ranges for the duration of the treatment period. 100 patients

were assigned to the Rapamune group. The patients in this group were administered a regimen consisting of fixed doses of Rapamune at 20 milligrams daily for the first three days followed by 10 milligrams daily through day 10.

Thereafter, sirolimus trough concentrations were maintained at a target range of 10 to 20 nanograms per milligram for the duration of the study period. Patients also continued to receive reduced doses of cyclosporine for the first month after randomization at a concentration range of 100 to 175 nanograms per milligram and were then tapered down to 100 to 150 nanograms per milligram through month 2.

The dose of cyclosporine was further tapered by 25 percent per week and cyclosporine was to be completely eliminated from the regimen by the end of month 3. The patients in this study also received standard tapering doses of corticosteroids.

[Slide.]

It is important to note that the efficacy and safety data from studies 310 and 212 were deliberately not integrated. The designs of the two studies, while similar, were distinct in

several important features. Time of randomization differed. Study 310 allowed us to maximize the opportunity to compare like patients at the onset of cyclosporine withdrawal.

Different target sirolimus and cyclosporine trough concentrations were also utilized in the two studies. Complete safety and efficacy data through 12 months will be presented for both studies. For study 310, cumulative safety data are presented for all patients through month 15 with limited data being available through month 24.

Efficacy Review

[Slide.]

DR. NEYLAN: The efficacy comparisons in each study will be now be reviewed.i

[Slide.]

This slide shows the similar distribution of key demographic variables among patients enrolled in study 310. Comparing the features of all enrolled patients to that of the randomized groups shows only a slightly higher rate of delayed graft function, shown here.

The groups were otherwise well matched for gender, ethnic origin, age, receipt of a first or

second allograft, ischemia time and degree of HLA mismatch. When compared to the UNOS database, the race disparity is obvious.

But other features are similar including rates of delayed graft function in the study groups that were slightly greater than that of the U.S. renal transplant population. Though not shown on this slide, there were also no differences observed in donor characteristics including donor source, ethnic origin or age.

[Slide.]

The intent-to-treat analysis of the primary efficacy endpoint for study 310, graft survival at twelve months, is shown here with a 95 percent confidence interval of the differences in rates. The twelve-month graft survival was equivalent and excellent in both groups. Rates were high in excess of 95 percent in both cohorts.

There were similar rates of physical and functional graft loss as well as graft loss secondary to patient death. Note also that there was 100 percent follow up for patients in both randomized groups.

[Slide.]

Similarly, patient survival in the

intent-to-treat population was equivalent at twelve months following transplantation. The survival rate exceeded 97 percent in both groups.

[Slide.]

This Kaplan-Meier plot shows the incidence of first-biopsy-confirmed acute-rejection episodes in study 310. In the prerandomization period, before month 3, there were similar rates of acute rejection for all enrolled patients. For month 3 through 12, there was an incremental increase in rejection frequency in the Rapamune arm. The combined incidence of acute rejection over the first twelve months was not statistically different for both randomized groups, 13.5 percent for the Rapamune plus cyclosporine group compared with 20 percent for the Rapamune group.

[Slide.]

How does the acute-rejection rate compare with other registration trials? The initial therapy provided low acute-rejection rates which meet the standards for immunosuppressive therapy for today's transplant recipient. Specifically, the use of Rapamune in combination with cyclosporine was associated with the rejection rate of only 12 percent for the entire enrolled

population of 525 patients.

These rejection rates compare favorably with recently published registration trials.

[Slide.]

At twelve months, acute-rejection rates in all enrolled patients, not just those randomized to the two treatment arms, were again equal to or better than recently published registration trials in which calcineurin inhibitors were included and maintained in the regimen.

[Slide.]

Following month 3 and the onset of cyclosporine elimination, the incremental increase in first biopsy-confirmed rejection was modest at 9.8 percent but was significantly higher than the rejection rate in the control arm at 4.2 percent.

Even though the rejection rates were low, an important question to ask is whether outcomes for those patients who had rejection episodes were worse than would be expected. Importantly, for patients experiencing rejection in either treatment arm, there was a single death in the Rapamune plus cyclosporine group and no deaths in the Rapamune group.

Additionally, there was only one graft

loss in each group.

[Slide.]

The histologic severity of acute-rejection episodes was similar in the two groups. The majority of these episodes were mild and no patient experienced an episode of severe acute rejection following cyclosporine elimination. The use of antibody therapy to treat acute rejection was also similar and was utilized in only two patients.

[Slide.]

Another important variable in assessing the impact of acute rejection is the potential effect on subsequent graft function. This analysis compares the change in glomerular-filtration rate from baseline to twelve months in randomized patients who subsequently did or did not experience an acute-rejection episode.

On the left, patients without acute rejection had experienced a change in renal function at twelve months consistent with the study as a whole. Specifically, function improved in patients in the Rapamune arm while it worsened for patients maintained in the Rapamune plus cyclosporine group.

On the right are depicted patients with

acute rejections after month 3. As might be expected, the GFR at twelve months was numerically lower for patients in either group who had experienced an episode of acute rejection. However, the GFR for rejectors in the Rapamune group remained stable through twelve months. This stability suggests that the adverse impact of acute rejection upon renal function appeared to be lessened with the elimination of cyclosporine.

[Slide.]

The combination of Rapamune plus cyclosporine in the first three months following transplantation maintained very low rejection rates which were equal to or better than those observed in recent registration trials. The incremental increase in acute rejection following cyclosporine elimination was statistically higher in the Rapamune group with an absolute difference of 6 percent.

This compares favorably with previous trials in which rates of rejection following elimination are equal to or greater than those observed in study 310. Episodes of rejection attending cyclosporine elimination were generally mild and clinically manageable. Importantly, there

were no episodes of severe rejection and only one graft loss was reported in the Rapamune group.

In addition, at twelve months, there were similar rates of acute rejection in the randomized groups. As expected, at twelve months, the mean GFRs in the rejectors were lower than those in the nonrejectors. But, importantly, there was no penalty in patients in whom cyclosporine was eliminated.

[Slide.]

Comparable rates of efficacy failure were demonstrated. These composite rates at twelve months following transplantation were primarily due to the occurrence of acute rejections with very few graft losses or patient deaths.

[Slide.]

Treatment failure for study 310 was defined as the first occurrence of rejection, graft loss, death or discontinuation of study medication. The overall treatment failure at twelve months was significantly higher with patients randomized to the Rapamune group. This was primarily due to the numerically higher rates of acute rejection and for discontinuations within the group.

On review of the clinical dataset, the

difference in the rate of treatment failure was no longer statistically significant.

Now let's examine what many would consider to be the most important efficacy endpoint in a study of cyclosporine elimination, namely the impact upon long-term graft function.

[Slide.]

Shown here is the intent-to-treat analysis of serum creatinine and glomerular-filtration rate for patients enrolled in study 310. This conservative analysis includes all enrolled patients including those discontinued from therapy and placed back on calcineurin inhibitors. For both renal-function parameters, there was a statistically significant improvement demonstrated at the twelve-month time point for the Rapamune group.

[Slide.]

In addition to the intent-to-treat analysis demonstrating excellent patient and graft survival and statistically significant improvements in renal function, the on-therapy analysis also showed a clear benefit for patients in whom cyclosporine was eliminated and who were maintained on concentration-controlled Rapamune.

This group included patients who may have experienced an episode of acute rejection but continued within the study and received study medication. The graph on the left shows serum creatinine. In the Rapamune treatment group, serum creatinine was significantly lower at all time points following randomization. It is also noteworthy that this improvement is sustained through 24 months of follow up.

The graph on the right shows calculated glomerular-filtration rates at these same time points. Again, the Rapamune-treated group had significantly higher GFRs at all time points persisting through month 24.

[Slide.]

The benefits of cyclosporine elimination on renal function were demonstrated by all patients on therapy through twelve months and longer regardless of their baseline renal function.

A quartile analysis was performed in which patients were segregated according to baseline renal function at the time of randomization. In all four quartiles, the change from baseline was favorable in comparison to patients maintained on cyclosporine including those with more advanced

degrees of renal insufficiency at baseline.

Notably, even those patients with normal renal function at baseline benefitted by the removal of cyclosporine nephrotoxicity and its consequent negative impact upon long-term renal function.

[Slide.]

In summary, the patients enrolled in study 310 were similar to that of the U.S. population with the exception of fewer black patients. At twelve months, following transplantation, there was equivalent patient and graft survival of greater than 97 percent and 95 percent, respectively. In addition, a low incidence of acute rejection at twelve months was similar in the two randomized groups and, perhaps most importantly, there was an immediate improvement in renal function following cyclosporine elimination which has been sustained through 24 months of follow up.

Next, we will review the key efficacy data for study 212.

[Slide.]

Key demographic variables among patients enrolled in study 212 were similar. The total enrolled patient population is similar to that of

the two randomized groups. These were well matched for gender, ethnic origin, age, ischemia time and degree of HLA mismatch.

The demographics are also similar to that of the UNOS population of renal-transplant recipients in the U.S. except for the study's exclusion of living donor recipients. Therefore, while study 212 is generally representative of the U.S. renal-transplant population, the 212 group was also at a somewhat higher risk given the absence of living-donor recipients.

Though not shown on this slide, the patients in both groups had similar donor characteristics including source, ethnic origin and age.

[Slide.]

Twelve-month graft survival in study 212 was similar in the two treatment groups being in excess of 92 percent in both. There was a slightly higher rate of graft loss due to physical or functional graft loss in the Rapamune plus cyclosporine group compared with the Rapamune group. Again, as with study 212, there was 100 percent patient follow up in both randomized groups.

[Slide.]

The intent-to-treat analysis of patient survival in study 212 was similar. At twelve months, patient survival was excellent and was at least 96 percent on both groups.

[Slide.]

This Kaplan-Meier plot shows the incidence of first biopsy-confirmed acute-rejection episodes in study 212. Prior to cyclosporine withdrawal, there were similar rates of acute rejection in both groups. Following month 2, there was an incremental increase in the rate of acute rejection in the Rapamune group but the difference between the randomized groups never achieved statistical significance.

The intent-to-treat analysis at month 12 demonstrated an incidence of acute rejection of 18.6 percent for the Rapamune plus cyclosporine group compared with 22 percent for the Rapamune-treated group.

As in study 310, it is important to examine the outcome in those patients who experienced acute rejection following the elimination of cyclosporine. Following month 2, there was a modest numerical increase in

first-biopsy-confirmed rejections at 14 percent compared with the rejection rate in the control arm of 6.2 percent.

Importantly, for patients experiencing rejection in either treatment arm, there was a single death and a single graft loss in the Rapamune group and no deaths or graft losses in the Rapamune plus cyclosporine group.

[Slide.]

As with study 310, the histologic severity of acute-rejection episodes was similar in the two randomized groups. The majority of these episodes were mild to moderate with only one patient in the Rapamune plus cyclosporine group experiencing an episode of severe acute rejection beyond the two month time point.

[Slide.]

This analysis compares the calculated GFR in patients who did or did not experience an acute-rejection episode following month 2 and the onset of cyclosporine elimination.

On the left, patients without acute rejection had experienced a change in renal function at twelve months consistent with the study as a whole. Specifically, function improved in

patients in the Rapamune arm.

On the right are depicted patients with acute rejections after month 2. As might be expected, the GFR at twelve months were numerically lower than nonrejectors for both groups. These findings are consistent with study 310 and suggest that renal function outcomes for those patients who had rejection episodes were within clinical expectations.

[Slide.]

Importantly, study 212 was also consistent with study 310 in demonstrating improved renal function in a variety of comparative analyses. Depicted here is the intent-to-treat analysis. The intent-to-treat population includes all enrolled patients including those who experienced an episode of acute rejection or had discontinued study medication.

In this group, calculated GFRs were significantly higher at six months and at twelve months in the Rapamune-treated patients.

[Slide.]

Study 212 demonstrated improved renal function in the primary efficacy population, namely those patients that remained on therapy and

rejection-free through month 6. The graph on the left shows serum creatinine compared with the Rapamune plus cyclosporine treated patients, Rapamune treated patients had significantly lower serum creatinines starting at month 6 and persisting through month 12.

The graph on the right shows calculated GFRs at these same time points. The Rapamune group, again, had significantly higher GFRs at month 6 compared to the Rapamune plus cyclosporine group and this difference persisted through twelve months.

[Slide.]

There was also improvement observed in directly measured GFRs in a subset of the primary analysis population. Patients in the Rapamune group with cyclosporine elimination had higher measured GFRs at both six and twelve months following transplantation.

[Slide.]

Improved renal function was also demonstrated in the on-therapy population. This group included patients who may have experienced an episode of acute rejection but continued within the study and received study medication. The graph on

the left shows serum creatinine. Compared with Rapamune plus cyclosporine treated patients, there was a trend toward lower serum creatinine at all time points in the Rapamune-treated cohort. At twelve months, the improvement in creatinine demonstrated statistical significance.

The graph on the right shows calculated GFRs at these same time points. Notably, GFRs were significantly higher at time point 6, nine and twelve months in comparison to the control group.

[Slide.]

As in study 310, the benefits of cyclosporine elimination on renal function were demonstrated by the majority of patients on therapy through twelve months regardless of their baseline renal function. Again, a quartile analysis was performed in which patients were segregated according to baseline renal function just prior to cyclosporine elimination.

The change from baseline was favorable in comparison to patients maintained on cyclosporine. As might be expected, patients with varying degrees of renal dysfunction also showed improvement.

[Slide.]

In summary, at month 12, studies 310 and

212 are consistent in their findings. Specifically, these studies demonstrated that following the elimination of cyclosporine, concentration-controlled Rapamune maintenance therapy results in the following: equivalent graft survival of 95 to 97 percent, equivalent patient survival of 96 to 98 percent, an incremental increase in mild to moderate acute-rejection episodes following cyclosporine elimination with an absolute difference of 6 to 8 percent versus controlled therapy.

This compares favorably with previous elimination trials and, perhaps most importantly, both studies demonstrated an immediate and sustained improvement in renal function.

This concludes my presentation of the efficacy data for studies 310 and 212.

Safety Data

DR. NEYLAN: I will now review the safety data for both studies.

[Slide.]

One-year data will be shown for graft loss, patient death and discontinuation from study medication. The cumulative safety experience for all enrolled patients will be shown for adverse

events including infection and malignancy. The cumulative on-therapy data will be presented for all laboratory parameters including blood pressure.

[Slide.]

The safety assessments will be reviewed in different categories including etiologies of graft loss in patient death, adverse events including those related to immunosuppression such as infection and malignancy and, finally, blood-pressure measurements and laboratory parameters.

[Slide.]

I have already shown you graft survival data for the randomized patients. Graft survival in the randomized groups was in excess of 95 percent. An analysis of overall graft survival for all patients enrolled in the study was also high at approximately 89 percent. This group included patients with severe acute or vascular rejection, sustained delayed graft function and other criteria that precluded randomization.

[Slide.]

The causes of graft loss in study 310 are shown in this slide. An intent-to-treat comparison of the randomized cohorts was conducted censoring

graft loss secondary to death. These data revealed similar incidences of graft loss due to infection, renal fibrosis, renal dysfunction, graft vascular thrombosis or recurrent primary disease.

The causes of graft loss in these two groups were not statistically different.

[Slide.]

This slide includes patient survival for all patients enrolled in the study. Patient survival in the overall population which includes the nonrandomized patients was in excess of 94 percent.

[Slide.]

The causes of patient death are shown here. An intent-to-treat analysis at twelve months demonstrated no significant differences in death due to cardiovascular cause or infection.

[Slide.]

Next we will review the adverse-event data including those events generally associated with immunosuppressive therapy such as infection and malignancy.

[Slide.]

The adverse events for this study were similar to the safety profile observed in

previously completed pivotal trials that supported the initial approval of Rapamune. What I want to focus on are changes in the profile when increased doses of Rapamune are utilized after cyclosporine elimination.

As is common in all renal transplant clinical trials, there were a number of reports of adverse events in study 310. These data represent new adverse events occurring following randomization. Shown are the statistically significant differences observed between the two groups.

Statistically higher in the Rapamune plus cyclosporine group were cyclosporine toxicity, increased creatinine, edema, hypertension and hyperuricemia. Significantly higher in the Rapamune group were hypokalemia, elevated SGOT and SGPT and thrombocytopenia.

[Slide.]

All patients in study 310 were followed for the occurrence of serious infections including those requiring hospitalization. In general, the results show no difference in infections in the two randomized groups and are consistent with the known safety profile. The only significant difference is

an increased reporting of Herpes zoster infection in the patients in the Rapamune plus cyclosporine group. There was no difference in the incidence of sepsis, CMV infection, pneumonia, Herpes simplex or urinary-tract infection.

[Slide.]

Similarly, there was no statistical difference in the reported incidence of neoplasia. Specifically, the rates of skin cancer, lymphoma, leukemia and other malignancies were similar and not different between the randomized groups. The overall rates of reporting in this study were also consistent with numerous other studies in which transplant recipients received similar levels of immunosuppression.

[Slide.]

The next safety parameter I would like to discuss is that of blood pressure. Hypertension is common in renal-transplant recipients and an important contributor to cardiovascular risk. In the next two slides, we will review blood-pressure measurements as well as the percentage of patients requiring antihypertensive medications in this study.

[Slide.]

The mean systolic and diastolic blood pressures are shown here. On the left, are shown mean systolic blood-pressure measurements. Compared with the Rapamune plus cyclosporine group, Rapamune-treated patients had significantly lower systolic blood pressures at all time points starting at month 6 and persisting through 24 months of follow up.

On the right are mean diastolic blood-pressure measurements. Similarly, statistically significantly lower diastolic blood-pressure measurements were observed from month 6 through 18 for Rapamune-treated patients.

[Slide.]

It is important to consider the need for antihypertensive agents in these patients. Although the study was not designed to capture specific dosages of antihypertensive medications, it was possible to analyze the need for combination regimens. The cumulative requirement for multidrug antihypertensive therapy was less in the Rapamune group at month 12. This difference was statistically significant.

Thus, the improvement in blood-pressure management demonstrated by the lowering of systolic

and diastolic means was also attended by a decreased need for multidrug therapy.

[Slide.]

We will next review several laboratory parameters. The first analysis will address the issue of lipid elevations, an important risk factor in renal-transplant recipients.

[Slide.]

In study 310, approximate 19 percent of the patients were receiving lipid-lowering medications prior to transplantation including statins and/or fibrates. Following initiation of study medication, 73 percent of patients in both randomized groups were receiving statins while up to 25 percent of patients in both groups were administered fibrates. The overall use of these agents in both randomized groups was similar.

[Slide.]

An observation made early in the clinical program was the effect of Rapamune on cholesterol and triglycerides. In study 310, the median fasting cholesterol concentrations in the two randomized groups were similar at month 12.

The range of values is depicted in these box-and-whisker plots. 80 percent of the patients

in each treatment group are contained within the respective box-and-whisker plots. Thus, the majority of patients were found to have cholesterol values at or below 250 milligrams per deciliter despite the fact that concentration-controlled Rapamune-treated patients had increase sirolimus trough levels as mandated by protocol.

The results observed in study 212 were similar.

[Slide.]

Measurements of fasting HDL and LDL cholesterol levels were also similar. For HDL cholesterol, the two randomized groups were similar except at month 18 when there was a statistically significant increase in the Rapamune group. LDL cholesterol, calculated for those patients who had triglycerides below 400 milligrams per deciliter was similar in the two randomized groups with the exception of month 3 when there was a significant increase in the Rapamune group.

[Slide.]

As with serum cholesterol, fasting triglycerides were similar in study 310 in the two randomized groups through twelve months of follow up. Again, despite the higher sirolimus

concentrations, the Rapamune-treated patients maintained fasting triglycerides in the majority of patients within the 150 to 250 milligram per deciliter range. The results observed in study 212 were similar.

[Slide.]

With regard to liver-function tests, SGPT and SGOT were measured at various time intervals. In the Rapamune-treated patients, SGPT was significantly higher for months 12 through 24. SGOT was significantly higher for months 12 through 18. At all other time points, these liver enzymes remained similar in the two randomized groups and below the upper limits of normal.

In study 212, the majority of patients also had transaminase levels below the upper limits of normal.

[Slide.]

Shown on this slide are the causes of elevated liver enzymes in a small number of patients with at least one SGPT value greater than five times the upper limit of normal. Approximately 50 percent of these patients had an infectious etiology as a potential cause for the SGPT elevation.

[Slide.]

The effects of Rapamune on bone-marrow-derived cells are consistent with its biologic activity in that small decreases in platelets, red cells and leukocytes have been observed. Most important, however, is that there is no evidence of chronic or irreversible bone-marrow dysfunction or depression.

In general, white blood-cell counts were similar in study 310 with the exception of statistically significant differences noted at months 3 and 6. However, it is important to note that the mean white-blood-cell counts remained within a clinically normal range for all of the patients.

Platelet counts for the two randomized groups were also similar. While statistically significant differences were observed at months 6, 15 and 18, mean platelet counts remained above 200,000 at all time points. It is also important to note that platelet counts remained stable as patients continued to receive Rapamune through month 24.

Similar results were observed in study 212.

[Slide.]

In summary, in study 310, there was equivalent patient and graft survival. In the Rapamune plus cyclosporine group, there was an increased incidence of cyclosporine toxicity, increased creatinine, edema, hypertension and hyperuricemia.

In the Rapamune group, there was an increased incidence of hypokalemia, increased SGOT, SGPT and thrombocytopenia. There were similar rates of infection and malignancy. Improved blood pressure followed cyclosporine elimination and there were similar effects on lipid profiles and hematologic parameters despite the higher trough-level concentrations in the Rapamune group following cyclosporine elimination.

[Slide.]

I will now review the safety data for study 212. This slide includes graft survival for all patients enrolled in the study. As previously demonstrated, similar rates were observed in the randomized group. The nonrandomized group demonstrated a lower graft-survival rate not inconsistent with that typically observed in patients with ATN or delayed graft function.

[Slide.]

Causes of graft loss in this study are shown here. An intent-to-treat comparison of the randomized cohorts was conducted censoring graft loss secondary to patient death. The data revealed a similar incidence of graft loss due to rejection, acute tubular necrosis and hemolytic uremic syndrome.

[Slide.]

As previous presented, similar patient survival was observed in the two randomized groups. Patient survival in the nonrandomized group was slightly lower.

[Slide.]

Causes of patient death in study 212 are shown here. Analysis at twelve months following transplantation demonstrated no significant differences in death due to cardiovascular cause, infection or pulmonary edema.

[Slide.]

Similar to study 310, there were a number of reports of adverse events in study 212. Again, I will primarily be emphasizing the statistically significant differences. Significantly higher in the Rapamune plus cyclosporine were hypertension, dyspnea, edema, hypervolemia and hypomagnesemia.

Significantly higher in the Rapamune group were thrombocytopenia, hypokalemia, diarrhea, abnormal liver-function tests and atrial fibrillation. With the exception of atrial fibrillation, these types of adverse events were previously observed in the pivotal clinical trials.

The increased incidence of atrial fibrillation in the Rapamune group is discussed in more detail in the next slide.

[Slide.]

In study 212, atrial fibrillation occurred in a total of nine patients. This included one patient in the Rapamune plus cyclosporine group and an additional eight patients in the Rapamune group. Six of these eight patients had episodes of atrial fibrillation occurring within the first 40 days following transplantation and thus prior to the elimination of cyclosporine.

All cases resolved promptly with therapy and, in the opinion of the investigators, none were considered related to study medication.

In the larger study, 310, the incidence of atrial fibrillation was 1.9 percent in the cyclosporine-plus-Rapamune group compared with 3.7 percent in the Rapamune group. This difference was

not statistically significant. Likewise, in previous registration trials, atrial fibrillation was uncommon and not statistical different from controlled therapies.

[Slide.]

The intent-to-treat analysis of infections in study 212 is listed here. Infections were typical of the general renal-transplant population and the data showed no statistical difference between the two randomized groups.

[Slide.]

As with study 310, the overall rates of malignancy observed in 212 were also similar and consistent with previously published studies in transplant recipients. By twelve months, a comparison of the two randomized groups showed no difference in the rates of nonmelanomtous skin cancer and one case of presumed post-transplant lymphoproliferative disease. There was one case of renal-cell carcinoma in a native kidney.

[Slide.]

In summary, in study 212, there was equivalent patient and graft survival. In the Rapamune plus cyclosporine group, there was an increased incidence of hypertension, dyspnea,

edema, hypervolemia and hypomagnesemia. In the Rapamune group, there was an increased incidence of thrombocytopenia, hypokalemia, diarrhea, increased SGOT, SGPT and atrial fibrillation.

The infrequent observation of atrial fibrillation was not considered by study investigators to be related to Rapamune. There were similar rates of infection and malignancy and there were similar effects on lipid profiles and hematologic parameters despite the higher trough-level concentrations in the Rapamune group following cyclosporine elimination.

To compete the overall safety profile, the next several slides will review patient outcomes in those patients discontinued from treatment as well as the overall success of cyclosporine elimination.

[Slide.]

The overall disposition of patients in study 310 is shown in this slide. As previously discussed, 525 patients were enrolled at the time of transplantation. 430 patients met the predetermined eligibility criteria at month 3 and were randomly assigned to one of the two treatment groups.

215 patients were assigned to each of the

groups. the overall rates of discontinuation in study 310 were similar to those observed in recent immunosuppressive registration trials. 18.1 percent of patients had discontinued by month 3 and 36.4 percent of patients had discontinued by month 12.

[Slide.]

The reasons for discontinuation in study 310 are listed here. A total of 95 patients, or 18.1 percent of the total population, were not randomized and were discontinued due to a variety of causes typical for patients in this early period following transplantation.

74 percent were discontinued for adverse events including infections, renal dysfunction, surgical complications, laboratory abnormalities and a small number of miscellaneous causes. 13 percent of these patients were discontinued because of the acute rejection.

Following randomization by month 12, the overall rate of discontinuation was higher in the Rapamune group. Acute rejection was an infrequent cause of discontinuation accounting for only 2 percent and 5 percent in the Rapamune plus cyclosporine and the Rapamune groups, respectively.

Upon review of the cumulative dataset which includes data for all patients at or beyond 15 months, the difference in the rate of discontinuation was no longer statistically significant.

[Slide.]

While the reasons for patient discontinuations for the study as a whole were similar to other immunosuppressive trials, it is important to look at the special group of patients in whom cyclosporine elimination was not or could not be successfully completed.

Given the present availability of other immunosuppressive agents, clinicians were able to choose from a variety of alternative regimens for these patients. Most patients remained on corticosteroids plus a calcineurin inhibitor and, in 26 percent of these cases, patients were converted from cyclosporine to tacrolimus.

In many of the cases, an antimetabolite was also added to the regimen. It is notable that in 19 percent of these cases, Rapamune was maintained while the calcineurin inhibitor was reintroduced.

Three deaths and two graft losses occurred

in the discontinued group. By month 12, there were no acute rejections reported in patients converting to alternative therapies.

[Slide.]

In the majority of patients randomized to the Rapamune group, cyclosporine elimination was successful. 50 percent of these patients accomplished this within the first 42 days and 90 percent were cyclosporine free by day 72 post randomization. In total, 92.6 percent of the patients were successfully withdrawn from cyclosporine.

[Slide.]

The overall disposition of patients in study 212 is shown in this slide. A total of 246 patients were enrolled at the time of transplant and randomly assigned to one of the two treatment groups. 97 patients were assigned to receive Rapamune plus cyclosporine and 100 to Rapamune.

The overall rate of discontinuation in study 212 was similar to that observed in other recent immunosuppressive registration trials with 29.7 percent of patients discontinued by month 12.

In the following slides, we will review the outcomes for these discontinued patients.

[Slide.]

The reasons for discontinuation in study 212 are listed here. A total of 49 patients were not randomized. Of these, 28 discontinued due to adverse events, acute rejection or other causes. Post randomization, a total of 45 patients were discontinued from the study by twelve months, 20 of these in the Rapamune plus cyclosporine group and 25 in the Rapamune group.

These discontinuations were similar in nature to those of study 310. Clinicians participating in study 212 chose to reinitate calcineurin inhibitors for most patients discontinued from the Rapamune group.

[Slide.]

As in study 310, the majority of patients randomized to the Rapamune group of study 212 had cyclosporine successfully eliminated. On the left is depicted an analysis of all patients randomized to the Rapamune group. 76 percent of patients randomized from the time of transplantation successfully eliminated cyclosporine.

On the right is an analysis of these patients who were eligible for cyclosporine elimination at month 2. Note the similar success

rate to that of study 310 in that 93 percent of these patients successfully had cyclosporine eliminated from the regimen.

Thus, in both studies, patients maintained on Rapamune plus cyclosporine for the first two to three months after transplantation emerged from the high-risk period and went on, in 92 to 93 percent of cases, to successfully eliminate cyclosporine.

[Slide.]

In conclusion, studies 310 and 212 are consistent in confirming the beneficial safety profile of Rapamune-based therapy following cyclosporine elimination. Both studies demonstrated excellent patient and graft survival, similar rates of infection and malignancy and significantly lower rates of several other cyclosporine-related adverse events.

In addition, study 310 demonstrated a significant and sustained improvement in blood pressure. Despite the higher concentration of Rapamune required when cyclosporine is eliminated, the overall Rapamune safety profile is similar to that observed when it is administered as a fixed 2 milligram dose in combination with cyclosporine.

[Slide.]

In addition, rates of discontinuations in these studies were similar to other immunosuppressive registration trials. The reasons for early discontinuation were typical of those observed in renal allograft recipients including surgical complications and delayed graft function.

Very few patients were discontinued due to acute rejection. In fact, in study 310, 70 percent of patients experiencing episodes of acute rejection in the first three months went on to randomization. As expected, various alternative therapies were available for patients discontinued from the studies.

Importantly, cyclosporine was successfully eliminated in the great majority of patients in the Rapamune group of both studies.

This concludes my presentation of the safety data. At this time, I would like to introduce Dr. James Zimmerman, Senior Director of Clinical Pharmacokinetics at Wyeth-Ayerst who will now review the pharmacokinetics of Rapamune concentration-controlled trials and sirolimus therapeutic drug-level monitoring in this patient population.

Dr. Zimmerman?

Pharmacokinetics

DR. ZIMMERMAN: Thank you, John. Good morning.

[Slide.]

In our original application, Rapamune was approved for a fixed-dose administration without the need for therapeutic drug monitoring or TDM. TDM was recommended in certain patient populations and to compensate for serious pharmacokinetic drug interactions but it was not required. Today we have proposed a new regimen that will require TDM. This new regimen is proposed based on safety and efficacy data from Rapamune concentration-controlled trials that involve cyclosporine elimination in which drug exposure was guided by TDM.

[Slide.]

My purpose today is to show you data to support the following four points. First, we have a sufficient understanding of sirolimus PK to apply therapeutic drug monitoring to guide treatment in renal-transplant patients. Secondly, we have a robust and reliable assay for sirolimus. Thirdly, the concentration range for sirolimus TDM has been defined and it is effective. Fourth, we have data

to show that transplant physicians can utilize TDM safely and efficaciously in post-transplant patients.

Now, before belaboring on these four points, I want to remind you of the conditions under which Rapamune is administered by fixed dose in concentration-controlled regimens.

[Slide.]

The currently approved Rapamune regimen is a fixed-dose regimen which was based on the administration of Rapamune four hours after a oral formulation of cyclosporine. The fixed-dose regimen is recommended for most patients during coadministration with cyclosporine.

[Slide.]

Concentration-controlled Rapamune administration is recommended during administration with cyclosporine under certain conditions; in pediatric patients, in hepatic impairment, during administration with strong inducers or inhibitors or the CYP3A P450 subfamily and P-glycoprotein and also after marked changes in cyclosporine doses.

Concentration control is required when administered without cyclosporine and it is the method of dose administration for the current

indication.

[Slide.]

Let me start with the assay methodology. Whole-blood sirolimus concentrations were measured during phase II and phase III clinical trials using an immunoassay or a chromatographic assay as we can see by the first two columns.

However, as shown in the third column, the immunoassay is not currently available for post-approval use. Instead, HPLC/UV or HPLC/MS/MS are being used at local and commercial laboratories. It is important to realize that the two assays provide different numerical values for sample analysis as shown in the column on the extreme right.

For example, chromatographic assay values are 20 percent lower than the immunoassay values. Consequently, the ranges for therapeutic drug monitoring are different for the two assays. In this presentation, sirolimus concentrations are expressed in terms of the immunoassay since the vast majority of the samples for pivotal phase III trials were measured by this method.

Turning now to the impact of sirolimus PK on TDM.

[Slide.]

The fact that sirolimus exhibits dose proportionality over a wide range and also shows linear Cmin versus AUC relationship simplifies concentration-controlled dosing. Dose proportionality has been demonstrated for sirolimus Cmax and AUC first in renal allograft patients after coadministration of Rapamune oral solution and cyclosporine over a dose range of 2 to 22 milligrams.

Secondly, in healthy volunteers after administration of Rapamune tablets over a dose range of 5 to 40 milligrams. Therefore, sirolimus trough levels would be expected to increase in simple proportion to the dose over a dose range of 2 to 40 milligrams.

Moreover, the correlation between sirolimus Cmin and AUC in renal allograft patients is excellent as shown by an r-squared value of 0.96. For the regression line over a concentration range of approximately 1 to 30 nanogram per ml. The experimental data is shown on the next slide.

[Slide.]

This figure is a plot of sirolimus 24-hour troughs on the Y axis and sirolimus 24-hour AUCs on

the X axis based on the administration of Rapamune oral solution in combination with cyclosporine during study 301. The individual data points were collected at months 1, 3 and 6 post transplant after doses of 2 and 5 milligrams per day in 42 patients.

Plotted along with the individual data is the regression line. These data show that troughs can be used for purposes of dose adjustments during sirolimus TDM and the range of concentrations is wide enough to cover the sirolimus target range during TDM as we will see in the final section of this presentation.

The important outcome of this relationship is that multiple samples do not have to be drawn during a dose interval at steady state which provides a convenience for the patient and reduces the cost of TDM.

[Slide.]

Next, there are three PK parameters that affect the implementation of Rapamune concentration-controlled dosing. These are the time to steady state, the loading dose and the maximum dose per day. The mean times to read steady state in renal-allograft patients during

coadministration of Rapamune oral solution and cyclosporine was five to seven days. That is without a loading dose although the time to state was as long as thirteen days in individual patients.

These results indicate that a blood sample for the determination of a steady-state trough should not be drawn for at least five to seven days after the previous dose adjustment when a loading dose is not administered.

A loading dose is necessary to quickly reach steady state and the mean estimated sirolimus loading dose determined in renal-allograft patients during coadministration of Rapamune oral solution and cyclosporine was three times the maintenance dose. When a loading dose is used, it may not be necessary to wait as long as five to seven days to draw a sample for purposes of dose adjustment.

The maximum dose on any day that was recommended in study 310 was 40 milligrams. It is also recommended, however, that a loading dose larger than 40 milligrams be administered in divided doses over two days.

Now, in the next series of slides, I want to discuss our experience with

concentration-controlled trials.

[Slide.]

Four studies provided data after one year post transplant as shown in this second column. Study 310, the pivotal study for the current submission, study 212, the supportive study for the current submission, and studies 207 and 210, which were early studies directly comparing Rapamune versus cyclosporine using concentration control.

Concentration-controlled data were obtained for both the tablet and the oral solution. The remainder of this presentation will focus on the one-year PK data but data beyond one year has also been presented to FDA.

[Slide.]

The sirolimus target ranges for cyclosporine withdrawal in studies 212 and 310 were set prospectively based on the results from phase II studies 207 and 210. For sample analysis by an immunoassay, these ranges were 10 to 20 nanogram per ml for study 212 and 20 to 30 nanogram per ml for study 310.

The adequacies of the prospective target ranges were supported be efficacy results and similarities in the mean sirolimus trough levels

for the two studies; that is 18 nanograms per ml for study 212 and 23 nanograms per ml for study 310.

[Slide.]

We evaluated the implementation of concentration control in four Rapamune studies by estimating the percentages of patients showing concentrations below, with and above the sirolimus target concentration ranges. This slide shows the average percentages of patients among studies and ranges for the sirolimus concentration-controlled treatments or Rapa groups in studies 207, 210, 212 and 310. These data are shown by the hatched purple bars.

A comparison of the data in the center figure with the data in the left and right figures shows that large majorities of the patients in all four studies fell within the target range. It is important to note that the vast majority of the investigators obtained these results using a central lab and did not have the benefit of an assay at the transplant site.

Based on averages among the four studies as shown by the purple bars 12 percent of patients were below the target range. 70 percent were

within the range and 18 percent were above the target range. Overall, 88 percent were above the lower limit of the target range.

[Slide.]

This figure shows the sirolimus and cyclosporine trough levels over time before and after randomization in the sirolimus concentration-controlled treatment or Rapa group of study 310. You are looking at the outcome of the first Rapamune clinical trial in which investigators were required to simultaneously withdraw cyclosporine while increasing the dose of Rapa. The vertical bar represents randomization at 90 days.

Trough concentration for cyclosporine are plotted on the left Y axis and for sirolimus and the right Y axis. The time is plotted on the X axis. I want to reiterate that the sirolimus concentrations and target range on this slide are for an immunoassay as are the concentrations and target ranges shown on subsequent slides.

Before randomization in this region, cyclosporine troughs, shown as triangles, gradually decreased over 90 days as doses were gradually decreased and sirolimus troughs, shown as circles,

remained stable at approximately 11 nanogram per ml during the fixed-dose time period.

After randomization, in this area, cyclosporine troughs decreased rapidly to near zero concentrations at 150 days as the doses were reduced and sirolimus troughs rapidly increased to reach the target range as doses were increased.

[Slide.]

Overall, the investigators were quite successful in this first Rapamune trial that required simultaneous adjustment in the dosages of two drugs and cyclosporine was eliminated in 50 percent of patients by week 6 after randomization. We can anticipate that the ability to achieve and maintain the sirolimus target range using TDM will improve in the future as more experience is obtained with cyclosporine withdrawal.

[Slide.]

This figure provides a summary of the sirolimus doses and troughs after reaching the target range in study 310 between 4.5 and twelve months post transplant. In the concentration-controlled treatment, as shown by the purple bars, a mean Rapamune dose of 8.4 milligrams per day produced mean sirolimus troughs of 23.3

nanograms per milligram which was within the target range for the study.

In the fixed-dose treatment, as shown by the red bars, a mean Rapamune dose of 2.1 milligrams per day produced a mean sirolimus trough of 10.8 nanograms per milligram. There appears to be a disparity between doses and concentrations since a fourfold increase in dose produces only a twofold increase in concentration. The apparent discrepancy between doses and troughs is due to the fact that cyclosporine produces about a twofold increase in the extent of absorption of sirolimus. Therefore, without the coadministration of cyclosporine, sirolimus troughs would be decreased by one half compared to those during coadministration with cyclosporine and, therefore, higher doses are required.

[Slide.]

Let me tell you now what we have learned about implementing sirolimus TDM. There are four parameters that I want to discuss which include the frequency of blood sampling for rapid determinations after randomization, the number of days required to reach the target range after randomization, the number of dose changes required

to reach the target range after randomization and the recommended target trough range for sirolimus TDM.

I will also be commenting on the availability of the sirolimus assay.

[Slide.]

In pivotal trial 310, blood samples were to be drawn weekly during the first month after the start of cyclosporine withdrawal, every two weeks during months 2 and 3, monthly during months 4 to 12 and every three months after month 12.

The actual number of samples required for the use of sirolimus TM in new patients will have to be individualized since the number of samples depends on the rate of CSA withdrawal and the time needed for sirolimus to reach the target range in the individual patient.

Based on an analysis of the number of days to reach the target range, 50 percent of patients reached the target range by approximately twenty days after randomization and also 90 percent of patients reached the target range by 68 days after randomization.

Based on an analysis of the number of dose changes to reach the target range, 50 percent of

patients reached the target range after two doses and 90 percent reached the target range after five doses--after dose changes.

[Slide.]

Turning our attention now to the sirolimus TDM range, we conducted a logistic-regression analysis of acute rejection using the post-randomization data but the results did now show significant p-values for either sirolimus or various patient parameters. This result is not too surprising since there were relatively few rejections post randomization and a single limited range of concentrations was investigated.

In the absence of the PK/PD model, the sirolimus TDM range was established based on distribution analysis of sirolimus troughs among nonrejectors and rejectors and clinical outcomes for studies 310 and 212.

The next slide shows the distribution of average sirolimus trough concentrations among nonrejectors in studies 310 and 212.

[Slide.]

The figure on the left shows the data for study 310 and the figure on the right is for study 212. For study 310, the average sirolimus trough

concentrations in individual patients were determined between six weeks post randomization and one year, and for study 212, the averages were determined between three weeks post randomization and one year.

The lengths of the blue bars in the figures represent the numbers of nonrejecting patients at a given concentration as determined by the SAS procunivariate statistical procedure. The dashed lines represent the 5th and 95th percentiles for the sirolimus distribution.

As you can see, the ranges for the two studies showed considerable overlap although the 212 distribution is shifted downward due to the lower protocol target range. We also observed considerable overlap for rejectors in the two studies, as shown in the next slide.

[Slide.]

In these figures, sirolimus trough concentrations in individual patients are plotted against the rejection times. The concentrations in the figures are those closest to the rejection time. The dashed lines are, again, the 5th and 95th percentiles for nonrejectors.

As you can see, the ranges for rejectors

were very similar for studies 310 and 212 and also a large fraction of the rejectors fell within the 5th to 95th percentiles for nonrejectors.

Now, one may question whether a fixed-dose regimen could be used in place of TDM. However, as shown in the next slide, sirolimus TDM considerably reduces the intersubject variability compared to a fixed-dose regimen.

[Slide.]

This figure provides a comparison of the distributions of average sirolimus troughs in nonrejectors beginning a six weeks after randomization in study 310. The box plot on the left is for actual data and the box plot on the right shows the actual concentrations normalized to an 8 milligram daily dose of sirolimus.

If patients in 310 had received an 8-milligram daily regimen without TDM, the range of sirolimus trough levels would have increased considerably and many patients would have exceeded the 95th percentile observed in study 310 and a number of patients would have fallen between the range of 40 to 70 nanograms per milligram. The data in this slide strongly argued for the need of sirolimus TDM.

The next slide provides our recommendations for a TDM range.

[Slide.]

A sirolimus TDM range of 15 to 25 nanograms per milligram, as determined by immunoassay, is recommended based on the distributions of sirolimus troughs among nonrejectors and rejectors in studies 310 and 212 and the very similar clinical outcomes in studies 310 and 212 with respect to graft survival, patient survival and improved renal function within Rapa treatments.

These similarities in clinical outcomes were achieved in spite of the different target ranges used in the two studies.

As the last topic under the implementation of sirolimus TDM, I want to comment on the availability of the sirolimus assay.

[Slide.]

Currently, there are 23 bioanalytical lamps that measure sirolimus concentrations by either an HPLC/UV or HPLC/MS/MS assay. Quest Diagnostics in San Juan Capistrano, California, is our central laboratory. Six additional laboratories analyzed samples on a commercial scale

and sixteen laboratories are located in transplant centers throughout the United States.

The two assay methods include the ranges to the 95th percentiles observed in concentration-controlled studies as shown by the footnotes in the table. The HPLC/UV method has a range of 2.5 to 75 nanograms per milligram and the HPLC/MS/MS method has a range of 1 to 50 nanograms per milligram.

[Slide.]

Turning to guidance that will be provided to physicians, physicians will be informed with respect to algorithms for estimating both a new maintenance dose and new loading dose. The maximum recommended dose of Rapamune per day, time of blood draws for dose adjustments, action guidelines based on assay results and the limitations of TDM.

In conclusion, experience with sirolimus TDM without cyclosporine coadministration has been obtained in four clinical trials during one year post transplant among 347 patients. Efficacy outcomes in the TDM groups were equivalent to the respective fixed-dose groups. Studies 310 and 212 provided data to define a range of sirolimus trough concentrations for TDM in the proposed indication.

The results show that TDM can guide the safe and effective use of sirolimus.

[Slide.]

For TDM without cyclosporine coadministration--that is, for the proposed indication--the recommended sirolimus TDM target range is 15 to 25 nanograms per milligram based on the immunoassay or 12 to 20 nanograms per milligram based on a chromatographic assay.

This concludes my presentation. Dr. Neylan will now close today's presentation with a few final remarks.

Concluding Remarks

DR. NEYLAN: Thank you, Jim.

[Slide.]

I would like to conclude our presentation today by emphasizing that within the past few years, great strides have been made in advancing the clinical science of renal transplantation. In general, these advances have come as a result of our improved understanding of the optimal use of available immunosuppressive agents.

While calcineurin inhibitors have played an important role in the past twenty years, long-term patient and graft survival remain

suboptimal and the persistent nephrotoxicity associated with maintenance cyclosporine continues to take its toll.

The emergence of Rapamune as a new therapeutic option has provided clinicians new opportunities to individualize therapies. Based on the data presented this morning, it is clear that we have made further progress still.

[Slide.]

The combined safety and efficacy data from studies 310 and 212 are consistent and provide compelling evidence that Rapamune may be utilized to spare the inherent nephrotoxicity long associated with chronic cyclosporine administration.

The benefits of concentration-controlled use of Rapamune with cyclosporine elimination include excellent patient and graft survival, a low rate of acute rejection following cyclosporine elimination and an acceptable safety profile.

[Slide.]

A regimen of maintenance Rapamune is associated with several distinct advantages when compared to long-term use of cyclosporine. These include significantly better renal function that is

sustained over time, significantly lower blood pressure that is also sustained and significantly lower incidence of several other cyclosporine-related adverse events.

[Slide.]

Based upon the population of renal-transplant recipients included in these two trials, it is reasonable to expect that these benefits can be realized by most patients now awaiting transplantation in the United States. Specifically, by initiating Rapamune plus cyclosporine and corticosteroids, clinicians can anticipate that most patients can be successfully withdrawn from cyclosporine.

In the current studies, greater than 90 percent of patients eligible two to four months after transplantation successfully completed cyclosporine elimination. Therefore, only a small number of patients will not be able to accomplish this goal because of complications in their clinical course or intolerance of the immunosuppressive regimen.

For these patients, alternative strategies are at hand and may be utilized according to clinical judgment.

[Slide.]

We are excited about these data and their implications for the transplant community. We believe that utilization of Rapamune in the proposed indication may significantly improve the practice of clinical transplantation and enhance the lives of transplant recipients.

In conclusion, I would like to acknowledge the patients and investigators who participated in these trials. Their diligence and their commitment has made all of this possible.

Thank you for your attention. We will now be pleased to address any questions you may have.

DR. ENGLUND: At this point, I would like to ask if there are any clarification questions, just clarification only. We will having the discussion questions later.

DR. HUNSICKER: I had a couple, just one clarification question.

DR. ENGLUND: Go ahead.

DR. HUNSICKER: One of the things that you said earlier is that a certain fraction of patients were removed or permitted not to be randomized because of basically physician judgment that their creatinine was too high. Could you tell us how

many and what the creatinines were? The issue has to do with what we actually about the group of patients who were randomized and on whom we have effective data.

DR. NEYLAN: Yes. Let's see if we can call up a slide looking at the nonrandomized patients.

DR. HUNSICKER: That is in study 310, primarily.

DR. NEYLAN: You want to look at study 310?

DR. HUNSICKER: Yes.

DR. NEYLAN: Let's show this first.

[Slide.]

To begin, in study 310, there were 95 patients who did not meet the randomization criteria at or before month 3. The reasons for discontinuation in study 310 are listed in the next slide.

[Slide.]

74 percent of those patients were discontinued because of adverse events prior to the randomization. These adverse events included issues of renal function like ATN, potentially renal-vein or renal-artery thrombosis, cyclosporine

toxicity. Another category listed as renal dysfunction, and then a host of the other complications that are not out of the usual sort in the more immediate post-operative period.

[Slide.]

The next slide shows that, in addition to this 74 percent, there were twelve of the 95 that were discontinued because of rejection. These were early rejections prior to the month-3 randomization. Nine of these patients had mild to moderate, one severe and one graft loss. Notably, 70 percent of the patients within the enrolled population that experienced rejection within the three-month period actually went on to randomization.

[Slide.]

Then finally, the remaining thirteen patients of this 95 nonrandomized group were discontinued for these listed reasons.

DR. HUNSICKER: If I can just clarify my question a bit. I think this is something that is going to have to actually eventually be dealt with by the FDA, the patients in whom we have a comparison are those who were randomized. That is the only group in whom we can make any judgment

about the relative efficacy.

We have to know very precisely what those randomized patients were so that we will be able to tell the public in the future what group of patients there is now data that you could possibly remove the cyclosporine. I think that I would not want to come across that we could remove cyclosporine in all patients because there are a substantial number of patients who never really had this tested.

DR. NEYLAN: We would certainly agree with that. So, in addition to the patients who declared themselves, if you will, in this early time point with either a severe rejection or a prolonged or more severe delayed graft function, we have those patients who emerged from this period at month 3, and it is those patients, indeed, in which the decision should be made.

We had a slide previously which I wanted to show.

[Slide.]

It shows the patients who came to month 3 and, at that point, were discontinued. I think this, perhaps, more aptly addresses the question you had asked originally which was what number of

the 95 actually, through physician decision at this three-month time point, elected not to, then, be put through the randomization. We see that there were five patients that fit the bill of a creatinine greater than 4.5, five patients that had either severe renal dysfunction or were on dialysis.

The remainder of the patients at this three-month visit mark, which was the time in which physicians decided whether to go on to randomization or discontinue, had these other issues for which the physicians decided not to continue them in the study.

DR. ENGLUND: Dr. Auchincloss?

DR. AUCHINCLOSS: A couple of reasonably quick questions. The steroid dose you mentioned as being the standard taper. Did that sort of typically end at 15 milligrams a day or were people going even lower?

DR. NEYLAN: The tapering went down to lower than 15 milligrams and we have the steroid dosing for the studies. In general, it came down to the range of about 10 milligrams per day.

Would you like to see that data?

DR. AUCHINCLOSS: No; I don't need to see

it. I just need to get a sense of it. Secondly, your S15 slide showing the remarkable similarity of use of lipitore in the two groups despite the fact that one is using a four-times-higher dose of rapamycin in the right-hand panel there. Were they using much more lipitore or dose doesn't matter when you get onto rapamycin?

DR. NEYLAN: Unfortunately, these studies were not designed a priori to collect actual dosing, so I am afraid I can't answer that question. The choice of lipid-lowering agents certainly included lipitore but it also include other HMG co-A-reductase inhibitors.

As you see, 73 percent of both groups were receiving some form. We are certainly interested in this and we are collecting these data now in other trials and trying to get an assessment of the dose response, if you will, to these agents. But we don't have that information for you, these studies, today.

DR. AUCHINCLOSS: Can I do one more?

DR. ENGLUND: One more.

DR. AUCHINCLOSS: The third one is that 212 is the one trial that actually had a number of black patients. I believe it was fifteen. And

then we had a slide later that showed rejectors just near the very end, and there were five spots for black rejectors. So five out of the fifteen rejected at some point in the rapamycin group; is that true?

DR. NEYLAN: Yes.

DR. AUCHINCLOSS: I know the numbers are small, but is there reason to think that blacks would handle this less well?

DR. NEYLAN: Well, actually, I think what I would like to do is, if I might, run through a couple of slides on this issue because, to give you the conclusion first, we think that, although the number of black patients was somewhat small within the collected database of these two studies, the results, in general, mirrored the expectations that might be seen in general clinical practice for these patients and, most importantly, the benefits seen with the cyclosporine elimination are also demonstrated in this group.

If I could have the first slide.

[Slide.]

We see that, indeed, in study 310 conducted in non-U.S. countries, the number of black patients was very small but was

representative of their representation within those general populations. We really won't touch on any of these data since the numbers are, indeed, too small to make much of them.

[Slide.]

Within study 212, 19 percent of the enrolled population was of black ethnicity. The distribution of their enrollment in the two randomized arms is shown here, 18.6 percent randomized to the control group of 212 and 15 percent to the treatment arm. 28.6 percent were not randomized.

[Slide.]

In the 212 Rapamune group, the cyclosporine elimination arm, as I said, there were fifteen that were enrolled. There were three that were eligible for cyclosporine taper by month 2. Two had experienced acute rejection episodes prior to that.

Of those thirteen eligible for cyclosporine taper, all completed the cyclosporine taper. Three had rejection episodes following the cyclosporine withdrawal at days 35, 64 and 122 following that elimination.

[Slide.]

The rates of rejection over time are shown here, are shown for black and non-black patients within 212. You will recall that month 2 was the point in this study at which patients went on the cyclosporine discontinuation or were maintained in the control treatment strategy.

Four black patients, at month 2 and, again, prior to cyclosporine elimination, not unexpectedly, we saw higher rates of acute rejection in black patients than nonblack patients in both treatment arms. By month 12, now following these patients on through the period of cyclosporine elimination for the Rapamune treatment arms, you see that black patients in the Rapamune treatment, as contrasted with the control, had similar rates of acute rejection, both 33 percent by month 12, this in contrast to the nonblack patients where we see results essentially mirroring that of the study as a whole with a slightly higher rate of acute rejection for the nonblack patients in the Rapamune treatment arm.

[Slide.]

Most importantly, though, the effect on blood pressure was also confirmed in black patients in the 212 study. We see that, in black patients,

these are now calculated GFRs at months 2 through 12, that there was a trend towards improvement in the Rapamune arm for black patients enrolled that, by month 12, was now statistically significantly different.

In fact, this represents a roughly 48 percent improvement.

[Slide.]

There was also a trend in mirroring the results in blood-pressure management as well for black patients although, again, with the small numbers, we don't achieve statistical significance. But, again, we see that four black patients, the systolic and diastolic pressures tended to be lower for black patients in the Rapamune arm than the Rapamune plus cyclosporine arm.

[Slide.]

Finally, in the last slide, we see that overall patient and graft survival at one year is essentially the same for black and nonblack patients in these two treatment arms, the black patient survival being 100 percent for the Rapamune arm, 94 percent for the Rapamune plus cyclosporine arm, and comparable to that of nonblack patient survival.

Graft survival is also comparable, 93 percent for the Rapamune arm compared with 94 percent for the control arm, again similar to the nonblack groups and none of these showed any statistical difference.

So, in sum, although the numbers are small, the outcomes in black patients in study 212 do mirror the study as a whole and, importantly, also show the same benefits in terms of renal function.

DR. ENGLUND: Dr. Abernethy?

DR. ABERNETHY: I have a couple. Looking at the severity of rejection in both studies across groups, do we have a chi square or some sort of analysis looking at the mild rejectors and the moderate rejectors? Just looking at the numbers, it would appear that the Rapamune-only group had more severe rejection.

DR. NEYLAN: If we could show again the 310 rejection histology slide.

[Slide.]

In the presentation I showed you, the rejections that we saw following randomization actually had no episodes of severe rejection in either of the two treatment groups. What we have

in the group randomized to the Rapamune was a predominance of mild rejections, 66.7 percent, and moderate rejections, either 2a or 2b, but, again, no severe rejections.

These were fairly similar to the severity seen of the rejectors in the control arm of 77.8 mild and then there are two types of moderate.

DR. ABERNETHY: I suppose one could do a chi-square analysis and see if that is different?

DR. NEYLAN: I would have to ask one of my statisticians. Robert, could you speak to that?

DR. GOLDBERG-ALBERTS: I am Robert Goldberg-Alberts, Rapamune project statistician. With the sparse numbers there, I wouldn't have done a chi square but I would be happy to get you an exact p-value for the difference in the distribution. I could have that for you after lunch, if you wish.

DR. NEYLAN: Thank you, Robert.

DR. ENGLUND: One more.

DR. ABERNETHY: What was your definition of hypokalemia and thrombocytopenia, just the numbers?

DR. NEYLAN: Yes. The definitions are slightly different depending on whether we are

looking at it from the listing of laboratory values or we are listing it as an investigator-initiated spontaneous adverse-event report.

In the case of the laboratory parameters, they simply are those of the laboratory standards. However, in the case of the spontaneous reporting of adverse events, we are simply relying on the investigator's personal view.

If I could have the potassium through time for study 310, what I would like to show is that, indeed, we saw in patients in whom cyclosporine was eliminated, that the cyclosporine effect in retarding potassium secretion was demonstrated on those patients and, in addition, the mild kaluretic effect that we have seen with Rapamune was also seen.

[Slide.]

This summary experience, while it created statistical difference between the treatment arms, did not bring patients down below the lower limits of normal for potassium. So, again, to reiterate, at month 3, as you would expect, these two groups are similar and then, as they proceed through the period in which cyclosporine is eliminated in the Rapamune arm, you begin to see statistical

difference which is maintained here at month 12 and here at month 24. Statistical difference, yes; but the Rapamune-treated patients are still maintaining potassiums above the lower limit of normal.

MR. LAWRENCE: To be absolutely precise about that, you are showing SEMs there. You are not showing standard deviations. What you really need to show is the fraction of patients that are below the level to say that, John.

I am not calling for another slide. I think that it is probably fine. But don't say that the potassiums are all fine because the mean is fine.

DR. NEYLAN: We brought 1500 slides, just to warn you.

DR. ENGLUND: Let's go on. Dr. Suthanthiran?

DR. SUTHANTHIRAN: John, I wanted to ask you about acute rejection. It is true at the end of the twelve months, both groups seemed to have a nonsignificant difference in the incidence of acute rejection. But if you look at post randomization, excluding the first three months when the patients are on cyclosporine, there is, in fact, an increase in the incidence of acute rejection.

I wonder, in your cyclosporine, you actually have three phases, an induction phase, a taper and a discontinuation. Is there a place in the taper time that there is a particular level of cyclosporine at which, when it goes below a certain threshold, you start seeing acute rejection?

DR. NEYLAN: First, as we are looking for the slide that I would like to show you showing the changing cyclosporine levels, we can first look at this.

[Slide.]

310, as you say, shows that, up to the point of randomization, there were identical and very low rates of acute rejection that were seen for all the patients enrolled in the study.

But, subsequent to the point of randomization and, with that, the onset of cyclosporine elimination in the Rapamune-treatment arm, you see an increment difference in the rates of rejection statistically significantly different here comparing new rates but in cumulative accounting, not statistically different there.

What I want to find is the histogram that shows the cyclosporine levels as they go through--I believe it is in your slide packet, Jim. What we

saw was that, not unexpectedly, with the attendant decrease in cyclosporine exposure, there was an--at the beginnings of the increase in these incremental rejection episodes following the randomization.

There was a window of time, in showing this histogram, between the elimination of cyclosporine completely.

Yes; this is the slide. Thank you.

[Slide.]

What we see here in study 310 are, in the red bars, the mean cyclosporine trough levels. Here is day 90, the point of randomization, the point at which cyclosporine is beginning to be tapered by the investigators for patients in the Rapamune arm.

In these line drawings, you see the rates of acute rejection for the patients randomized to the Rapamune arm and the patients randomized to the control arm. So, following the cyclosporine troughs, you can see that, at this point, things are fairly similar and there begins an incremental increase at or about the time that cyclosporine is being completely eliminated.

This incremental increase appears to continue a bit longer beyond the point at which, at

least for the mean, the cyclosporine has been completely eliminated. This may relate to, also, the rapidity at which the investigators were achieving the target ranges for Rapamune.

So, again, we have two moving targets here. We have cyclosporine coming down and Rapamune, of course, being adjusted upward to achieve the new target ranges.

DR. ENGLUND: Dr. DeGruttola had a question.

DR. DeGRUTTOLA: I just had a question on a similar point. You made a statement in the summary that there are similar incidents, similar rates of acute rejection, between the two groups, the 13.4 and the 20 percent with a p-value of 0.08. I am just wondering what the definition of similar rates is there.

Usually, statistically, when you describe something as similar, we are saying we can reject a difference of a certain amount or define a window of equivalence. I was wondering if that is how similar is defined or is it just reflecting the fact that the p-value doesn't happen to be below 0.05?

DR. NEYLAN: I see Jim Burke shaking his

head. I think I will ask him to address this question. Jim, if you could first identify yourself at the microphone.

DR. BURKE: Jim Burke, Wyeth-Ayerst Research. It is the latter that is true, that we call them similar because the p was not less than 0.05.

DR. DeGRUTTOLA: Another question that I had was regarding the analyses of cholesterol values and triglycerides and so on. Are those done on an intent-to-treat or on an on-therapy population?

DR. BURKE: These are on-therapy.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: John, that was a really nice presentation. I have a couple of questions. As you know, most patients entered into trials tend to be somewhat selected. And then you selected again, throwing out 18 percent of the patients in the 310 trial and 20 percent of the patients in the 212 trial. These were the nonrandomized patients.

Then you end up with patients who have extremely good outcomes. What were the patient and graft survival rates, rejection rates and resistant rates in the nonrandomized patients in both 310 and

212?

DR. NEYLAN: Let's show this slide while we are getting that data for you.

[Slide.]

This is first to look at the study 310 and compare the demographic features of the patients who were not randomized against those patients who went on to randomization. They are actually the same, or at least similar, with two exceptions.

As you might expect, the nonrandomized patients had a higher percentage of delayed graft function and a higher percentage of acute rejection than the patients who went on to randomization. And that addresses your point that, from a clinical-utility standpoint, these are both studies in which patients are enrolled but then followed through a critical window of time, a high-risk window of time.

Those patients who get to that subsequent time point are the ones that are logically candidates for this kind of strategy.

[Slide.]

This next slide shows the breakdown of the histologic grade of rejections by twelve months comparing the two randomized groups to that of the

nonrandomized group. To walk you through it is to say we have this period of time prior to the point of actual randomization. These patients went on to, of course, be randomized but their rejection episodes occurred in that early period of time.

As I say, 70 percent of patients that had acute rejections within the first three months actually went on to randomization. So that is the first point. We have mandated by protocol that only the severe rejection episodes would be disallowed from being considered for randomization subsequently at three months.

In contrast, we have, during this same window of time, this early three-month, the types of rejection, the histologic grades of rejections seen for the nonrandomized group. Being nonrandomized, then, we have only follow up for those. You see a small number of patients that, in the follow-up period, had rejection episode within that time frame.

Does this address your question?

DR. SHAPIRO: It doesn't discuss the patient and graft survival.

DR. NEYLAN: All right. Show this slide, please.

[Slide.]

What we saw for the treatment arms in study 310 was the overall one-year graft survival that was comparable, actually numerically superior, for the Rapamune treatment arm. These are the causes of graft loss within these groups. In comparison, we see the 95 patients who, again, were not randomized at the three-month mark and the causes of graft loss in this group.

DR. ENGLUND: Dr. Mannon?

DR. MANNON: My question relates more to the TDM aspect. I guess these results are based on the immunoassay and, in your conclusion, you related both either targets towards the immunoassay or the HPLC. Is the expectation that the immunoassay may be eventually available and, if not, do you think we could obtain comparable results if we stuck with HPLC?

DR. NEYLAN: I think I can just tackle this, Jim, if you don't mind. I think what we have seen is that there is a clear correlation between the immunoassay and the HPLC methodology so we can readily adapt values and put them in the context of what we have seen with these studies and the immunoassay.

Those centers are available now and they include both the central laboratories as well as, in some cases, on site within the transplant centers. As to the future, yes; an immunoassay is, indeed, in our future. At long last, I am happy to report that we are now working hand-in-hand with a company who will in, I hope, the very near future have a immunoassay out and available in a manner similar to the assays available for other immunosuppressants.

DR. MANNON: My last question again relates to levels. Were patients in either of these studies required or encouraged to be on a particular diet for the morning meal or was there any follow up or guidance regarding their diet?

DR. NEYLAN: No; there was no specific dietary restriction.

DR. ENGLUND: Dr. Ebert?

DR. EBERT: A couple of questions related also to TDM. First of all, it appears from your serum-concentration ranges that you have established, certainly there appears to be some evidence for the lower level, not going below a certain level, based on the fact that you had a higher number of rejectors.

But I am curious if you have any evidence in your upper level that you are looking for from a target range. Were there any adverse events that were correlated with exceeding that value.

DR. NEYLAN: Jim, do you want to say just very briefly? We did, indeed, look at that.

DR. ZIMMERMAN: We did look at several lab parameters. We looked at potassium. We looked at liver-function tests and I believe triglycerides and cholesterol and we did not find any trends for patients above 25 nanograms per milligram that would lead us to believe that there is a relationship there.

DR. EBERT: The second question is I realize you had to do a number of serum concentrations to titrate your regimens. Were there any population parameters, age, preexisting liver disease, et cetera, that might have helped you to more closely predict the ultimate maintenance dose?

DR. NEYLAN: We don't think so because we conducted the logistic regression analysis for the time period after randomization up to one year. We looked at factors such as HLA mismatch, donor-related--can we bring up that slide? I don't

have all the parameters. We looked at about five or six different parameters in that regression, also sirolimus concentrations But we could not find the relationship.

[Slide.]

This is for 310. As you can see, we have both drug concentrations there, gender, increasing recipient age, cadaveric HLA mismatch, increased ischemia time, increased donor age and number of rejections. Except for increasing donor age, there were no significant p-values.

DR. EBERT: These are things that predict rejection; is that correct?

DR. NEYLAN: That's correct.

DR. EBERT: I am looking at were there patient-related variables that predicted the drug clearance, the final dose that was required to be achieved in those patients.

DR. NEYLAN: We didn't do it in this population but, from all of our previous data with the tablet submission and the oral-solution submission, we did not find any patient-related factors that would help.

DR. ENGLUND: I think with that, we are going to actually take a break now. There is going

to be time for questions after lunch, after the FDA proposal. So let's take a break now. We are going to start at ten minutes after 11:00, fifteen minutes.

[Break.]

DR. ENGLUND: We will now hear from the FDA Presentation.

FDA Presentation

DR. TIERNAN: Good morning.

[Slide.]

My name is Rosemary Tiernan and I work in the Division of Special Pathogens and Immunologic Drug Products. I would now like to begin the FDA presentation of our review of Rapamune for the indication of cyclosporine withdrawal in renal transplantation.

[Slide.]

Before I begin, I would just like to acknowledge the efforts of the members of the Rapamune review team who are listed on this slide. I would especially like to thank our statisticians Dr. Cheryl Dixon and Dr. Karen Higgins.

[Slide.]

The presentation will cover the following areas; background information regarding the initial

approval of Rapamune in 1999 and the phase IV commitments that were negotiated. They will be briefly reviewed. I will highlight certain issues regarding the design of the clinical studies submitted in the current NDA to support a labeling change.

Efficacy and safety considerations will be discussed. Finally, our Division Director, Dr. Renata Albrecht, will present the questions to the advisory committee

[Slide.]

The basis of the initial approval for the prevention of acute rejection in renal transplantation included two randomized, double-blind, phase III studies, study 301 and 302, comparing Rapamune, 2 milligrams and 5 milligrams to azathioprine or placebo. Both studies demonstrated noninferiority with respect to 12-month patient and graft survival and a significant reduction in the incidence of rejection at six months.

Despite a lower rate of acute rejection at six months post transplant, renal function, as measured by serum creatinine, and calculated GFR was decreased at twelve months in the

Rapamune-treatment groups compared to controls.

[Slide.]

As a phase IV commitment, the applicant agreed to report long-term follow-up safety and efficacy data from studies 301 and 302. It was requested the data pertaining to GFR and serum creatinine be included as follow-up information and be collected throughout the entire duration of the study whether or not patients remained on study drug.

Based on 24-month data of only those patients who remained on assigned therapy, renal function continued to be decreased in the Rapamune treatment groups compared to controls.

[Slide.]

It had been noted in the double-blind studies 301 and 302 that mean and median whole-blood cyclosporine concentrations had remained at or above the upper limit of the specified target concentration ranges. An additional commitment was to evaluate the optimum therapeutic range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus.

Proposed sirolimus concentration ranges

were based on preliminary PK/PD analyses on a subset of patients in the phase III studies. The concentration ranges were evaluated prospectively in subsequent controlled trials including those that we will be discussing today.

[Slide.]

The applicant is proposing to amend the label to include a consideration of cyclosporine withdrawal at two to four months after transplantation and the use of concentration-controlled sirolimus adjusted to 15 to 25 nanograms per milligram when used without cyclosporine.

[Slide.]

The application for the labeling change is supported by two studies that utilize cyclosporine withdrawal with Rapamune in concentration-controlled regimen. Study 310 was an open-label non-IND study conducted in Europe, Canada and Australia with randomization at month 3 post transplant. Study 212 was an open-label study conducted in the U.S. and Europe with randomization at days 2 to 7 post transplant and we are in general agreement with the applicant's description of these studies and the reported results.

[Slide.]

In the cyclosporine-withdrawal arm, the dosage of sirolimus was increased after withdrawal and was adjusted to maintain whole-blood concentrations by immunoassay. Study 310 targeted trough levels of 20 to 30 nanograms per milligram while study 212 targeted trough levels of 10 to 20 nanograms per milligram.

[Slide.]

The strengths of these studies include the randomized controlled design, the quality of the concentration control of cyclosporine and sirolimus and the quality of follow up for patient and graft survival. Weaknesses of the study include the open-label study design which creates a potential for bias in the assessment of acute rejection episodes were comparative safety, the lack of adequate representation of subpopulations of interest such as African-Americans and Hispanics and the early randomized in study 212 allowed for dropout before reaching the time of cyclosporine withdrawal.

[Slide.]

We would now like to briefly cover the following efficacy considerations; the patient

population, discontinuations during treatment, patient and graft survival at twelve months, acute rejection after cyclosporine withdrawal and renal function at twelve months.

[Slide.]

Study 310 excluded high-risk transplant recipients from randomization to cyclosporine maintenance or withdrawal at two to four months after transplantation. Based on protocol-specified criteria which included Banff grade III acute-rejection episodes or vascular rejections occurring four weeks before random assignment, dialysis dependency, serum creatinine greater than 400 micromoles per liter or inadequate renal function in the opinion of the investigator to support cyclosporine elimination.

[Slide.]

In study 212, patients were randomized at an earlier time than in study 310. Patients with adequate renal function, as determined by the investigator, were randomly assigned within 48 hours after transplantation to cyclosporine maintenance or withdrawal. The remaining patients were eligible for randomization if their acute tubular necrosis or delayed graft function had

resolved sufficiently by the seventh day to allow them to receive cyclosporine A. Patients whose acute tubular necrosis or delayed graft function had not resolved by day 7 after transplantation were not randomized.

[Slide.]

Discontinuation after randomized assignment to treatment is problematic in open-label studies and it is difficult to determine if the actual regimen led to the discontinuation or if it was due to patient or physician concern over randomized treatment. More patients discontinued during assigned treatment in the Rapamune arm compared to the Rapamune plus cyclosporine arm. This difference is statistically significant in study 310.

However, all patients were followed through twelve months for rejection, graft loss and death whether they continued assigned treatment or not and the majority also had retrievable renal-function information.

[Slide.]

This table depicts the reasons for discontinuation in study 310. Although the overall rate of discontinuation in study 310 is

significantly higher for the Rapa treatment arm, comparison of the individual reasons for discontinuation fail to show any noteworthy differences.

[Slide.]

We are in general agreement with the applicant's description and report of patient and graft survival at twelve months after transplantation. As the applicant discussed earlier, patients and graft-survival rates were high, well over 90 percent, despite the difference in discontinuation from study drug between treatment groups in study 310, patient and graft survival among those in the Rapa arm was not inferior to those in the Rapamune plus cyclosporine arm.

[Slide.]

This slide presents the rates of acute rejection following cyclosporine withdrawal for the two studies. There was an excess of acute-rejection episodes observed in the Rapa arm compared to the Rapamune plus cyclosporine arm. This was consistent across both studies.

The excess in acute rejection, however, was not associated with a detectable decrease in

patient or graft survival at twelve months after transplantation as show in the previous slide by the high patient and graft survival rates.

[Slide.]

Renal function at twelve months post transplantation was measured by serum creatinine and GFR as calculated by the Nankivell method. Rather than performing an on-therapy analysis, the analysis of renal function that we will present attempted to include all patients with a functioning graft at twelve months including those who discontinued study drug.

There was a small amount of missing data reflected by the numbers of subjects included in the following tables. Overall renal function is better for patients in the Rapa arm. However, patients who experienced an episode of rejection had worse renal function regardless of which treatment group they were assigned.

[Slide.]

This slide presents the mean GFR at twelve months post renal transplant. In both studies, significant increases in GFR are noted for the Rapa treatment arms when compared to the Rapamune plus cyclosporine arm.

[Slide.]

This slide presents similar results for serum creatinine and creatinine results are significantly better in the Rapa arm.

[Slide.]

The next two slides present that and serum creatinine results by post-transplantation rejection status. In patients who have not had a rejection within the first twelve months post transplant, the improvement in GFR in the Rapa arm compared to Rapa plus cyclosporine remains. However, patients who experience a rejection have decreased GFR regardless of treatment.

[Slide.]

This slide presents similar results for serum creatinine. In patients who have not had a rejection within the first twelve months post transplant, the improvement in serum creatinine in the Rapa arm compared to Rapamune plus cyclosporine remains and, once again, patients who experience rejection have decreased renal function regardless of treatment.

[Slide.]

Safety considerations that we will present will include defining the exposure to sirolimus, a

review of the original Rapamune NDA adverse-event profile for the 5 milligram dose compared to the 2 milligram dose and then we will highlight specific adverse events that occurred in the current two pivotal trials.

[Slide.]

The mean trough concentration for sirolimus following 2-milligram and 5-milligram doses in the original NDA, study 310, are depicted on this slide. Note that the observed sirolimus trough concentrations in the current study 310, in the sirolimus concentration arm, are comparable to those observed in the 5-milligram arm of study 310.

[Slide.]

Trough concentrations were determined using an immunoassay method in the clinical trials and the applicant is proposing a validated HPLC methodology for therapeutic dose monitoring. This involves sending samples to analytical centers, laboratories, for determining the trough concentrations.

[Slide.]

The original Rapamune NDA was approved in September of 1999 and, at that time, when considering treatment-emergent adverse events that

occurred at a frequency of greater than 20 percent, a significantly higher incidence of fever, diarrhea, anemia, leukopenia, thrombocytopenia and hyperlipidemia occurred with the use of the higher 5-milligram dose of Rapamune when compared to the 2-milligram dose.

Consequently, our safety review focused on ascertaining whether these side effects would be more problematic in the current studies which utilize concentration-controlled Rapamune with higher drug exposure and, indeed, diarrhea in study 212 and thrombocytopenia in both studies 212 and 310 occurred at a significantly higher incidence in the Rapa treatment arm.

The incidence of hypercholesterolemia and hypertriglyceridemia and the use of lipid-lowering agents was not significantly different across the two treatment arms in study 212 and 310.

[Slide.]

Now, considering treatment-emergent adverse events that occurred in the original NDA at a frequency of greater than 5 percent and less than 20 percent, one notes a significantly higher incidence of chills, face edema, hypotension, hypokalemia, increased LDH, skin ulcer,

lymphocoele, tachycardia, insomnia and epistaxis with the use of the higher 5-milligram dose of Rapamune when compared to the 2-milligram dose.

In the present studies, 310 and 212, hypokalemia occurred in a significantly greater frequency in the Rapa arm.

[Slide.]

There were discontinuations for elevated liver-function test in the Rapa arm in study 310. Hepatitis B virus and hepatitis C virus data was not available on all patients. There was an increased incidence of elevated LFTs again in the Rapa arm versus the Rapamune plus cyclosporine treatment arms of both studies. There were no deaths in study 212 or 310 which were due to hepatic failure or attributable to study drug.

[Slide.]

The majority of the patients in the two studies were at lower risk to develop CMV infection. Approximately 12 percent of patients in study 310 were high risk with CMV-donor positivity, recipient-negative for CMV. There were no significant differences in the incidence of infection across treatment arms except for the higher incidence of Herpes zoster in the Rapamune

plus cyclosporine arm in study 310 and a higher incidence of fungal dermatitis in the Rapa arm in study 212 which Wyeth has already discussed.

There were no detectable differences in the treatment arms related to malignancy or post-transplant liver proliferative disease.

[Slide.]

To summarize, finally, please consider the risks and benefits of utilizing concentration-controlled Rapamune in a cyclosporine withdrawal regimen for renal-transplant patients. The risk of cyclosporine withdrawal include the surge of early mild rejection seen in these studies coupled with higher exposure to sirolimus and the associated adverse events such as thrombocytopenia, hypokalemia and elevated liver-function tests.

The benefit of cyclosporine withdrawal include the less cyclosporine-associated toxicities and mean renal function was improved in those patients who did not experience rejection.

That's the conclusion for the FDA review. Fairly brief.

DR. ENGLUND: Questions?

DR. ABERNETHY: With your review of the data, what do you believe the definition of

hypokalemia and thrombocytopenia was? I am just trying to understand. Is it less than the other group?

DR. TIERNAN: It is less than the other treatment arm; right.

DR. ABERNETHY: But we are really not talking about below 3.5 or below 50,000?

DR. TIERNAN: No. It is more of a relative--

DR. HUNSICKER: One thing I didn't get from the rapid thing. I, of course, have the advantage of the briefing document from Wyeth-Ayerst and only a brief thing from you. When you did the analysis for creatinine on an intent-to-treat basis rather than on a, whatever they called it, the basis that excluded patients who were not still on drugs. If you include all the patients, including the patients who rejected and whatever, what was the difference at the last analysis at one year? What was the difference in creatinine between those that were on the Rapamune and those that were on the Rapamune plus cyclosporine?

DR. TIERNAN: Dr. Cavaille-Coll, do you want to--

DR. CAVAILLE-COLL: I think we want to look again at slide 20, please.

[Slide.]

I have to first apologize that these analyses are not in the briefing package we gave you. We had to have our briefing package prepared a month ago and we only received the data that allows us to do these within the last few days.

The numbers, the n's, we see here show the numbers of patients for whom we were able to retrieve data. We believe that we have data on practically all the patients that still had a functioning graft. This represents, basically, the serum creatinine in micromoles per milliliter at twelve months for the different groups. This did not separate them out for whether they rejected or did not reject.

DR. HUNSICKER: This includes rejectors and nonrejectors.

DR. CAVAILLE-COLL: Yes.

DR. HUNSICKER: So long as they still have a functioning graft.

DR. CAVAILLE-COLL: Yes.

DR. HUNSICKER: And we have the problem of the loss because of a nonfunctioning graft and we

would have to deal with that if they were uneven. But they are relatively even so we are going to be able to ignore that.

DR. CAVAILLE-COLL: Actually, since these were very low-risk patients already, there were very few graft losses and deaths.

DR. HUNSICKER: I want to say this now as sort of a preparation to what I would like to say later on about the relationship between rejection and creatinine that, at the end of the day, taking all the patients, the patients assigned to Rapamune on an intent-to-treat basis wound up with about a 13, which is about--what does that translate, about 1 milligram per deciliter difference?

DR. ENGLUND: Who could translate the micromoles into milligrams per deciliter?

DR. HUNSICKER: It is about 0.1. It is about a 0.1 milligram per deciliter difference.

DR. CAVAILLE-COLL: Yes.

DR. HUNSICKER: In the favor of Rapamune even taking into account the increased numbers of rejections.

DR. CAVAILLE-COLL: Do you want to also see the next slide, 22, which will show you how it breaks down by rejector and nonrejector?

DR. HUNSICKER: Yes.

[Slide.]

I actually did see that one and what I noticed was that amongst the rejectors, there is no difference meaning that--well, I will just simply say there is no difference whereas there is a substantial difference in the nonrejectors. But at least it is not worse in the rejectors.

DR. CAVAILLE-COLL: I think that is what the slide says; yes.

DR. ENGLUND: Other questions? Dr. Suthanthiran?

DR. SUTHANTHIRAN: In both these studies, this is a concentration-controlled trial keeping sirolimus levels at 15 to 25. Do we have any data in terms of whether these levels are actually therapeutic? Is there any relationship between these levels and the absence or presence of acute rejection because when I looked at earlier data when it was presented, it appeared that the majority of patients, rejectors or nonrejectors, fell within this 15 to 25 nanograms per milligram, because we are going to place a lot of emphasis on keeping patients at these levels.

I wonder whether keeping them at this

level really has a clinical benefit in terms of either absence or presence of rejection or in terms of creatinine levels or in terms of clearance. I don't know whether the FDA looked at it.

DR. ENGLUND: Could the FDA respond to that?

DR. CAVAILLE-COLL: We didn't look at that specifically. Again, I must say that the information that we had on the retrievable information on twelve-month data for creatinine clearance, for creatinine and GFR really we have only had for less than two weeks. The company made a very good effort to try to retrieve that since that was not something that they had planned to collect originally under their protocols.

DR. ENGLUND: So we don't have, really, that much intent-to-treat pharmacokinetics at twelve months?

DR. ABERNETHY: I think that the issue at least some of us are feeling is that there has been no rationale presented yet for therapeutic drug monitoring with this drug. I think we are seeking that rationale.

DR. ENGLUND: We certainly want to discuss that after the FDA presentation. So, be

forewarned.

Do we have any other questions concerning the FDA presentation specifically that was given to us here?

DR. HUNSICKER: I guess I would like to ask the FDA, as they discussed with the sponsor the planning of this trial, there are two things that I find surprising. The first is that a lot of the analyses, the toxicity analyses, which are really the basis on which a superiority is being proposed, were not done on an intent-to-treat basis making it very difficult to understand.

Was this an understanding that you all had beforehand?

DR. CAVAILLE-COLL: The FDA had very little input in the planning of these studies. Study 310 was conducted outside the U.S. and not under the U.S. IND. Most of the planning of study 212, FDA had very little input on that

DR. HUNSICKER: Okay.

DR. CAVAILLE-COLL: As far as analysis for safety, it is customary to do an analysis in the population of all patients who received at least one dose of study drug. Another variation, though, is to do an analysis only based on patients who are

still on the study drug up to a certain number of days after discontinuation of study drug.

DR. HUNSICKER: Yes. I guess the reason I am coming down on this though is that the role of, in quotations now, toxicity here is very different in this application from the typical one in which you have a major comparison in which you are showing superiority and you just want to make sure you are not killing people or doing something nasty on the side.

There the toxicity is really supportive of the major conclusion. In this particular situation, the whole world has been turned upside down. You are showing equivalence for what we consider to be--or looking at the question of equivalence--for what are the major outcomes and you are justifying this new agent on the basis of less toxicity.

Under those circumstances, it seems to me that there is a real requirement that the toxicity analysis be done the same way that we would have done any other analysis for a major outcome; that is to say, on an intent-to-treat basis. We have to see all of the data.

DR. ENGLUND: Are there any more

questions?

DR. DeGRUTTOLA: A brief follow up on that question. I thought that was an excellent point and I think one of the issues here is whether toxicities are likely to persist after therapy has been discontinued.

On the one hand, there is the issue of whether comparisons are interpretable because they are based on the randomized populations which I think the previous speaker mentioned and the other issue I think pertains to the persistence of toxicity. So I think reconsidering this issue in the discussion about how to interpret the toxicity results with those issues in mind--

DR. HUNSICKER: I do have another question for the FDA when it is my turn again.

DR. ENGLUND: What I would like to propose is to finish up FDA questions and then, since we have a little bit of time, to go back to our pharmacokinetics questions yet before lunch. So, if we have any other questions, if this is an FDA question having to do with this presentation.

DR. HUNSICKER: This is a--I am almost embarrassed to say it is probably a legal question but there is an issue here about the requirement

for a sponsor to show sufficient numbers of major subpopulations of the United States for us to be able to say anything.

My question is--here, I will tell you in advance my opinion that we don't have enough information about blacks or hispanics to be able to say anything very substantial about them. We just simply don't have the data. I don't think that the small numbers of patients that were randomized to the 212, I guess it was, trial are sufficient really to give us any confidence about where things are going to be, particularly if you take it from the point of view that this is a group in which we know the risks, both acutely and longer term, are much higher.

The question is what do we have to say at the end of the day about the entire application when it does not have enough information about subpopulations? Can we say that this is a reasonable proposal for people who are in the population, that they were studied but that we don't have information, or do we have to say, "You really have to show information about your subpopulations before you come to us." I don't know the answer to that.

DR. ALBRECHT: I would like to say that what we are looking for you to say to us, from a patient-management scientific approach, is is the absence of that data so critical that, in fact, it is not possible to recommend whether there is a set of patients that can responsibly be managed with this regimen or whether the absence of that information is such that, in fact, it precludes putting the drug on the market because of possible risks for patients by not having that information.

In the end, when we approve a regimen, what we need to do is be able to provide labeling that can be followed by clinicians and others to manage patients. If, after deliberation, you believe that labeling cannot be written which can overcome some of these limitations that you are identifying, then it would be good if you were to let us know that so that we can then proceed accordingly.

DR. HUNSICKER: My shy partner over here who is the representative of the public interest has shoved over to me just the single datum that currently on the UNOS renal waiting list, African-Americans constitute 35 percent of the population.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: Can I ask a corollary question. The pivotal trial here is entirely non-USA patients, the 310. What are the implications of that in terms of approving a change in the labeling for USA patients?

DR. ALBRECHT: The regulations do allow the FDA to take into consideration data from foreign trials when making a decision about marketing and approving a drug product. However, the caveats to that are that the foreign data are of the quality and caliber that would be requested to be provided from US patients in addition to which the results of such studies must be applicable to populations within the United States.

If those parameters are met, then we are to consider foreign data in making a decision.

DR. ENGLUND: Dr. Johnson.

DR. JOHNSON: I have another question about the labeling. What are the federal limitations on what the label can say in respect to ethnic populations? Is there such a thing?

DR. ALBRECHT: Are you asking whether, if there is an absence of data, we can put such information into the package insert?

DR. JOHNSON: I guess that is my question.

DR. ALBRECHT: Just wanted to make sure. Again, we can put into the labeling information that factually reflects studies that were conducted and the results from such studies with the caveat that such labeling should then be able to direct physicians to properly use the drug in managing the patients that they would encounter in their practice.

Again, to follow up Dr. Hunsicker's question, we will look to you to give us guidance on whether the absence of certain subsets of the population are such that they would actually preclude clinicians being able to effectively use a particular drug regimen.

DR. JOHNSON: I guess my question is a little bit more to the point and that is I am not really asking whether or not somewhere within the insert that we can place that, "This drug was not studied in the subpopulation." I guess what I am asking specifically in the labeling statement, can we have limitations upon which groups this drug should be approved for for the current labeling indications.

DR. ALBRECHT: I think the short answer is

yes.

DR. ENGLUND: With that, we have a little bit of time. I really think now would be a good time to go back. We have such good pharmacologic expertise on the panel and with Wyeth-Ayerst. Perhaps, if you would like to, Dr. Abernethy, just rephrase briefly your one sentence and we could have a response from the company.

DR. ABERNETHY: I think the issue is that, with the data from these two studies presented, we really didn't see good data suggesting that a better outcome could be obtained by bracketing concentration ranges. If that data is absent, then the clinician part of my says it is easy. If there is a question, you just give a higher dose because there is no toxicity to pay for that.

In the FDA presentation, there was some data from historical studies that did suggest some dose relationship to some of the side effects. I am just trying to get a feel because the data we are seeing here is at a higher concentration range than any of the stuff that that came from.

DR. BURKE: I am Jim Burke with Wyeth-Ayerst Research. I have a slide coming up.

[Slide.]

This is a slide of the PK/PD analysis during the first 75 days following transplantation. It is up to 75 days. We looked at all the different possible explanatory factors that could lead to rejection.

Here is a simplified diagram showing only the effect of cyclosporine and sirolimus. So one can see that, indeed, there is a concentration effect between the concentrations of cyclosporine and the concentrations of sirolimus in outcome.

This was done in all patients during the first 75 days. So we have 525 patients in a fairly large range of concentrations. If one looks at the data after randomization and one wants to look at those that went on to Rapamune therapy, the number of acute rejections have gone down considerably and also the sample size has gone down to 215 patients.

So the power of doing an analysis of the relationship between effect and concentration after randomization is limited by those factors. Indeed, one should remember that we only studied a single concentration range after randomization. Although you have a few outliers, you should consider all of the outcome as part of the population.

So we defined the concentration as the

distribution of the concentrations in that population that was studied. Could we have used higher concentrations? Should you worry about higher concentrations? For that, I think you should go back to two earlier studies that were done, studies 207 and 210.

We started off on concentrations targeted at a mean of 30 milligrams per milliliter in the first two months. In those studies, although the overall safety and efficacy was acceptable, if one looks at toxicities at those higher concentrations, cholesterol, triglycerides, hypokalemia, they were considered unacceptable for chronic maintenance.

So when we designed study 310, we had those data available so we chose a lower range of concentration rather than retesting a higher concentration where we had observed toxicities.

DR. HUNSICKER: My recollection is that there was a slide shown, I think at the end of the pharmacokinetic section, which dealt with the values of sirolimus levels that were observed and what would have been observed if there had not been dose correction. That showed predominantly that there was an excess--the imputed, the presumed, levels would have been higher. There were very few

lower levels.

That is my recollection of that study; that is to say, using the non-dose-adjusted thing, you had very few people who were below the lower limits.

DR. BURKE: What we have heard now is that there is a weak relationship between the sirolimus levels above that and toxicities. There is probably some but we haven't seen strong relationships. So the argument from your data that you present, as I see it, is that the advantage of the dose monitoring is primarily to avoid excessively high doses for which we don't have very much toxicity demonstrated to us as opposed to--this is the slide over here--the possibility of having excessive low levels which would be associated with rejection.

I am aware of some things that I can't cite to you because they are in the literature. One was a regression in the earlier pivotal trials of the actual achieved levels with rejection that showed that people who were higher than, I guess it was 8 or something like that, very rarely had rejection episodes.

I believe that there are other data in the

literature that show, with low-dose cyclosporine, that also there is a critical relationship between the lower end, that you need to get above a certain level to avoid rejection.

But the question, I think, that is being implicitly put is whether we really are achieving anything on the low end here with the TDM as opposed to just simply avoiding the high end for which we have not yet defined toxicities.

DR. BURKE: Certainly, this slide does demonstrate the preference of doing therapeutic drug monitoring over giving a fixed dose. If one goes back to the toxicity and the data from the previous studies, actually the concentration-effect relationships on study 310 that I just showed you were very similar to the pooled data analysis of 301 and 302.

So we have reproduced that. What is the cutoff on the lower end? Well, in this early period where we do have sufficient rejections and a sufficient distribution of data, we were able to do an analysis where we dichotomized the data based on cutoffs of the lower end of recommended levels.

That was at 5 for sirolimus and 150 for cyclosporine. Indeed, we do find that, if they are

below those levels, they have a significant increase of the incidence of acute rejection. We can do that during that early period. I will admit that, in the later period, in the maintenance period, we don't have sufficient evidence to do that.

But I think the ranges that we are recommending will avoid clinicians treating patients with too low levels. We have seen that there are a few additional rejections and we certainly don't want to increase that number.

DR. HUNSICKER: Getting back to what is up there, and I am going to throw in a little bit--believe it or not, I take care of patients and I also have noticed that sometimes the levels are much lower than you expect. I have used sirolimus levels to adjust that.

But what you have here is a predicted--the range that you would get if you did TDM as opposed to what you would have had had you used an 8-milligram fixed-dose regimen and you would make the adjustments based on the proportionality of dosing levels.

What you see is that, at the bottom level, which is the risk for rejection where I think that

the data are fairly solid, there isn't a hell of a lot of difference. What you are really seeing is that you are avoiding higher levels with your drug monitoring. That is where--at least, I have taken the argument from that side of the table. There isn't a hell of a lot of evidence that there is much toxicity there.

It does bring in complexity. So the question is does the avoidance of those higher levels really justify the complexity of the issue.

DR. BURKE: I will go back and did see a slide showing the relationship between concentration and lipids and I think there is another parameter during those earlier phase II studies. You can put that up.

[Slide.]

To repeat the design of this study, we compared cyclosporine direction to sirolimus from the time of transplantation. There were about 40 patients in each group. As I say, the sirolimus concentrations were targeted at 30 during the first two months. After two months, the concentrations were to be reduced to a target concentration of about 15. You can see they are slightly higher than that.

Let's take a look at this early period when the concentrations are high, the average got as high as 35. You can see, in the yellow, the triglycerides that got up to over 4 millimole. I think that is over 400 milligrams per deciliter. Cholesterol; the average was up to 8, which is--I am trying to convert that. That is about 300 milligrams per deciliter. So it would not be reasonable to treat a population at those high concentrations for a maintenance therapy.

When you see that the sirolimus concentrations have been increased to levels very similar to those they were recommending, a mean slightly less than 20, you can see that there was an improvement in these laboratory parameters. Here I have shown two parameters. I could also show others that are affected by sirolimus. This is platelets.

So I think there was reasonably justification in the study design not to study much higher levels of concentration. Indeed, there is reasonable evidence that we should put that in our labeling today to avoid toxicities.

I have one more I will show you here, the SGPT values.

[Slide.]

You can see, once again, higher levels in the beginning and lower levels later when the concentrations are decreased. It is not quite as evident. I know they were very nice on these platelets. So there is evidence for us to instruct clinicians not to target very high levels.

On the lower end, to go back to the one slide we showed, you saw, whether you had given it on dose or whether you had given it on therapeutic drug concentration, there are a number of values that are low.

You have to realize that that presentation is an intent-to-treat presentation, that it includes data on patients, even those that discontinued a few days after randomization and did not have time to have their target concentrations increased.

So it is an extremely vast population. If one went out further, one would find very few patients that are below what we are recommending. So you shouldn't confuse that intent-to-treat population with what patients are actually receiving beyond six months, twelve months, and so on.

DR. HUNSICKER: Let me just do one last stab as sort of a provocateur here, the issue having been raised. Then I am going to cede to the pharmacologists who raised this question in the first place.

I can imagine three policies. One is you just give a fixed dose and you ignore what is happening. The second is you give what you have got, you would get therapeutic dose monitoring. The third is that you give a fixed dose and, as long as you stay out of trouble, you do what you are doing and, if you find that you have got some more toxicities, you go back and check your dose. Or, if you find that you are having a rejection, you recheck that dose.

What I am trying to get across is that I am not sure that we need to absolutely, in the indication, nail people to the requirement for this kind of therapeutic monitoring. I think that it might be sufficient to advise them that you can have levels that are lower than you expect and there is a lower level that you should be achieving and that you can find out about this. Of you can have toxicity and you can find out about the level with a TDX or with whatever measurement you are

using, rather than require that it be done in every case.

I think that--I am imputing to you what your question was, but I think that is really the issue that we are raising. We have to tie this to therapeutic dose monitoring.

DR. SUTHANTHIRAN: May I make a point. My question has been rephrased and I have been called a pharmacologist. I don't find anything bad about it, but the issue I was trying to make, I think your first slide made the point that, when you use different levels of sirolimus and different concentrations of cyclosporine, if the sirolimus concentration is high, you can reduce the incidence of rejection even with the lower levels of cyclosporine. There is a synergy between the lower levels of cyclosporine and high trough levels of sirolimus.

That point is very clear and you had enough cases in the first three months. My concern was, after the patient is randomized, when we suggest certain levels, 15 to 25, there is really not much data to support that 50 to 25 levels, in fact, prevents acute rejection because the number of patients who had acute rejection were in the 15

to 25 nanogram level. In fact, 16 out of 23 patients who had acute rejection were within this suggested target.

It appears to me a higher target level may be problematical from the toxicity perspective and the current data doesn't tell us what is the actual level we need to keep the patient at in order to prevent an acute rejection episode.

I wonder whether we could, in fact, go a little bit under the level. Maybe we will avoid some of the toxicity and have the same therapeutic benefit. This was the point I was trying to make, whether there is any data you analyzed or the FDA analyzed that tells us that a particular level of sirolimus is therapeutic in terms of preventing an episode of acute rejection.

DR. BURKE: The data that we do have is simply the quartiles that we presented. We know that, beyond a certain point, those 207 and 210 patients are now out to five or six years, about a quarter of those patients. They haven't lost their grafts. They haven't had an increase in their creatinine. They haven't had a rejection.

That doesn't mean that additional work does not need to be done, and this is always very

difficult when you are talking about long-term outcome, how do you target levels. Indeed, additional work probably needs to be done in that early post randomization period, or after three months, to learn how to better adjust those concentrations.

So additional work does need to be done but the evidence we have today does support the concentrations that we are recommending.

DR. NEYLAN: I don't know if this would help so I need to ask permission first. But we have additional data for 310. As you know, this is a five-year study. Most of these patients are now approaching the three-year mark. So, on this issue of the relationship between the suggested target range and the incidence of acute rejection, we do have data that is subsequent to the twelve-month mark on rejection frequency in these randomized arms.

I will again remind you that the randomized arm in 310 to the Rapamune maintenance therapy was downregulated in the Rapamune exposure to approximately the range that we are suggesting today.

So the question is, first, would that data

be of any use in addressing your question and, if so, would we be allowed to show it.

DR. SUTHANTHIRAN: I think so. If you can show that patients who are kept at the levels you suggest had a lesser incidence of acute rejection subsequently compared to patients who had lower than that level, I think it will support the idea that keeping the sirolimus at a particular level would be of benefit.

DR. ENGLUND: Yes; if you are going to be showing levels and rejection after the twelve-month period.

DR. NEYLAN: Let me show you, then, the trough levels first.

DR. ENGLUND: Wait. I think we need to hear from the division.

DR. NEYLAN: Oh; I'm sorry.

DR. ALBRECHT: I just wanted to comment. I don't believe that information has been submitted to the FDA for our review.

DR. NEYLAN: No; it hasn't.

DR. ALBRECHT: So we would be hearing your viewpoint, but we could not comment on it from the division.

DR. ENGLUND: Are we allowed to see it?

DR. ALBRECHT: Yes.

DR. HUNSICKER: Can they show it is the question.

DR. ALBRECHT: Having said what we said, certainly you can show it.

DR. NEYLAN: Do I have permission to show it? First, let's see the rejection slide. Then we will go back to that slide.

[Slide.]

This is the follow up then beyond the twelve-month mark onto 24 months for study 310. What we have seen in that, after the twelve-month mark, there have been no rejections in the Rapamune maintenance group and only two rejections in the Rapamune plus cyclosporine group.

The Rapamune maintenance group, again, is a group of patients that are receiving Rapamune doses at the suggested target range. I should also comment here that there were a handful of rejections seen in both of these groups at the twelve-month mark because of protocol biopsies.

If we could go to the next slide.

DR. HUNSICKER: Were those protocol biopsy rejections clinically manifest?

DR. NEYLAN: No; they were not.

DR. HUNSICKER: So we don't even know they are rejections other than by histological criteria.

DR. NEYLAN: Right. Exactly so.

DR. HUNSICKER: Just so that some of the nonnephrology and nontransplant people are aware of that, there has been a lot of debate about what "rejection" on histology means. There has been a lot of debate about the meaning of rejection found on histology without clinical correlates.

I don't take a side on that but I think that does put a very different picture on that little cluster of rejections that happens, if they are not clinically manifest but simply the consequence of protocol biopsies. It is not ever clear that they are rejection.

DR. NEYLAN: Right. But, again, let me emphasize the point that, at the twelve- to 24-month mark, there were no subsequent rejections in the Rapamune maintenance group. This group was receiving, now, on average, 6 milligrams of Rapamune today and maintaining mean sirolimus trough concentrations as measured either by the MS or by the immunoassay within this suggested target range today.

So, again, I just wanted to add that in

case it sheds any additional light on the discussion.

DR. CAVAILLE-COLL: May I ask a question, since we have not seen this data. The previous slide, please, that graph.

[Slide.]

Does this represent all patients randomized or does this just represent those patients who are still on study therapy at up to month 24 and, if so, what proportion are still on study therapy at month 24?

DR. NEYLAN: Jim, since you have access to the 310.

DR. BURKE: This is all randomized patients so that we are counting 215 patients in both groups. The number of patients on therapy is nearly identical, 145 and 146.

DR. CAVAILLE-COLL: Thank you.

DR. ENGLUND: Dr. Ebert?

DR. EBERT: Another question that relates to these two graphs that I have, the second graph that you showed I believe showed the mean concentrations over time. But I am assuming there was probably a pretty wide variation in the concentrations over a given period of time.

I think this really relates to my questions about what was your strategy for dosing and adjusting doses after randomization and did you, in fact, perhaps, have--and I don't know if you did or not, but did you have a group where maybe the adjustment took longer, you had a longer period of time where concentrations were low and whether that early adjustment period might have contributed to the fact that you saw rejections early on in the trial.

If you went back to that three-line graph with the cyclosporine and the sirolimus concentrations, as you start to drop off on your cyclosporine concentrations, you do somewhat compensate by increasing the sirolimus concentrations, but I am not sure if you do that completely.

So, the bottom line is I am wondering if maybe just not being aggressive enough early on may have contributed to some of the rejections that you saw.

DR. NEYLAN: If we could show the core slide from the pharmacokinetics showing the divergence of cyclosporine taper and sirolimus concentration ranges. Yes; this slide.

[Slide.]

This is the slide I believe you were referring to that shows the overlap period in which the cyclosporine is coming down. These are the mean trough levels of cyclosporine for the group and the sirolimus concentrations are coming up and are, at this point, just entering into the target range.

Yes; there is a window of time here in which that overlap is occurring and it is at least possible, from a clinician's standpoint, that some of these patients may have been experiencing rejection because there was, at the time, a relative decrease in net immunosuppression.

We have those two studies which both sought, at a time point post-transplant, to have clinicians change these two important variables in the immunosuppressive regimen. Both of these studies were somewhat groundbreaking. So I think it is not surprising that clinicians were exhibiting some degree of caution in making these changes.

I believe that, as this is better understood, that the rapidity of this change can be improved upon.

DR. ENGLUND: One more question?

DR. AUCHINCLOSS: It is actually a subject that I want to come back to this afternoon at some length, but if you could just put up D10. There is all this talk about how we are changing multiple drugs at the same time, but that wasn't true in study 212, was it? They were already, from day 10, on high-dose sirolimus.

When they withdraw their cyclosporine in the withdrawal group, that is a month or two later; right?

DR. NEYLAN: That's correct. The only difference is the target range of the sirolimus.

DR. AUCHINCLOSS: Oh; I understand. It is a slightly lower target range.

DR. NEYLAN: Which was slightly lower. When you adjust that for HPLC--

DR. AUCHINCLOSS: But there is only one adjustment at the time of cyclosporine withdrawal in this group of patients.

DR. NEYLAN: That's correct.

DR. AUCHINCLOSS: The other thing that I didn't understand, and this is what I want to talk about this afternoon, is that these two groups are completely different from early on. The top group,

that never had cyclosporine withdrawn, was the low-dose sirolimus and moderately high-dose cyclosporine whereas the group that eventually gets withdrawn is the low-dose cyclosporine from the beginning with high-dose sirolimus from the beginning; right?

So there is no comparison that you can make between these two groups when it comes time for the cyclosporine withdrawal in group No. 2. Events have already happened in the group above, and we will look at that this afternoon, that are completely separate from what--that don't have anything to do with cyclosporine withdrawal.

So I am interesting in looking at what happens in the second group, the cyclosporine-withdrawal group. I can only compare what has happened up until that time in that group with what happens to it afterwards. It is a very strange trial design.

DR. NEYLAN: You are right in pointing out that the phase II trial, 212, was asking a slightly different question than the pivotal trial upon which, obviously, the bulk of this indication is resting.

This question specifically about whether,

right from the beginning, lower exposures to cyclosporine coupled with the combination of a concentration-controlled use of Rapamune might be beneficial was one of the questions that was being asked by this study.

DR. AUCHINCLOSS: If you put up the E21 results, it looked to me like you got a great protocol there.

DR. NEYLAN: If you are about to show the rejection rates--is that what this is? Yes.

DR. AUCHINCLOSS: At the time that you came to cyclosporine withdrawal, you have got a 6 percent rate of accumulated rejections.

[Slide.]

What you did, when you showed these results, is you compared the cyclosporine arm to the red arm and you said, "Gee; you know it all comes out the same." The red arm was bad to begin with, or certainly less good. What I see when I look at that slide, is you have a 6 percent rate of rejection up until the moment of cyclosporine withdrawal and now, suddenly, you are 20 percent within six months afterwards.

I think you get 10 to 15 percent acute-rejection rates when you withdraw

cyclosporine. Don't look at the red bar. Just look at blue bar. That is what happens when you withdraw cyclosporine.

What I find most amazing is that the levels of cyclosporine at the time of withdrawal were only 100 to 150.

DR. NEYLAN: Right.

DR. AUCHINCLOSS: You have got a fantastic synergy. Why do you want to tell people to withdraw cyclosporine? Tell them to go to low-dose cyclosporine.

DR. NEYLAN: What we are trying to do with these two studies is basically define the margins, if you will, of how to use cyclosporine and sirolimus. On the one hand, we have the pivotal trials--

DR. AUCHINCLOSS: And you have defined it.

DR. NEYLAN: On the one hand we have the pivotal trials that were approved in '99.

DR. AUCHINCLOSS: Well, I think the pivotal trial shows pretty clearly that you get a 10 to 15 percent acute-rejection hit if you withdraw cyclosporine.

DR. HUNSICKER: I actually calculated the difference and it is--well, we will do it later

this afternoon.

DR. AUCHINCLOSS: This one goes from 5 to 20. That one went from 10 to 20, something like that.

DR. NEYLAN: What we have with these two sets of trials is, on the one hand, with the original trials, rejection rates that were in the range of 15 to 20 percent and the potential detrimental impact upon renal function when the combination was used in relatively full dosage for both in the long term.

On the other hand, we have now these sets of studies which define, if you will, a different limit where we can see similar rates of rejection, in this case in the range of about 20 percent, and, with that, the elimination of cyclosporine, a vastly different outcome in terms of renal function.

I think what you are suggesting is that there may also be opportunities to explore variations in between these two margins; that is, the combination in some lower dose or concentration-controlled mediated fashion, of both of these drugs in a maintenance regimen. I certainly would not discount that.

The goal, though, today is to convince you that these two studies also represent a safe and effective way to use Rapamune and that safe and effective way is that, in fact, in many patients, we can eliminate the calcineurin inhibitors.

DR. AUCHINCLOSS: There is no doubt about that. Probably about 80 percent of them, maybe even 90 percent, of them. But you have portrayed to us, and you intend to portray in the intended labeling, the notion that there is not going to be any increase in acute rejection. To me, your data strongly indicate otherwise, that you will, in 10 percent of your patients, pay a price with an acute-rejection episode that wouldn't have occurred otherwise.

DR. NEYLAN: I would not want to argue with you that there is not an incremental increase in rejection.

DR. AUCHINCLOSS: Shouldn't that go into a labeling change, that when you consider cyclosporine withdrawal, it is quite likely that there is a 10 percent or some finite risk, some measurable risk, to your patient population?

DR. NEYLAN: I am reasonably confident that, when all of this gets to the stage of

labeling discussion, that the data will be a part of that label. The data clearly demonstrates that, in fact, that incremental increase is there, yes. One other--

DR. ENGLUND: Final sentence, or sentences.

DR. NEYLAN: I was just going to--very quickly, then, if we could show this next slide.

[Slide.]

I was just going to raise the point that, even with lower doses of cyclosporine, in combination, there is potentially a penalty to pay in terms of renal function. This is a study that was done in psoriatic patients, so non-transplant patients. It looks at mean creatinine over a period of treatment in which these patients either received cyclosporine at relatively conventional doses for transplantation or received sirolimus as monotherapy.

The middle group is a group receiving low-dose cyclosporine and this same dose of sirolimus. You can see the spectrum of renal function.

DR. AUCHINCLOSS: I agree with you. I know you want to go to lunch, so save E29 for me.

We will come back to that this afternoon.

DR. ENGLUND: Good. We are going to break now for lunch.

[Whereupon, at 12:15 p.m., the proceedings were recessed to be resumed at 1:10 p.m.]

A F T E R N O O N  P R O C E E D I N G S

[1:15 p.m.]

DR. ENGLUND: We are now back from lunch. I would now like to open the meeting for the open public hearing. We have one registered speaker who is going be talking to us, Dr. Alan Wilkinson. He has some slides, too.

Open Public Hearing

DR. WILKINSON: I didn't realize I was, in fact, the entire joint public but I am pleased to be there and I would like to commend the presentations teams on the thoroughness of the presentation.

I am here really to provide both, I suppose, an experienced and a naive viewpoint on the studies. I am a nephrologist, transplant nephrologist, at UCLA. I am here in part as a consultant to Novartis and they have paid for my trip here.

I have also done studies for all of the companies that make immunosuppressant drugs and have, in fact, lectured and received honoraria for speaking for both Novartis, Wyeth-Ayerst, Fugisawa, Abbott. I don't think I am too selective in my--

[Slide.]

What I wanted to talk about was my perception of where study 301 stands in terms of what we do, and also where we stand as transplant physicians with regard to cyclosporine and withdrawing cyclosporine. I know that when John presented the data, he used still the half-life of transplants for about ten years.

I think it is true, but I think we just need to remind ourselves of this paper from Harry Hiriharan that appeared in the New England Journal of Medicine where, if you took out people who had died--and, of course, we include death as an endpoint in many of these things and that is not necessarily fair to the transplanted organ.

If you took out people who died and looked at living donors, the recipients of living donors, then the half-life is approaching forty years. This is in a calcineurin-inhibitor-rich environment. For cadaveric transplants, where the donor characteristics, of course, are less certain and there is pre-death injury presumably that we think affects the kidney, even in kidneys that are set up to be very subject to the effects of calcineurin inhibitors, even there, the half-life is approaching twenty years.

This is the UNOS data that was used. The USRDS data is, perhaps, a little less optimistic than that. But I think we have to accept that, during the calcineurin-inhibitor period, we have improved transplant survival dramatically. That isn't to say that the TOR inhibitors, Rapamune and potentially Certicam are not advances in what we do, but I think we have to place them in context of where we are coming from.

I wanted just to start off with saying, in addition, that I am not somebody who is particular in favor of using calcineurin inhibitors in high dose. I have written quite extensively on the effects of calcineurin inhibitors, or rather, on renal dysfunction in recipients of heart and liver transplants and, in fact, have just done a big review on liver-transplant recipients and renal function and dysfunction in those patients, large parts of which are, of course, due to calcineurin inhibitors. Some of it is due to injuries to the kidneys separate from that in liver recipients.

But, certainly, I am not in favor of keeping calcineurin inhibitors there if we can avoid having them. I also wanted to talk a little bit before I went further on sort of the power and

authority of this committee before us here today. I think it is true that the committee here has enormous power in terms of deciding what drugs are approved and how they are used to some extent.

But I think the labeling confers authority on the usage of drugs which goes beyond, in a sense, the power of committee. So, if you, as a committee, say that a drug should be used in a different way, that confers authority on that usage and, to some extent, we have to look at your fairness to the producer of the drug, in this case, Wyeth. Is it fair? Is the data they are bringing to you such that it is fair to them to change the labeling.

But, at the same time, I think you have to be fair to both physicians and patients in this and make sure that labeling doesn't put physicians, particularly, in a difficult circumstance when they choose to use different protocols in patients because, if we have labeling that says that, for example, the use of cyclosporine with Rapamune beyond three months in low-risk patients is something that is not recommend, if we continue to do that, that, to some extent, I think, puts us at some risk.

So I think we have to be very careful as you make determinations about labeling what impact that has on clinical practice or what impact that has on standard of care and what impact that has on the legal liability of physicians who are prescribing these drugs.

Remember that you have approved sirolimus for use with cyclosporine and prednisone. Sirolimus is used in large numbers of patients with tacrolimus. Although you are debating today whether, in fact, it is feasible to withdraw cyclosporine from patients on sirolimus, there are many patients out there on whom that has already been done in circumstances where physicians thought that was a sensible thing to do.

So, really, what you are looking at here is a trial which has addressed that. But we have to remember what clinical practice is achieving in the community and remember that the labeling of drugs and their usage are, in a sense, two separate things, whether the FDA likes that or not. But I would like to believe that the labeling of drugs should make it as simple as possible for the prescribers within the safety of those agents.

I also think the question before you here

today is different from the question before the European committee that addressed this issue because, in that case, they had actually refused, and I thought it was the wrong decision--they refused to approve sirolimus when it was first presented to them and then only approved it when it was presented to them with the improvement in renal function.

I think that the analysis actually misconstrued what was shown by the study, by the withdrawal study, because one comment they made in their scientific analysis of that data was that they recommended that sirolimus not be used with cyclosporine because there was evidence of additive nephrotoxicity when the two were used together.

As it happens in that study, there is no arm which shows whether there is additive toxicity when you have cyclosporine and sirolimus used together. If you had had an arm in that study where you had actually withdrawn sirolimus, you might have shown that. But you don't actually have that to show in that study.

If we go back to the 301 and 302 studies and look at the comparator arms in both of those studies, the GFRs in the comparator arms--in the

American study, azathioprine was used. In the European study a placebo was used.

But if you look at the GFRs at twelve months in the control arms of both those studies, they are as robust as the GFRs in the Rapamune-withdrawal study before you today. So, I think when we look at GFR and look at outcome, we have to be very careful not to jump from GFR to a recommendation about the usage of drugs.

I don't think any of us would go back to say that the correct protocol to use today is cyclosporine, prednisone and azathioprine. I think there would be few people who would argue for that although many centers may still be doing that. So I think that is an important thing to recognize.

I also think if you look at the change in GFR--let me get to that in a moment. Can you move on one?

[Slide.]

The other thing which I think is important in all the data, and Dr. Hunsicker, I am sure, will talk to this at length later this afternoon, is that rejection is one of the best predictors of a less-good long-term outcome. If you look at the patients in whom the half-life has improved, it is

those patients who have not had a rejection. So rejection is a very profound effector of long-term graft function.

We shouldn't trivialize that, I think. I know, in this study, it didn't reach statistical significance. But we should not trivialize the effect of rejection on long-term graft outcome. Remember, for each patient, their graft is the only one. In these venues, we discuss large trials and lots of numbers but, for each patient, their graft is the only one.

The other thing which may be addressed later is the predictability using the serum creatinine at one year or at some time period in terms of long-term graft function. I would like to remind you that that data holds best for patients that were on calcineurin inhibitors because that is the population in which that study was done.

[Slide.]

We have no really good data long-term in these studies. So I think my concerns are that we don't really know the effects of late acute rejection in this group yet. The data is still very early. Even the two-year data is still early compared to the long-term data.

The improved renal function certainly is there but, in any study in which you withdraw cyclosporine, you are going to get improved renal function. In fact, the delta GFR in this study is, perhaps, surprisingly small. If you look back at some of the old studies done by Curtis and Luke and some other studies, they had bigger improvements in renal function when they switched from cyclosporine-prednisone to prednisone-azathioprine which suggests that the effect of cyclosporine at this point is less than it maybe was in those studies.

The other thing which I think we should realize is that the patients who had rejection, if we look at their renal function subsequent to rejection, it was brought down to a greater extent than the patients who were on the cyclosporine-sirolimus arm, that the end result for the two groups was equivalent but the starting point was actually better for the Rapamune group.

So the effect of rejection in patients--I know it is small numbers but we are, in fact, arguing from small numbers, the effect of rejection was greater in those patients on sirolimus and prednisone only.

The other thing which I think is important in that data is that the GFR in the cyclosporine-prednisone-treated patients was, in fact, stable, that there was no decline. So when we talk about additive toxicity and progressive toxicity in those patients who were kept on cyclosporine, there was no proof of that in that study.

The GFRs were certainly lower. We would expect that in patients treated with cyclosporine. We don't know if those patients were taken off cyclosporine now at two years whether, in fact, their GFRs would improve to the same extent and that they would have GFRs equivalent to those patients maintained on cyclosporine because the effect on GFR of cyclosporine is, of course, twofold.

There is the hemodynamic effect of cyclosporine which affects the flow of blood into the glomerulus, the afferent arteriolic constriction, so the pressure in the glomerulus is reduced. I am going to show a slide at end of a blood-pressure study which is interesting at this context.

So cyclosporine has an effect on the

glomerulus by affecting flow in, and cyclosporine also has an effect because of its tissue toxicities which the experts on this committee are on as well. So what we don't know in the study is whether the continued reduction in GFR compared to the sirolimus group is, in fact, occasioned by injury to the kidney or whether it is occasioned just by perpetuation of the hemodynamic effect of cyclosporine.

You might even argue, and I have actually wondered about this for the TOR inhibitors, whether, because they affect intimal hyperplasia, perhaps reduce that, and whether they, in fact, might be protective against some of the fibrosis we see so that a combination of a TOR inhibitor and a calcineurin inhibitor might actually mitigate some of the long-term toxicities even though, when you just look at the GFR and the creatinines, that may not, at first blush, be apparent.

So I think we just don't know that data and, for that reason, I am anxious about us moving along too fast. So I think the relationship you have between renal function at a given time and long-term outcomes, we don't know. I have covered my concern that labeling shouldn't be too directly

prescriptive, that it should allow us a great deal of freedom in using these drugs.

[Slide.]

The other issue I think before us is that, because of the way studies are done, the comparator drug here is cyclosporine. That is not the only calcineurin inhibitor. The FDA would rule here on one agent within a class of drugs. I think that, to me, again, is not something I would like to see done because we don't have comparable data using tacrolimus. There are many people, I think, right across this room who, I think, have favored tacrolimus over cyclosporine and who believe that you can, very effectively, use low-dose cyclosporine and TOR inhibitor regimens to achieve excellent outcomes.

Of course, these studies, too, don't always include an anti-R2 inhibitor and the rejection rates on those studies are very low and the increase in rejection in this study may be unacceptable in that context.

A lot of the discussion here I think is reverberating now about where you can or couldn't discontinue cyclosporine. I would be concerned if every transplant nephrologist and surgeon in this

country did not know the data that we have presented here today. I would be dismayed if people were making adjustments to immunosuppression and yet didn't know this data.

It has been published. It ought to be known. So I don't think there is any question that this ought to be known by people changing the doses and the way in which we use drugs.

But I, for example, am an African. I don't look like an African at first sight but, in one definition, I am an African. I was born in South Africa. When I get my citizenship, I will be an African-American. To some extent, the decision as to whether or not you are African-American or not is your own decision.

There is also, in a sense, the prejudicial decision in this country of who is and who isn't an African-American. I am a South African and so I am very sensitive to these issues. At the height of apartheid in South Africa, if you did HLA typing and looked at genetic mix within the white Africaner race, about 40 percent of them showed evidence of African parentage.

So when we talk about subgroups and cleanly dividing subgroups of patients up so it is

safe in this group, it is not safe in that group, I think we have to be very careful in what we are doing.

I wanted, also, just to remind you of the steroid-withdrawal studies where we have had studies that have looked quite good in the short term where the five-year data, perhaps, doesn't look quite as good. So, again, I think we have to be careful.

I would also like to just mention again the potential cost. You have to use considerably more Rapamune to get an adequate level when you take cyclosporine away. Of course, you don't have to pay for the cyclosporine anymore.

[Slide.]

Then, finally, if I could just show you one last slide, just to go back to the GFR, I wanted to show you this slide because I like to think of kidney transplants as, in every patient with a kidney transplant, to some extent, there is some renal, chronic kidney, disease. I think we can presume that most kidney transplants have had some injury.

If you look at how we treat patients these days with chronic kidney disease, particularly

patients with proteinuria, the recommendation is that we use ACE inhibitors aggressively. We use ACE inhibitors aggressively even though we know that the GFR falls. The GFR falls, not because you are doing anything to the afferent arteriole leading into the glomerulus, but because you are opening up the efferent arteriole.

But the net effect is a reduction in glomerular pressure. Now, the other effects of ACE inhibitors, I am not going to get into that in too great detail here, but in all the metaanalyses of the protection of kidneys in patients with chronic kidney disease, the dihydropyridine, the nifedipine family, has been shown to be less good in protecting kidneys than ACE inhibitors. The reduction in proteinuria and the maintenance of GFR has been less good.

The title of this paper was Sustained Increase in Glomerular Filtration Rate in Kidney Transplant Patients with Hypertension Treated with Nifedipine. You can see here--unfortunately, the baseline was post treatment so they don't actually have a baseline before they were put on nifedipine.

But nifedipine is a calcium channel blocker and the argument for why this was good was

that it counteracted some of the afferent construction of cyclosporine. These patients were treated with cyclosporine and azathioprine and prednisone.

When placed on nifedipine, the GFR rose over twelve months to 56 compared to 46 where as those on lisinopril, an ACE inhibitor, remained the same. The take-home message that the authors put into this paper that, therefore, we should be treating patients with hypertension who have renal transplants with nifedipine and not with ACE inhibitors because the GFR is better.

In fact, in this presentation today, there has been discussion about the lower blood pressures in patients on sirolimus. But patients on sirolimus don't have the afferent construction that cyclosporine confers on the patients we give it to.

When you treat somebody with the dihydropyridine for blood pressure, you lower the blood pressure, but you also open up the afferent arteriole. So, if you don't drop the mean arterial pressures sufficiently, the actual pressure reflected on the glomerulus may actually be higher than it was when the afferent arteriole was constructed and the mean arterial pressure was

higher.

So we don't know if you have got a slightly lower blood pressure, not at the target level we would recommend now for patients with kidney disease, a slightly lower systemic blood pressure, mean arterial blood pressure, but a wide-open afferent arteriole, whether, long-term, that will be good or bad for the kidneys.

That is true for this study, to some extent, and it is true for the sirolimus studies as well. Over the short term, it certainly looks good. The GFRs are higher.

There is also a paper recently published in the Journal of Urology I wanted to bring to committee's attention, and that was a paper that looked at the long-term GFRs in transplant donors. It was a patient that had actually twenty years, so, of course, much longer than this. But the GFRs in those patients were actually, for the men, I think roughly 73. Corrected for age, they ran at about 68 to 67.

So the GFRs we are achieving with sirolimus and with azathioprine and with placebo were actually almost as good as you can get with a single kidney. You have a mild reduction in the

GFR with cyclosporine, that's true. But, provided the calcineurin inhibitors are not actually injuring the kidney over long-term, and we don't know that yet. I am not pretending we know that. But, with low doses, it may be that we could successfully use both combination of calcineurin inhibitors and the TOR inhibitors and actually achieve long-term GFRs which are very good, long-term creatinines that are very good.

So, if you could go back one.

[Slide.]

I just wanted to say we have, in fact, many studies now that are being published and are underway looking at combinations of either sirolimus or certicam with low-dose cyclosporine or tacrolimus in which the outcomes, in terms of rejection, are very good and which the outcomes in renal function appear to be better than when the higher doses of calcineurin inhibitor were used.

The doses of calcineurin inhibitor in these studies, which are called low-dose, are actually still quite high-dose in the context of those studies. I think there was a question earlier about that in terms of what we do.

I think I would be hesitant at this point

with what we know from what is front of us today to, in a sense, change the prescription boundaries of this drug to an extent beyond which I think the current evidence actually allows us to do.

Thank you very much.

DR. ENGLUND: Thank you.

For the committee, are there any questions regarding this presentation?

For the sponsor, any comments or questions?

DR. NEYLAN: No.

DR. ENGLUND: Are there any other speakers that wanted to say anything at this point in time--not from the table. At this point in time, then, I would like to close the Open Public Hearing and I would like to ask Dr. Albrecht to give us the charge.

## Charge to the Committee

DR. ALBRECHT: We would like to ask you to discuss three questions, and specifically to vote on the first one. So, while we are waiting for the slide to go up, let me go ahead and start the first question.

[Slide.]

Do the data presented support the

effectiveness or efficacy and safety of cyclosporine withdrawal and concentration-controlled sirolimus two to four months after kidney transplantation in patients treated initially with a regimen of sirolimus, cyclosporine and corticosteroids?

If I could elaborate a little bit on that question. We heard from Dr. Neylan the results from these studies where the patient survival graft-loss rates were reported as comparable. Then we did see presentations of slides, for example slide E8 in which acute rejection was reported to be statistically significantly different in favor of the Rapamune and cyclosporine, for example slide E13 where treatment failure showed a difference of 25.6 versus 37 percent.

So we would appreciate it if you could discuss the significance of those kinds of results within these studies. In addition, for example, if we think about slides E15 and E27, as was noted before, some of these analyses represent on-treatment patient subsets, not the intent-to-treat population, so, therefore, do not take into consideration all the patients that were randomized. We would appreciate you addressing

that as well.

Briefly, as far as during your deliberation of safety, again, which sets are presented and, for example, for slide S33 where we learned that discontinuation was 18 percent versus 27 percent and, again, the lower number in favor of the Rapamune plus cyclosporine arm.

If we can go to the next slide.

[Slide.]

If, after you consider these factors, the answer to the first question you believe is yes, should this consideration for this regimen be restricted to a particular subpopulation or, conversely, is there a particular subpopulation for which cyclosporine withdrawal should not be considered.

I think this has already been touched on during the earlier discussions so, specifically, the factor that between 18 to 20 percent of the patients in these studies, in fact, did not go on to randomization and how they reflect the patients that could not participate.

We have already heard that 94 percent of the patients, for example, in study 310 were white and a relative underrepresentation of other

patients.

Then, to continue, if the answer is no, what additional studies would be needed to support approval of such a maintenance regimen.

[Slide.]

On the question that I just finished speaking about, we would actually like a formal vote. On the following two, we are looking basically for your suggestions, namely, what additional phase IV studies would you recommend. I say phase IV because the drug Rapamune, of course, is already approved and, therefore, we have asked for some phase IV studies but others may be appropriate based on today's meeting.

[Slide.]

Finally, the last slide, and this is an area that is of great interest to us and we would like to ask if you have any comments or recommendations regarding study design and/or endpoints for controlled clinical trials that are intended to support the safety and efficacy of maintenance immunosuppressive regimes in renal transplantation.

DR. ENGLUND: Thank you.

Subcommittee Discussion and Vote

DR. ENGLUND: This is the discussion phase. I would like to give everyone around the table a chance to--why don't we go around the table. It will be easier. Dr. Mannon?

DR. MANNON: Do you want me to address each of these questions in turn?

DR. ENGLUND: No, no. I think we should just address question 1. I think we should address question 1, just the first part here because then we are going to have to go further on.

Yes?

DR. JOHNSON: May I ask a question. I thought, after lunch, we were going to have an opportunity to ask the sponsor some additional questions before discussion. Is that not true?

DR. ENGLUND: There is, but my intention, although we can talk about that, was as it relates to each of these three questions. The sponsor is here and they are available to answer our questions. So this is not voting. This is discussion.

DR. MANNON: Let me pass to Dr. Hunsicker first and then come back to me.

DR. ENGLUND: We don't have to do it around the table. If we have people that want to

respond to somebody else on the committee, then we can do that, too.

DR. HUNSICKER: It will surprise nobody that I have some thoughts on these issues and I have something that I have sort of organized to day.

You would like us to address these questions one at a time, but they are interleaved and if you don't mind, madame chairman, I would like to have permission to interleave them to some extent.

DR. ENGLUND: To some extent is fine.

DR. HUNSICKER: Okay. I want to start out with that we are in a new category here. I have already said this. The usual thing that we have looked at is to show that an agent, a drug, is more effective than either a placebo or a comparator and that it is relatively safe. The emphasis has been on the type I kind of analysis, can we be sure that this is better than what the alternative is. And the safety stuff has, to some extent, been supportive.

What we have today is the first of what I suspect is going to be a series of studies that really turn this paradigm upside-down entirely.

The efficacy issue is one of equivalence. The sponsor is not trying to convince us that the new regimen is superior to the old regimen in terms of the traditional hard outcomes but, rather, they are arguing that it is as good as that and that the side effects which will come down under the area of toxicities, if you will, are better.

I think it is important for to move down this line, but I think we have to do some things that are different from what was done today in order to go down this line.

Let me turn first to the issue of equivalence. The nature of an equivalence trial is basically that it is looking for type II error rather than type I error. You are trying to show that there is no real likelihood that there is a difference greater than a certain amount that would have happened with your new drug compared to the others or, perhaps, that it is superior.

To do that, what you really need to look at is confidence intervals. P-values are utterly meaningless in dealing with a type I error. No significant difference doesn't mean that there isn't a difference. It just means that you can't determine that there is a difference. You all know

that.

So what I would like to urge the sponsor today, if he does more along this line, or other sponsors in the future, is to phrase their analysis of equivalence in terms of confidence intervals and we ought to have, in advance, a statement of how much of a difference makes a difference.

So, for instance, if we say that equivalence is that the treatment is no more than 10 percent worse than whatever, we can come to agreement that if, in fact, the confidence interval doesn't include 10 percent that they have shown equivalence. But we need to have agreement before we start that that 10 percent is an appropriate number.

My own personal opinion is that 10 percent would be a reasonable number for acute rejection but it would not be a reasonable number any longer for graft survival. A 10 percent difference in graft survival between two regimens is clearly clinically meaningful.

So I found myself--what I, in fact, had to do, I went back when I got the briefing document and went through and calculated confidence intervals for all of these things. In fact, the

sponsor does relatively well for some of them but clearly not well for others.

The fact of the matter is that numerically the new regimen did better than the comparator regimen, the Rapamune plus cyclosporine regimen, with respect to graft survival and, because of that, the confidence intervals, in fact, are reasonable and don't suggest that there is a high likelihood that the new regimen is going to be worse within the period of time that we are looking at with respect to graft survival.

But it would have been a whole lot easier had these things been all explained in advance and clearly so we knew what we were accepting as equivalence. Now, with respect to rejection, it is clear that the new regimen is not as good as the old regimen. I have to say here that rejection, in my community--I don't know what FDA thinks about it--rejection has had sort of a dual life because it is a clinically meaningful outcome on its own. And I don't want ever to forget that.

So the fact that the new regimen is clearly less good than the old regimen with respect to rejection episodes can't be washed away, but it also has been used in our community as a predictor

of what is coming downstream and I have to talk about that separately.

When I say that the rejection episode was clearly higher, if you look at pivotal study 310, I think is the number--if you look at the number of rejection episodes following randomization, it is clearly higher in the patients that were assigned to the withdrawal of cyclosporine.

Is that disastrous? No; I don't know that that is disastrous, but it can't be ignored and we have to have that clearly stated up front.

Then, when we turn to the issue of the toxicity things, traditionally, it has been done that toxicity is based on treated patients or something like that. But today, now, we are really basing our long-term judgment on the acceptability of this regimen, on what it promises to us in terms of toxicity. For that, it seems to me, we have to insist on intent-to-treat analyses, across the board.

We have to understand what is--if we are going to say that this is a better way to go because of less toxicity, we have to understand that that is true for the entire randomized population.

I also think we have to distinguish between what I would call clinically apparent and numerically apparent toxicities. What I mean by clinically apparent toxicity is that an infectious episode, a pneumonia, or whatever, is clinically apparent but changes in blood pressures and changes in creatinines are not important today. They are important for what they may mean for the future and there is a smaller degree of certainty as to what their significance is for the future and we have to look at these in terms of what they mean for the future.

So I would like to see all of these analyses within intent-to-treat analyses and I would like to see a distinction between the clinically evident things today and the long-term outcome. This is because what I see as the issue before us today, the tradeoff of an increased frequency of rejection when you withdraw cyclosporine, which is as clinically meaningful outcome, increased today, for which you receive as compensation better serum creatinine and the hope of long-term better outcome with respect to graft survival.

Turning to that, I have already spoken

informally to the sponsor and said that I think that there is a more appropriate analysis than the analysis that we have of the renal function and progression over time.

First of all, to look at the patients at risk at each time point and take the average over time is statistically not an appropriate way to look at what is happening over time. There is a different group of patients at risk in each pool and you really can't compare the values from time to time.

The issue here is critical. Is there, in fact, a difference of creatinine over time, an analysis which I would like to suggest is a reasonable one. There may be other ways of doing this, to do a GEE analysis on the delta from baseline, the baseline being the time just immediate before randomization.

So what you are looking for is whether there is a stepped decrease in the first period of time and what is the trend of the creatinine after that time, or clearance or whatever other measure that you are having.

Most of my colleagues here, both in the audience and around this table, know that I have

done an analysis of what I call intercepts and slopes on creatinine clearance following renal transplantation. The results of this analysis which involved some 48,000 patients from the UNOS database are, in essence, that you can, on average, treat the progression of renal disease over time as linear loss of renal function, of GFR or creatinine clearance over time, just as you can with native kidneys.

If this is the case, if my analysis is correct, which I believe it is and it represents the reality--and I would like to just call Alan Wilkinson's caveat into consideration here; this analysis was done virtually entirely on patients who were receiving calcineurin inhibitors. So there is some question of whether it would be extrapolatable across.

If there is a difference in serum creatinine today and if there is no difference in slope--that is to say, if there is a step decrease--that step decrease will translate into longer graft life. The term that I have there is that about 2.5 milliliters of GFR is equivalent, on average, all other things being equal, to one year of graft life.

So if you have an improvement, a step improvement, of somewhere between 5 and 10 millimeters per minute better GFR estimate at one year or six months or whatever the time is, the anticipation is that that would lead to a two to four year improvement in graft life for the patients that were on the Rapamune-only regimen.

But this is conditional that the trends of serum creatinine or creatinine clearance following that time don't converge. That we don't really know. We have no idea what is happening to the difference over time. So we have a promissory note in exchange for a payment of an increased rejection rate which is a clinically important event and we need to know how solid that promissory note is before we can know whether this is a reasonable bargain or not.

I am going to go off that to the second series of questions that I have about this application. Section 2 in my little list of notes here has to do with approval and indication. I constantly annoy my friends at the FDA by pointing out that most of the transplant community pays no attention to what goes into an indication anyway. We never read the damned things and we do whatever

we please.

So the question comes up, then, what is the impact of approval and what is the impact of the indication. I, for one, believe that it is essential that our community continue to explore the issue of calcineurin-free regimens. I think that there is, from these data and other data that I am aware of with respect to sirolimus, the suggestion that, in fact, there may be major long-term improvements--may be. But it is a long way from saying that we have to continue these things, to say that we should say that they have now met the standard of use everywhere.

So the question comes up how right are we for calcineurin withdrawal and who should be doing it. I am lucky because I don't get to vote today, you know. I just get to express my opinion and raise the questions and let the rest of the committee decide to vote.

I think we have to explore this but I am not sure that I want this explored primarily in the least-expert groups of patients. If I ask myself where the approval of the FDA and where the indication would have the greatest effect, it is likely to have the greatest effect amongst the

people who are not as thoroughly involved in all of these issues themselves; i.e., in the less expert people.

That troubles me because I would like to see these issues addressed first in the most expert group of people. I have a feeling that what I am telling you I think it is still investigational. I am not sure we know the long-term impact.

This is complicated by the fact that we have a major limitation in the population about which we could say anything. We have already discussed the fact that there are no African-Americans. There are no Hispanics. Some of the groups in whom our problems are greatest are not represented with sufficient numbers, in my opinion, for us to be able to say anything.

I want to make sure that that does not say that there is not a benefit. I just don't think that it is at all established that there is a benefit or a harm. I think we do not know what would happen in African-Americans. I don't think we would know what would happen in Hispanics.

I also don't think we really know what would happen in people with initial ATN because, largely, those people are delayed graft function.

Those people were not randomized and so we have really no idea what would happen in this group.

In fact, the group that wound up getting randomized is still very fuzzy in my mind. One of the charges I would put to the FDA is it has got to be very clear what were the patients in whom this experiment was really done because, clearly, we don't know anything beyond the patients in whom the experiment was done.

Now, if an indication can be drafted that says that this should be done only in patients who don't have initial graft dysfunction, have not had a type III rejection within the first six months, whose creatinine is less than thus and such, and so forth, and who, by the way, are neither African-American nor Hispanic because we can't say anything about that.

If you can come up with an indication, that would be fine but I think it is going to be so complicated that I am not quite sure where you are going to wind up.

So my issues here are first methodologic. I want to have the way we present these kinds of studies changed so that we know exactly what at cost is, the potential cost, when we are talking

about equivalence and then exactly what the benefit is that we would see on the other end from the reduction in toxicity.

In this case, this means, what can we extrapolate to in terms of long-term graft survival. I have problems with whether this has reached a state of ripeness that I really want to have the least expert people in our community begin doing it which is what I think is implied by approval and by the indication and I really have some reservations about what the population is in whom we could say that this has now been established as safe and effective.

DR. ENGLUND: Did you have any specific questions for the sponsor?

DR. HUNSICKER: No. I was giving a philosophic tirade and I am sorry for that, but I am asked what my opinions are about these things and you now know my opinions. I feel good about this because I have to leave at 3:30 because I have got to make a plane to get home.

I know that the sponsor--I have spoken with them about some of these things in between--has some slides that they would like eventually to show that relates to the question of

whether there is a trend in creatinine or clearance or something over time that can be established. If you want them to show that, that would be fine with me.

I am happy to tell my folks at the FDA that they have got to establish that there is as reasonable likelihood that a short-term delta creatinine is going to translate into a long-term graft survival before I am going to feel that that is a benefit that will balance the increased rate of rejection early.

DR. ENGLUND: Let's go on and see. I heard you say you didn't have any questions, so let's go on. If someone has a question, or I might have a question--

MR. LAWRENCE: First I would like to thank the FDA for inviting me to participate in this. It is always reassuring to the patient community to know that at least somebody was there with their best interests up front. Even though the physicians and the pharmaceuticals are laboring on our behalf all the time, we still like to be there, so thank you for that.

I agree with everybody here. Everyone has said things that are intelligent and compelling

but, coming at this from a lawyer's viewpoint, the question that hasn't been precisely answered for me is what, exactly, are we supposed to be doing here. What words are we supposed to be changing?

In the stuff that you sent out several weeks ago that we all go to review before this, it says that the application is proposing to modify the indication that says that Rapamune shall be used in concert with cyclosporine. This says that the applicant is proposing to modify that to allow consideration of cyclosporine withdrawal.

Then I see the slides that were presented by Wyeth and it says cyclosporine withdrawal should be considered. This is much more directive. I think that there are probably a large number of patients who would benefit by having cyclosporine withdrawn. I take cyclosporine, myself. I am not unaware of the renal implications of taking this drug.

I also gather from comments that have been made by all of the knowledgeable people here that there are probably some patients in whom it should not be withdrawn or the jury is certainly still out. I am not here representing UNOS, who is my employer, but on the UNOS website, anybody can pick

up these data that I am about to give you.

The current waiting list which is tragically approaching 90,000 or something--it is a lot of people waiting for organs in this country. Caucasians represent 42.3 percent of the current renal waiting list. This is renal waiting list. Hispanics, 14.5, Asians, 5.6 and blacks, 35.1 So the data that we have seen today actually applies most directly to 42.3 percent of the waiting list.

That is simply an insufficient representation to support language which is direct, saying that cyclosporine withdrawal should be considered. I think that the use of the word "should" would be of much more interest to my fellow lawyers than it would be to physicians, most of whom--I spoke to a number of them before coming here and they said, "We don't care what they say because we are going to do what we feel is right for our patient anyway."

That may be, in reality, how medicine is practiced, but I don't think that a case has been made to be as directive as it should be. I would like to see something along the lines of cyclosporine withdrawal "may" be considered because, obviously, it would be in the interest of

many patients that cyclosporine, in fact, be withdrawn. I think that is conclusively true for many patients, but it is also conclusively true to me that that does not apply to all patients.

Therefore, saying that cyclosporine withdrawal should be considered is too strong a statement. I would just suggest that I would agree with Wyeth that withdrawing cyclosporine, where that can be done without any deleterious effect, should be done, in fact, and probably that is a majority of patients although what that means, I don't know.

So I would suggest simply reconsidering the terminology we are using here. Thank you.

DR. ENGLUND: Thank you.

DR. MANNON: I let Dr. Hunsicker go first because I knew he would--not that I knew that he had his plane but because I knew that he would have a lot of things to say.

Just a couple of things that may be in agreement with him and may not be totally in agreement with him, and the comments that I heard earlier today is that the question always comes as to who is doing this. Yes; I think that transplant nephrologists and surgeons do have ways of using

drugs in different fashions that may not be on the label, necessarily.

How it is being done is also important. The issue is that, if the label goes in a certain way, it means that anybody who has that kind of certification can and it may not be in a large academic center. It may be in a smaller transplant center. I think that is one of the concerns is that if this labeling goes as black and white, will everybody be doing it that way or is that on the entree for people to go ahead and do.

Clearly, there are caveats to doing that therapy. I do have questions about the applicability. Again, I think the race issue is one that was again reiterated by a number of people around this table. The issues of children are obviously not addressed in this and that is a small population. But, again, that should be addressed.

I also wanted to point out that in these studies, this was a very large population of cadaverics. In fact, living transplants were a minority of about 60 patients that were in the 212 study. Again, should the indications--I know in my practice, when we see living transplants, we tend to ease off on immunosuppression based on their

long-term outcomes.

I think the issues, again, that were brought up regarding delayed graft function and ATN, we don't know enough, I guess, based on the randomization about how to manage them. Along those lines is should there be indications regarding ischemic time. Can we tease apart the patients that had those rejection episodes based on maybe they had more prolonged hold time.

PRA or highly sensitized patients, how are they in this population and how are they thrown in and is there a way of going back and looking at the data collected by the sponsor to say that maybe that would be an indicator of someone that you would not really choose.

I think if I went around this room and said, "You have a PRA of 90 percent," the majority of us would probably not choose to put that person as a withdrawal patient, per se, but maybe there is data available.

My last, I guess, sort of point is about the monitoring. I have a lot of practical clinical experience about monitoring in this drug. Although there are eighteen centers available, I want to point out that, for most of us, we Fed-Ex our

samples or UPS our samples, so there is a 24-hour delay to get the sample to be monitored and another 24 hours, about a one-day turnaround time. So you are talking about a total of 48 hours which, although the drug has a fairly long half-life, it is sometimes difficult to monitor.

I think the availability of the more rapid, less labor-intensive, test would be--there are two issues. One is should we be monitoring these patients. I know that was brought up. The other issue is if we are going to monitor them, what is the best way to do that.

I think if you are going to have a mass, a large number of centers doing numbers of these tests, it will become a very important issue as far as the turnaround time and documenting--I think it would be helpful--I know that they talked about doing an algorithm on the labeling. It would be important for us to look at that algorithm, perhaps, and sort of decide if that would be of any help in the long-term monitoring of the patients.

DR. ENGLUND: We are going to go around the room, but I think in terms of the monitoring issue, perhaps could we spend a minute or two? Are there any other comments about the monitoring as we

go around? It really is implied in the part of the question that it would be part of the approval to do it, as has been done in the study.

Dr. Shapiro?

DR. SHAPIRO: I would just have a comment about monitoring. I guess two-and-a-half years ago, the position was that this drug did not require monitoring. We learned, at least in my case, the hard way that that was not correct. Even now in the context of this particular protocol, we found that we have not been able to use sirolimus safely without close monitoring.

I think that is probably a consensus among most people who are involved in transplantation.

DR. AUCHINCLOSS: I was going to say the same thing. I can't imagine trying to use this drug in any protocol at this point without monitoring.

DR. MANNON: It is difficult. We can't even agree about what the--I know one question was can you predict the level based on the patient or the race or the age or the weight. I can tell you, in my limited experience, it has been difficult to tell when you use a loading dose of 15 and then go on 5. We have been trying to look at peak--post

load doses to see if we can predict.

So I agree. I think you need--monitoring, for me, has been essential.

DR. HUNSICKER: Very briefly, a comment about monitoring. I agree with the people who have spoken who say that, in fact, we do monitor the use of this drug. The question I would have is whether the specific recommendations as to monitoring are based on anything other than grabbing some numbers out of the air.

I would not, at all, mind if this is an indicated drug, having an indication saying that there is a high variability of bioavailabilty and that it might be wise to check the levels. But to tie yourself to a specific monitoring program, as was described to us, on the amount of information we have to say that that makes sense would be difficult for me.

DR. ENGLUND: Dr. Abernethy?

DR. ABERNETHY: I would support that assertion, to simply say that, in my clinical experience, monitoring is essential. One can say that about many drugs. However, then, at a later point in time, one looks at the data, it sometimes turns out that the data support that that was a

correct statement and other times it turns out that that just was a clinical impression that doesn't stand up to scrutiny.

I think, at this point, I don't know. I haven't seen data either in the material we were provided or this morning that told me that we know that there is a therapeutic index such that, particularly at the high end of the concentration range, that we know where we should put a cutoff on that.

If that is correct, clinically as well as with the data, then the correct response, I believe, is that one simply increases the dose when there is a question about whether things are happening the way they should. If that is incorrect, then I think we need more data in order to assert that it is incorrect.

DR. SHAPIRO: There was the figure that the sponsor had shown showing that there were lower rejection rates with higher sirolimus levels and this interacted with the amount of cyclosporine patients were receiving also. So it is not completely pulled out of the air.

DR. ABERNETHY: That is very complicated because when you have those two drugs together,

they are interacting both pharmacokinetically with each other as well as pharmacodynamically. So that was an interesting chart without confidence intervals and without data points. I will have to say, I would have to really look at that data a long time before I could come to any conclusion about what it was trying to tell me.

I am not saying it is incorrect. I am just saying I can't look at a slide like that and say, "Oh; right."

DR. ENGLUND: Dr. Ebert?

DR. EBERT: Just maybe a short addendum to that. Again, most of the association that we are seeing here is largely, at least in my opinion, kind of a post-hoc analysis where patients were at least initially dosed on the drug, subsequently or retrospectively, were found to have certain outcomes associated with certain serum concentrations.

I think that differs from what might be considered to be a concentration-controlled prospective study where patients are randomized or targeted different target concentrations and then looking at outcomes. I am not sure that the two are equivalent as far as the conclusions that we

can draw.

DR. ENGLUND: Back to general comments about question No. 1?

DR. AUCHINCLOSS: The question is do the data support the safety and efficacy of cyclosporine withdrawal. I think, in a general sense, the answer to that question is yes. But the problem is, well, yes, it is apparent that that would be true for some patients, that there would be some associated risk and that there would be some associated benefit.

The problem is that both from limitations of numbers and from study design, it is very hard for us to answer precisely any of those aspects of where this efficacy applies. I think it is clear that we are talking about a group of patients that, in general, are doing well and I would second the comments of others that there are distinct populations including African-Americans about whom I would have tremendous concern.

What is the risk? I have no doubt that there is, indeed, a risk of acute-rejection episodes precipitated by cyclosporine withdrawal. It looks to me like it is about 10 percent. I am sure there are other side effects of high-dose

sirolimus. We saw dose-response curves for cholesterol, et cetera. So there is some additional risk by going to this protocol.

What are the benefits? Clearly, you are going to get rid of some side effects of cyclosporine. I have no doubt that there will be an improvement in renal function and I believe those data. What I don't know is what the long-term consequences of that are.

So what does all that mean to me as a clinician? From the data that I have seen today, I think I would consider cyclosporine withdrawal in a group of patients who are on sirolimus who are generally doing well but who are tolerating cyclosporine in some fashion very poorly and who demonstrated the capacity to tolerate Rapamune without side effects, or without major side effects.

I am not sure exactly how you turn that into a label. I am sure that the labeling words "should--" the word "should" should not be the one that is used. Frankly, I really think overall, at this point, that the data that we have are insufficient and premature to define the answers to these kinds of questions that make a labeling

change appropriate at this point.

DR. ABERNETHY: I really don't have much to add. I think that we, saying it slightly differently, are handicapped by trial design and that we are looking at a very selected group. I am struggling with how to generalize that effectively or if it, perhaps, should be generalized.

DR. ENGLUND: Dr. DeGruttola?

DR. DeGRUTTOLA: I have a number of comments. I think what Dr. Hunsicker and Dr. Auchincloss were referring to is what statisticians refer to as a surrogate-endpoint problem. We have evidence that there is adverse effect on acute rejection which is not, apparently, a clinical event but indicative of potentially future higher risk of clinical event. And we have apparent benefit on some measures of kidney function although it is not clear whether those would translate into longer-term benefits.

In addition, there is a concern about whether creatinine levels measured at a particular time have the same meaning regardless of the treatment that a patient is on. In other words, does a benefit in creatinine levels that results from a treatment have the same impact as naturally

having better creatinine level.

I think, to answer those questions generally requires longer-term follow up to understand the relationship between treatment, the surrogates of creatinine or measures of acute rejection and the longer-term clinical benefit in the absence of compelling evidence that we can infer longer-term benefit from the shorter-term outcome. That is difficult.

I think that the problem of interpretation of results would exist anyway, but it is compounded by the fact that we have been presented with a lot of as-treated analysis and, as Dr. Albrecht pointed out, the analyses that we saw of creatinine and GFR looked at the as-treated population or on-therapy population and such results are harder to interpret.

The FDA analysis provided us with intent-to-treat comparisons showing a benefit of the Rapamune alone which was useful. But the FDA analysis just gives us the two-by-two tables. The sponsor's analysis gives us the time trends which are really valuable to know for the reasons that Drs. Hunsicker and Auchincloss pointed out. We would really like to have some sense of whether

these are persisting or increasing.

It is precisely when you are trying to evaluate time trends in these effects that the difference between an intent-to-treat and an as-treated population would be so important to know because, in an as-treated or on-therapy population, where the populations are changing, it is hard to interpret the time trends.

So I think that it would certainly be useful to able to see the intent-to-treat analysis at least to give us a sense of whether the effects are increasing as they appear to be from the on-therapy analysis, the effects of benefit of the Rapamune alone on creatinine.

I believe that there may be additional evidence in support of a relationship between markers like creatinine and longer-term outcomes. I would be very interested in seeing such results from the sponsor if we can request that.

DR. ENGLUND: Would you like to show them now?

DR. NEYLAN: Yes; I would. Thank you. What I wanted to do was to show you some of the longer-term data and also look at some of the different analyses that address some of the

concerns.

[Slide.]

First, just a reminder, this first slide, we have the intent-to-treat analysis of renal function which concurs with the FDA analysis that the patients in 310 had enjoyed an improvement in both the mean serum creatinine and the calculated GFRs which was statistically significant.

What I would like to do is call up the slides that look at the slope intercept analyses. This is, I think, an analysis that is probably somewhat near and dear to Dr. Hunsicker.

[Slide.]

Calling up this first slide, looking at UNOS data, this recent publication from Johnson and colleagues looked at over 100,000 renal-transplant patients within the UNOS database between 1988 and 1998. As Dr. Hunsicker has pointed out to us both today and in his prior publications, it is important to consider not only where you are starting from but how quickly you are getting to the next place.

So the baseline creatinine as well as the rate of change in that creatinine are important measures when determining the likely success or

lack thereof of a kidney transplant. Indeed, in the best-case scenario, looking at this large database, when you start off with a great creatinine and you have a very small change in that creatinine from the six-month to the twelve-month mark, you can expect a half-life of 11.6 years.

If, on the other hand, you see a more rapid change, and, by change, I mean increase in serum creatinine, over this time point from six to twelve months, then that half-life is decreased and so on down the way. If you start off at baseline with a poorer functioning graft, you will have a reduced half-life even if your rate of change is relatively minor.

The worst-case scenario, of course, is when you start off with a poorly functioning graft and see a rate of change that is greater. There, the half-lifes are, of course, the worst. Taking this kind of approach, we looked at our own data and if we can show the next slide.

[Slide.]

What we looked at was a kind of similar slope-intercept analysis and looked at, in the case of the 310 patients, the patients who had the serum creatinines that were either excellent or greater

than 1.5. We looked at the rate of change between six and twelve months.

Is this correctly labeled, this creatinine? Is that at twelve months?

DR. BURKE: That is creatinine at twelve months.

DR. NEYLAN: Looking, then, at this baseline and the rate of change of getting there, you can see the following. You see in the Rapamune group that there is a preponderance of the patients who fit this bill--namely, excellent creatinines and a small rate of change. Again, the six-to-twelve-month mark is relevant because, as was alluded to, with the relief of cyclosporine and the relief of that vasoconstriction, one would expect that the short-term change up to six months might one thing but, subsequent to that, rate of change may well be related to other factors.

So we see this rate of change being the least in the Rapamune group compared to roughly half as many patients in the control group and so on down the way. Conversely, at the bottom, we see more patients, or twice as many, in the control group that start off with a worse baseline and have a more rapid rate of change.

[Slide.]

We also did another analysis that is a slope analysis of patients in the next slide who--this is 24 months. Is this data part of the package? Could you turn that slide off for a second?

DR. BURKE: That includes data that is not part of the package. It is creatinines after twelve months.

DR. CAVAILLE-COLL: May I ask you a question about the previous slide where you were showing--you were applying Johnson's analysis to your data. Was that submitted to the application and does that analysis include all patients treated or just the information on patients on therapy?

DR. NEYLAN: That is an on-therapy analysis, I believe.

DR. CAVAILLE-COLL: An on-therapy analysis? Was that analysis submitted to the application?

DR. NEYLAN: No; excuse me. Was that--

DR. BURKE: The analysis was not submitted. The data that was used for that analysis is in the application.

DR. CAVAILLE-COLL: So it is the

on-therapy analysis. It is the on-therapy data that you submitted to the application. It is not an intent-to-treat analysis.

DR. BURKE: No.

DR. CAVAILLE-COLL: And it is not an analysis that you have submitted to the FDA for review.

DR. BURKE: That's correct.

DR. CAVAILLE-COLL: Okay. Thank you.

DR. NEYLAN: So, rather than show you the other slope intercept which includes 24 months, what I would like to show it completor's analysis. One of the problems that we have in fulfilling the more rigorous statistical requirements of intent-to-treat is, in this case, the problematic return to calcineurin inhibitors which can occur in patients discontinued from the treatment group which then creates a kind of convergence. That makes it sometimes challenging to discern important clinical differences.

[Slide.]

One way to get around that is to do a completor's analysis. Here we have, again, an analysis that is taken from the dataset that FDA has received, although this particular analysis

that was--rather the dataset is within your hands. The analysis that we did was separate.

DR. CAVAILLE-COLL: Do we have the dataset up to 24 months?

DR. NEYLAN: Yes; you do.

DR. CAVAILLE-COLL: That does not include all the subjects on the study, then?

DR. NEYLAN: What this shows, working backward, is a completors' analysis so it includes only those patients who, from the starting point on through, are successfully treated in either group. So it takes away that bias of patients who are dropping out along the way in an on-therapy analysis.

What we see here with the mean creatinines is, again, data which is representative of the other datasets that we have shown you, namely that serum creatinines in the control group stabilize or slightly increase over this time period whereas the slope of the treatment arm is stable or, in fact, slightly downward.

I would certainly be open to any inquiries about that.

DR. ENGLUND: Dr. DeGruttola?

DR. DeGRUTTOLA: I just wanted to comment

on a couple of points. I think that the intent-to-treat analysis is valuable even if patients do end up crossing over to another treatment because that is the information that you really want, what is the outcome when you intend to treat a patient in a particular way but the reality is you may not necessarily be able to treat them in the way that you want to, and finding out whether there is, in fact, a benefit, in terms of creatinine, over time for patients who are intended to be treated with Rapa is exactly what you want to know.

If you do something like a completors' analysis, you are getting sort of a filtration effect in the populations. You are taking out the people that are having difficulty, so you may see an effect that is increasing but that may be purely artifact of who is left in that population.

While I think that there are questions of interpretation when you do the intent-to-treat because patients are switching therapy, you can do analyses that will tend to indicate whether the fact that the curves are coming together results from the changes in therapy for the population who must change therapy or loss of an effect in the

patients who remain on therapy.

You can do additional analyses to help with the interpretation, but the most directly interpretable analysis will be the intent-to-treat. The fact that patients have to change therapy is a result. It is an important outcome of the study and I don't think that you can solve the problem by doing the completors' analysis.

DR. NEYLAN: I apologize if I meant to suggest that we were solving the problem. But, in addition to the intent-to-treat analysis which shows the benefit, I was just hoping to provide some additional analyses which, while not perfect, can help to address some of the issues of patient dropout and, again, the challenges of comparing these groups of patients when the alternative to not staying within the study is most typically a return to the calcineurin inhibitor.

DR. DeGRUTTOLA: I think the problem is that we have the intent-to-treat analysis for the two-by-two table but we don't have the intent-to-treat analysis over time, which means that we can't get a valid estimate of the time trend. I think that is concern.

If you want to do completor analysis as an

additional analysis in order to help with the interpretation, that is okay. But I think that it would be valuable to be able to see the time trend for the intent-to-treat analysis to see what is going on.

DR. NEYLAN: I will ask the group. Do we have any time-trend analysis?

DR. BURKE: We are unable to provide an intention-to-treat time analysis at this time. We recently gathered the intent-to-treat at twelve months. We will be gathering additional time points but, at this present time, we cannot provide time analysis on intent-to-treat.

DR. NEYLAN: We may be able to very shortly.

DR. ENGLUND: I am going to interrupt as a prerogative here. In the specific slides that I would be interested in as intent-to-treat are E15 and E28.

DR. NEYLAN: Could we call those up.

DR. ENGLUND: You are showing me here improved renal function and these are really nice slides, but it is not intent-to-treat.

DR. HUNSICKER: There are two things. First of all, it is not intent-to-treat and the

second thing is that the people at risk are different at different times. They have got to do a proper analysis. I think that it would not serve Wyeth-Ayerst. It would not serve the FDA and it wouldn't serve reality for us to try to squeeze out an analysis between now and two hours from now.

I thoroughly second your comment about intention to treat and I am not going to say anything further. I think that this is a given. We have solved these problems long since. We don't have to resolve them. This is the standard.

I do want, for the purposes of the record, to put in a comment about the timing from which you are measuring slope and why I am so insistent upon that. There is, as has already been said by I guess it was Alan, a strong understanding that the acute effect of administering a calcineurin inhibitor is that you get a vasospasm in the kidney and that results in an acute decrease in renal function.

When you take off the calcineurin inhibitor, if you do it within a short period of time, that returns. So you have an acute effect that is vasomotor. You then have, we think, as a result of calcineurin inhibitors, progressive

fibrosis and other long-term changes of the kidneys that are not likely to be reversed when you reverse the cyclosporine.

The reason I make this comment is that if you are going to do a slope analysis, you have to make sure that your slope finishes after you have had the completion of your acute effect or the acute effect will be bundled in with your chronic effect.

That you showed, for instance, in the two-by-two analysis that the creatinines were still superior at 23 months or whatever the last time period was, doesn't really answer the slope question because that buries into that delta the effect of taking off the cyclosporine acutely. So, what we need to do is to get an estimate of what has happened acutely with the removal of the cyclosporine and then what the trends are long-term, independent of changes in cyclosporine dosing.

DR. NEYLAN: We have an analysis that is, again, based on the dataset that has been submitted to FDA but the analysis, itself, was not part of the packet and that is a slope analysis at a later time point.

Would it be all right to show that? I think it helps to address some of the questions you are relaying about the acute versus chronic effects.

DR. CAVAILLE-COLL: Is this the on-therapy analysis or intent-to-treat analysis?

DR. NEYLAN: This is an on-therapy, is it not?

DR. CAVAILLE-COLL: Because you submitted two datasets to us. You submitted to us very recently which I think is a closer intent-to-treat. Then there is the original data set with the application which was just on-therapy.

DR. NEYLAN: So this is on-therapy. Jim, I might ask you, again, since this is your data, to speak to it.

DR. BURKE: I will be showing two slides.

[Slide.]

They are slopes of creatinine over time. This shows data between six and 24 months, but, indeed, any patient for which we could determine a slope after six months was included in this analysis. So, even if they didn't complete twelve months, if they had a slope between six and twelve months, they are included. So this is sort of

between an on-therapy and a total intent-to-treat.

Let's look at two things, first of all, the slopes. If one looks at the slopes, one can see that, in both cases, they are significantly different from zero. We see that here. One takes a look at the slopes. One is negative for the group. That still includes cyclosporine which means their renal function is decreasing. In the patients for which had they had cyclosporine limited, the slope is positive showing that their renal function is improving.

If one takes at a look at the difference between those two, it is significant. So the two slopes are not converging. The time at which this was done; at six months, the initial effect of eliminating cyclosporine is no longer there, so we are looking at a true evolution after that. But if one wants to be even more conservative, I would to show the next slide.

DR. ABERNETHY: If I could interrupt and show my statistical ignorance here, but, doesn't this get us back to this issue of looking at equivalence of these slopes versus looking at differences between these slopes and are these 5 percent confidence intervals--I mean, am I headed

in the right direction with that thought?

DR. DeGRUTTOLA: Is the question the fact that the confidence intervals don't overlap imply a difference in the slopes?

DR. ABERNETHY: Apply nonequivalence, which is what is being suggested, I think.

DR. DeGRUTTOLA: I think that, on the face of it, it does appear that those slopes are different and the fact that you are rejecting zero implies that there are differences between those slopes.

DR. HUNSICKER: Not only are the individual slopes different from zero but the difference in the slopes, the slopes, themselves, differ by class.

DR. BURKE: That's right. Once again, in one group, those that are on cyclosporine, their renal function is decreasing. Those that cyclosporine has been removed, their renal function is improving.

So, one more slide.

[Slide.]

This is more conservative. We are looking at a slope after twelve months. One can see that the slope analysis for those who remain on

cyclosporine is still negative and significantly different from zero. On the other hand, the slope for Rapamune is, one would say, not significantly different from zero. So it is neither--it is flat.

Once again, the difference between the two treatments is significant.

DR. CAVAILLE-COLL: On those slides, do you have the actual n's of the numbers that are included in each one of those analyses? Which subset of the study is being looked at here?

DR. BURKE: I don't have them on the slide. Obviously, in the first set, to be included, they would have to be on-therapy at six months and have at least two points to be able to determine the slope. So, in the first analysis, if one looks at the rate of discontinuation before six months, let's say there were about 190 or 200 patients, approximately, in each group. So it is not an intent-to-treat analysis. We do exclude those that discontinued before we could establish the slope. But they didn't have to complete twelve months to be included.

DR. NEYLAN: Thank you for the opportunity to present that data.

DR. ENGLUND: Are there specifically more

questions relating to what has just been discussed now?

DR. HUNSICKER: Could I just say, from my point of view as an amateur statistician, that these are very encouraging data but this is still not the definitive analysis. It needs to be done right and we shouldn't try to rush this.

I am willing to trust that, between the company and FDA, that they can look at this and make sure that they have got the best possible analysis. But this is not a trivial issue. This really is at the nub of where I said--we are asking whether we are paying for the increased number of rejection episodes with something substantial. It has got to be convincing.

DR. ENGLUND: Dr. Ebert, would you like to--

DR. EBERT: I don't really have a lot to add to what has been discussed. I think, maybe to summarize my own thoughts, it appears that the efficacy really depends on the definition that one uses. If you are talking about acute rejection, obviously, there is a difference. If you are talking about renal function at a later time, at least from the twelve-month data, it appears that

there may not be a difference.

One is kind of, I think, challenged to decide whether the early rejections are more of a bump in the road or are they considered to be failures. I agree that the analysis needs some improvement. I would like to see the intent-to-treat analysis of renal function over time to be able to try to get an overall determination of the efficacy with this particular intervention.

With regards to the monitoring, again, I think there is some evidence for concentration versus effect. I don't know that it is strong enough that, as noted earlier, if we should get into the "should" say side of "should" monitor versus perhaps making a statement and saying that the majority of patients who experienced rejection had a concentration below X and that elevated lipid concentrations were associated with a concentration above X and then maybe leave it at that and to try to enable the clinician to use those serum creatinines in patients where it is indicated.

DR. ENGLUND: Thank you.

DR. SUTHANTHIRAN: I think, over the last decade, we have been basically adding on

immunosuppressive drugs. We went from one to two to three to four drugs. So I think philosophically to try to keep transplant patients on a lesser number of immunosuppressives is a very attractive option.

I actually had a lot of difficulty with this question about what should be the answer, like many other members here. I think the data clearly shows that the patient survival and the graft survival are very similar. You don't pay a price by holding back cyclosporine. The creatinine and creatinine clearances are better. We don't know what the significance is.

Clearly, some of the complications suggest the number of hypertensive drugs you may need. Blood pressure seems to be better with cyclosporine withdrawal. These all I would put on the paucity side of supporting cyclosporine reduction and withdrawal.

On the other hand, I do think that the incidence of acute rejection is increased. If you see the data from the point of randomization, then the increase is real, both in the 310 study as well as the 212 study. Almost all of the drugs we have approved in the last four to five years,

mycophenolate, Rapamycin, IL2-receptor antibodies, were all approved on the basis of the ability to reduce acute rejection in the six months.

In fact, that was the endpoint we all used. Now, we are coming up with a strategy that actually increases the acute rejection. On the other hand, this acute rejection doesn't seem to extol a very heavy price in terms of a one-year graft-survival rate. So I am very concerned about this acute-rejection increase.

The other issue is that, in both the studies, about 20 percent of the patients were nonrandomized. In other words, this kind of an approach is probably not applicable to broad-based patients but, perhaps, to more of a lower-risk patient population that are much more a selected patient population.

So this is all the data we have. I think it is very difficult for us to make a very strong case, either to vote no or to vote yes. But, as an advisory committee, we have to come up with some calculation and we can't take the Larry Hunsicker route saying, "I have got a flight at 3:30." So we need to make some recommendation.

I kind of lean towards a qualified yes. I

am not at all comfortable with the way the sponsor's proposed indication of how this should be changed. I share the view that the word "should" be done. I think it is a very important point.

The proposed indication, I probably would be more comfortable about would be to remove the word "initially." Here it says, "It is recommended Rapamune be used initially." I don't think we need that word and just leave it as it was originally.

Then, the second part of the statement where it says, "Cyclosporine withdrawal should be considered two to four months after transplantation," maybe--I don't know whether this is feasible. One way of defining it may be cyclosporine reduction or withdrawal may be considered in a selected patient population.

I think, of all the protocols that were used today and the data we saw, the best protocol was the patients in 212 in group B who were on low-dose cyclosporine and a good dose of rapamycin. They had a very nice, about an 8 to 10 percent, acute-rejection rate before they were randomized and then they went into what was intended in the study.

Mechanistically, there is some good data

to support synergy between cyclosporine and rapamycin. I am not sure we need to have an abstinence protocol, complete elimination. We may get the best bang for the buck by having a smaller dose of cyclosporine and have the option rather than have the recommendation that it should be eliminated.

So my suggestion would be to consider this indication statement that would say something like not just withdrawal but, "Cyclosporine reduction or withdrawal may be considered." I think it is very important to point out that this is in a subset of patients, that we simply don't have the data to recommend it universally, given the patient population we have studied.

Also, it is very clear in the 18 percent discontinuation in 310 and the 20 percent nonrandomized in 212 that we need to focus it on a very select population of patients. That would be my thoughts at this time.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: I don't have a lot to add to what Dr. Suthanthiran said. I guess if I had to answer the question it would be, "Yes, but." I am not convinced that having, as the pivotal trial of

a large non-U.S. population makes it remotely applicable to U.S. populations which I think are more heterogeneous.

The analysis has done a lot of selecting out, 18 percent in 310, 20 percent in 212, and the selected-out patients did very poorly, as I guess one would have expected. And then we had 37 percent failure in the 310, in the group randomized to Rapa. So you are dealing with sufficient winnowing that you get close to a cherry-picking situation with relatively small numbers of patients who, in fact, did quite well.

I share all the concerns about intent-to-treat but the reality is that there are some very convincing data about how well the patients who made it through the gauntlet of getting randomized and not having an efficacy failure, they did quite well but they certainly do not represent the mainstream of the patients that I transplant and I don't think they represent a great deal of the mainstream of the patients waiting for kidneys right now.

If you are going to say that this is okay to do, you are going to have to word it in a very careful way because, otherwise, you will open the

door to having a lot of kidneys ruined by people that are doing this in the wrong way and applying this to the wrong patients.

I think there are some very narrow indications for patients who have sailed through their transplant and are doing quite well who may be able to tolerate the increased risk of rejection who will do well without a calcineurin inhibitor.

What is less well defined is who those patients are. I am not sure we have enough data to say with confidence who those patients are and who those patients are not.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I would like to make a comment and, perhaps, Dr. Neylan can respond if he it appropriate, but I am somewhat troubled by the data with respect to the charge that the committee has given us. My difficulty is that, as a practitioner, I would utilize the drug very much similar as the sponsor has suggested in many instances.

But, as a committee member, in respect to evaluating the data, particularly in regards to safety, I am having some difficulty. The difficulty, really, revolves around the question of

consistency with respect to the fact that the data that is presented is not consistent with the target population.

I don't want to beat the dead horse but the main emphasis of the data is the preservation of renal function with the removal of the calcineurin inhibitor. However, in previous studies that were shown here a few years ago when the drug was first approved, the sponsor showed that the African-American population was not comparative to the Caucasian population with respect to rejection, particularly at the lower doses.

We are now presented with data that really shows, or a study that really shows, no data with respect to this subgroup. It is pretty easy to say, "Okay; well, let's just exclude that subgroup in the labeling," but I don't think it is that easy. As was mentioned, demographic data that was given in the presentation stated that 23 percent of kidney recipients in the United States are black.

But, in reality, as was noted, 35 percent of the waiting list is black and UNOS is dealing with that disparity by lessening, and maybe even eliminating, HLA matching with regards to kidneys

in the future and, therefore, that population will likely expand and, in some areas, may represent 50 percent or half of the patients who are going to be transplanted.

We also showed that the benefit in eliminating the calcineurin inhibitor, to some degree, is eliminated in those patients who have a rejection episode. Therefore, if you have half of the group, just hypothesizing, that may be eligible for a protocol such as this, who you know are a higher responder group, who may have a higher incidence of rejection, those folks may, indeed, have very little benefit from this regimen and, in reality, may be harmed by this because we don't know.

Maybe the rejection rates in this group are going to be zero. Maybe 10. Maybe a third. Maybe a half. We just don't know and so it is very troubling for me to sit back and think about how you would label this given the data that we have to evaluate and given the demographics of the United States renal-transplant population and what that population is likely to look like a few years from now.

DR. NEYLAN: I would be happy to respond

if you like.

DR. ENGLUND: Actually, I doubt that you could.

DR. NEYLAN: I would like to. Thank you. First, we certainly don't want to give the impression that the data from 310 and 212 should be universally applied or rather one-size-fits-all kinds of thinking. In fact, in the proposed labeling document that we have sent to FDA, we have said that the data in black patients in insufficient to make a specific recommendation.

The current labeling for Rapamune has looked, as you mention, quite thoroughly at the potential difference that black patients might well require a different dosing strategy and, indeed, the 301 study is supportive of that idea in that, from the efficacy standpoint, the acute rejections were statistical lower for black patients in the 5-milligram dosing arm as opposed to the 2-milligram.

However, we realize that that, in itself, is not enough and we have continued additional studies and we have postmarketing agreements with FDA to continue in these efforts to expand our understanding of how Rapamune is best utilized in

black patients.

I think one of the overriding concerns for us in presenting this data on top of the previous data is that we want to afford clinicians the opportunity to optimize and individualize treatment strategies. I think Dr. Hunsicker has intimated earlier that we are long past the early days of transplantation where we can look at a kind of one-size-fits-all approach. I dare say, also as Dr. Hunsicker mentioned earlier, that in near-future applications to this committee, many other groups may be proposing strategies which look at the long-term maintenance to start from a sort of nonequivalence standpoint and say, "Okay; that is the bench where we have to stay level but, from there, what can we do to reduce long-term toxicities?"

So what we have shown you today is a balance of some tradeoff. We will agree with everything you have said that this isn't meant to fit all patients. But we want to get this out there because we think it represents a potential viable option for some patients.

We studied the patients we did because that is who we had at hand. But we know our job

isn't finished. We have additional studies to do and we want to take those on.

DR. ENGLUND: While I have you up there, my question is what is being planned or actually done in terms of pediatric studies?

DR. NEYLAN: I'm glad you asked. We have three pediatric studies ongoing now. Two of them are being done in concert with Napratix and NIH. The first is a large-scale study of some 400 patients looking at the use of Rapamune in combination with cyclosporine to determine whether steroid withdrawal is feasible in this group of patients in which corticosteroid complications are especially problematic.

We have a second large-scale study also being done in concert with napratix looking at the potential efficacy of Rapamune in combination with either of the calcineurin inhibitors for high-risk pediatric recipients, those being defined as patients who have had at least one prior episode of acute rejection.

There, we are looking at not only longer-term graft survival but also examining histology at later dates. Finally, we have a study being done through an NIH grant looking at

calcineurin-inhibitor-free regimens in the pediatric population. So we fully recognize our responsibilities in that area as well and we are moving forward.

DR. ENGLUND: Do you have any studies ongoing that haven't been mentioned here in terms of African-American and Hispanic populations?

DR. NEYLAN: Yes; we do, and we have ongoing discussions with FDA about future trials as well. One of those is, indeed, a postmarketing commitment that stems from the original submission of the 301 and 302 data.

DR. ENGLUND: Dr. Hunsicker?

DR. HUNSICKER: On a slightly different tack, I noticed, of course, that you had a lot of biopsies at twelve months. Do you have anything to say about what you found in the biopsies in terms of fibrosis?

DR. NEYLAN: We, unfortunately, have run into much the same problem that other protocols have in their attempt to incorporation protocol biopsies into the regimens. If we could show this next slide.

[Slide.]

What we found, in asking all principal

investigators to obtain protocol biopsies in all patients enrolled in 310 was that many of them were fairly good at getting the baseline biopsies, those biopsies at the time of transplantation. But, unfortunately, we had a much lesser number, roughly a third of the study population obtaining twelve-month biopsies as dictated by the protocol.

So our ability to analyze the paired biopsies in these two treatment groups is severely limited by the small numbers. What we found with those small numbers is that the composite score, the chronic allograft damage index, which is a summation of individual elements 0 through 3 for the six categories and can be ranked, therefore, from a summation score of 0 to 18, was, for both groups, on the order of about 3.5 and not statistically different.

We found that there was probably a little bit of sampling bias as well in obtaining these biopsies in the net slide.

[Slide.]

In that, again, of these very small numbers of patients, the renal function at the time in which these biopsies were obtained was somewhat different for the yes/no of obtaining biopsies

between these two treatment arms so that, for the Rapamune group, the biopsies were more likely to be obtained. These are numeric trends, not statistically significant. But the GFRs tended to be slightly lower for those that got biopsies as opposed to those that did not whereas, for the control group, the GFRs were just the opposite. They tended to be slightly more than those that did not.

Given that this is an open-label study and clinicians knowing full well that patients are going to have an important element of the regimen removed, it is not surprising that there was as sort of differential predisposition to this kind of behavior.

I should add that, as I said, this study is five years. We held an investigator's meeting in the fall just at the time now where the patients are starting to enter the three-year mark. We have exhorted, extolled and badgered in any way we can the investigators to obtain three-year biopsies on as many patients as possible because we, again, do have a number of baseline biopsies.

So, even if these investigators haven't gotten the one-year biopsies, we are hoping they

will get the three. It may be that the difference in function that we are seeing may be more easily expressed in the histology with a longer period of time on these two separate regimens.

So we are certainly anxious to see those three-year biopsies and certainly, as the data becomes available, they will be brought before the FDA.

DR. HUNSICKER: I guess I find myself with another question for my FDA hosts over here, and specifically Dr. Cavaille-Coll, I have spoken with you about this before. Let us assume that they submit, and you agree to, an analysis of the creatinines over time that is very rigorous and that shows something similar to what we have seen here which is a diverging trend, a trend for the creatinine to be rising or to be more negative, if you will, in the continued cyclosporine and Rapa as opposed to the rapamycin, itself.

Let's assume that the qualified yesses I heard some of turn out to be the majority opinion. I don't know quite what I am asking here but what I am trying to get across is that it would seem to me this is one area where it is absolutely crucial that these patients be followed long-term in an

intent-to-treat fashion so we find out whether these early changes do, in fact, mature into a difference in graft survival, which is what we are looking for.

I think that this is one of the places where whether you speak about this in terms of accelerated approval with ultimate validation later on or however you want to term it, we have got to assure that if there is an indication given, we have to confirm what this means in the long haul.

DR. CAVAILLE-COLL: Are you suggesting that, before we take any kind of decision, that we should be looking at the analysis you are proposing at these folks up to 24 months as they are entering their third year and that that should be the intent-to-treat analysis including all the patients that were in the study that still have a kidney to generate.

DR. HUNSICKER: It is not going to be a trivial issue because there are some patients who are going to be lost because they have failed, and that is obviously an informative failure and you have got to figure out how you are going to analyze that, whether you do it by medians, or whatever.

But I believe that. I am going to assume

you are going to get some recommendation. All of what we do, all of what my colleagues do because I don't vote today, is a recommendation to you anyway. What I am suggesting is that, however this comes out, my feeling is that I would not want to act, were I voting, until I saw the results of a really well-done slope analysis because I think we are trying to bet a known, maybe not too great, negative today against a promise of something that may be substantial and I want to have that promise of what is substantial in terms of creatinine be tied down as best I can.

But, no matter how you do it or we do or anybody does it today or tomorrow or the day after, the proof of the pudding is going to be in what happens five years from now. I think that one of the things that is essential is that there be an understanding that, if there an approval given of some form, that this approval has to be validated, if you will, downstream by seeing whether these differences in function, in fact, translate ultimately into differences in graft survival.

DR. ALBRECHT: If I may go ahead and sort of paraphrase what I think you said and, really, in a sense, review some of the options that actually

are available to us. I think the issue you raise about, let's say, five-year follow-up data in the setting of a regulatory decision earlier than that, under the regulatory options available to us, we could take such a course if we were to approve and indication and then request a phase-IV commitment for data long-term.

That is certainly one approach and that would be the kind of approach where we felt that a decision at this time was based on adequate information and one that we could comfortably reach. Clearly, this is why we are asking you to assist us with making this decision and that, in fact, the long-term data is just to confirm and make us comfortable that the hypotheses and decisions we made early are, in fact, confirmed.

However, if, to take it to the next stage, if we are dealing with--we are construing surrogate endpoints where we believe they are likely to predict the long-term outcome but we really don't have the data on which to make that conclusion, then there is, under the regulation, a section called Subpart H in 314.500 where what we say is this is an approval based on a surrogate which we believe will have predictive value long-term

clinically but we are not certain.

As part of that action, the company is required to continue clinical trials--in this case, the long-term follow up for example--and provide such information to, in fact, confirm or show that these results are not consistent over time and then the regulatory action would follow based on those results.

Having gone over those two, I think what we would like to ask you, as the committee, as you are discussing and voting on this, is to provide us your best advice on whether you believe the findings now, the likelihood is that what we would be doing long-term is confirming--or whether the information is such that, at this point, it would premature for you to expect that these results are predictive.

In fact, the final option really would be to say the information we have is so preliminary that we do need further data before we can even reach a decision. So I think those are the three options before us and we look to you for guidance on which of those really you believe scientifically and clinically are supported by the data presented.

DR. ENGLUND: Are there any comments

before we proceed with voting on No. 1?

DR. SHAPIRO: I have a question for John. Do you think that, if you had more time, more follow up, maybe an additional trial that would strengthen and sort of amplify in the data that you have presented, that that would make your position a little bit stronger but, perhaps, also, more generalizable and would it be worth it from Wyeth's point of view to try to do that to increase everybody's confidence in your claim?

Right now, everybody is sort of saying, "Yeah, well, for a very small subset of patients who are doing really well, this is probably a good thing but they represent not a huge number of patients whom we are transplanting today in real life."

The question is, if you had more information, would it be stronger from the company's point of view to have a stronger indication.

DR. NEYLAN: Let me address that in two parts. One, yes. Wyeth is, in fact, even now, undertaking a variety of studies which further explore this issue, the issue of the use of a reduced calcineurin inhibitor, the issue of

continued exploration of a withdrawal strategy.

In fact, in that latter point, we are now initiating one of the largest clinical trials in the maintenance population that has ever been undertaken and that is a randomized comparative analysis for the maintenance population of a continuance of calcineurin inhibitors versus a conversion and taking patients with all ranges of renal function.

We are building into that protocol biopsies and a variety of what I believe are going to be very important elements to help the community better understand these issues as they relate to the long-term care of recipients.

So the commitment is there. It is ongoing. What we have with these two studies, however, is now two-year data for 310, emerging three-year data, and a commitment to go to five. At each of these time points, these twelve-month time points, we are seeing a consistency or a confirmation, if you will, of the elements that have come before.

So, while the commitment to continue this study and continue the reporting of its results is there, I think it would be difficult for us to

start from scratch at this point already having put in so much time and effort. I think it would be a disappointment if we were not able to move forward with the indication today.

DR. ENGLUND: Dr. Hunsicker?

DR. HUNSICKER: Could I respond to your comments, which were very clarifying for me. You know that I am not going to vote but I can still give you my opinion and that is, if I can start with the last one and move forward, I think it would be unjust to the sponsor to say that we just don't know anything.

There are issues of how to apply what we have here. We don't know quite who the population is at this point and that has got to be addressed as a separate issue. But if you take the population that we have seen, the data that we have are fairly convincing that the cost is small but real and it appears that the long-term benefit is going to be real.

That remains to be qualified by what I have said. I want you people to do a proper, and to agree on a proper, analysis of this issue that is--intention-to-treat and all that. I have said that, so I don't have to go over it again.

But if, in fact, the outcome were to show that there is this initial improvement in function and that, in fact, over time, that difference in function between the cyclosporine and the other arm widens rather than constricts so that there is a presumption that the creatinine is getting better in time relatively speaking, the sirolimus-only arm, it seems to me you have as good data as you are going to have that there is likely to be a long-term benefit short of actually doing the experiment.

So I would not feel, given the restrictions that I have said about what the population is, that it would be just to say that these folks haven't shown you anything.

On the other hand, if we go to the other extreme, is this already cold-cocked? No; it can't be because no one yet has done an interventional study in which they have said, "I am going to do something to lower the creatinine," some intervention to lower to creatinine, and show that this transforms ultimately into prolonged graft survival.

I think the rationale behind it is strong. I have written about that. I have talked about

that. I believe it. I think that it is reasonable to think that but it has never been shown. I would go on further to say that our obligation to make sure we know what the outcome is of an intervention that lowers the serum creatinine or preserves GFR acutely and to see whether this translates is very important because, as Dr. Neylan said, you are likely to see a whole mess of this coming down the pike an we have got to settle this once and for all.

Is the presumption that a lowering of creatinine and widening of things leads to better graft survival in fact supported--in fact supported--by our data at the end of time. So I don't think that you can say that it has been shown because it hasn't. Nobody has shown that.

So I find myself very much in the middle here, as Marc knows that I have for years. I think that this is something for which there is very strong presumption, a basis, perhaps, for early approval but with the requirement that this assumption that an early improvement in function will translate into longer graft survival must be documented.

MR. LAWRENCE: A point of clarification,

if I could. We are about to vote on Question 1 but I am not sure what Question 1 says. The company is asking for language that says that cyclosporine should be withdrawn, or should be considered to be withdrawn, after two to four months. Is that what we are voting on, that they have shown us sufficient data to say that that is--

DR. ENGLUND: We are not voting on the wording. We are not voting on the "should" or "may." We are voting on does the--and we can ask for clarification, but we are voting, does the data support the contention that withdrawing cyclosporine is safe and effective.

DR. ALBRECHT: That's correct. The question is not how we should label the product but whether the committee does believe that the data that Wyeth has presented show that this regimen is safe and is effective.

Actually, if I may comment a little further, having heard the discussion, I find that it would probably be reasonable to paraphrase the second part of that question to, if the answer is yes, not just the population or subpopulation that, perhaps, could be discussed but I also got the sense that, perhaps, as part of that question, if

the committee does believe yes is the direction in which the members would like to vote, what additional information would be needed before that yes could take place.

DR. ENGLUND: So the FDA is letting us ask for more information.

DR. ALBRECHT: The more information could, of course, be more analyses.

DR. ENGLUND: From what we already have. At this point, what I would like to do is briefly summarize. I am putting, perhaps, my perspective but I will try to be global. Then, at this point, I would like us to vote on question 1 because I think we have to vote on question 1 before we can decide if we are going to answer a. or b. We are not going to answer both of them because it depends on how question 1 goes.

I think, at this point, I have several comments. Number one, I think we need to congratulate the pharmaceutical company for proposing and carrying out a relatively complicated study in the withdrawal of immunosuppressives. To my knowledge, this is the first study that I have seen that has been carried out with 100 percent compliance. In the era--in my field of more

antivirals, I never get that. I think this is amazing and they are to be congratulated and that we appreciate the work that has gone to give us this kind of numbers.

I also think that the theory and the theoretical concerns as to what they are using as our endpoints are good. The fact that they can't tell us for sure what elevated creatinine means at one year is not--they should not be penalized for that because that is the state of the art.

So I think we, on the committee, recognize some of the good work that has gone into this but, in reviewing the comments from the different speakers, I think we have, as a group and as a committee, certain sincere difficulties and I am going to just briefly go over them.

We have, as a group, a very big issue with the population. To my knowledge, we did not show living related donors in Americans. That is, perhaps, going to be a very big population that we would be concerned about. We have different ethnicities that have not been addressed, at least in our country, and these are big issues from my point of view that the pediatric data, of course, is still barely getting started. I feel that is an

issue.

So we have patient-population concerns. And then I think we have some big analysis concerns that, with the help of our statisticians and pharmacology colleagues, we really have some concerns about what is intention-to-treat, what is a really appropriate comparison.

I have concerns about the toxicity and safety. I mean, what is a low potassium? I don't care of people's platelet count is 10,000 less. I care if they are thrombocytopenic and I wasn't able to get good values as to what some of our toxicities really were. So I think that there is some more analysis, that I think the data is here. I think the committee as a whole has raised some of these issues.

Last, but not least, is the use of surrogate endpoints which we, as a committee, and with our specialties, have to realize that that is, in fact, the state of the art today. I think that is important for us to realize. As much as we do want more, that is what we have today.

So, with that, I have tried to summarize a lot of people's concerns and comments, at the risk of adding a little bit of my personal

interpretation.

With that, I think I would like to take a vote and I would like to start at this end of the table because we have started at that end of the table first. For this vote, we really have to say yes or no to question 1, or abstain, I guess. But, do the data presented support the effectiveness and safety of cyclosporine withdrawal two to four months after kidney transplantation in patients treated originally with a combination regimen of sirolimus, cyclosporine and corticosteroids?

Could you please say your name before you vote so it can be taken down in the minutes.

Dr. Johnson?

DR. JOHNSON: Lynt Johnson. I guess I would say no with a qualifier. But I guess it gets registered as a no and it relates to the lack of data representing the African-American population which may, in turn, be a group that has benefit from this regimen. As I got the sense of it, it seems like it was more leaning towards yes with the restriction of a population. I would hate to restrict that population which may have benefit. I just don't know.

So, with the absence of that data, it is very hard for me to support question No. 1.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: Ron Shapiro. Yes, but with many of the same qualifications.

DR. SUTHANTHIRAN: Suthanthiran. I actually think you can't split question 1 from 1a because we are really saying yes or no to the first question. I would say that I would say a qualified yes in the sense--if the proposed indication is as stated by the sponsor, we can't vote yes. I can't vote yes on it.

But, if that is modified to say that "may" be considered for withdrawal in certain low-risk patients, I would vote yes. So I think, in my mind, Question 1 and 1a and 1b are so inextricably linked, I would find it difficult to--

DR. ENGLUND: Okay; so you are a yes qualified as opposed to a no qualified.

DR. SUTHANTHIRAN: With the modification in the proposed indication.

DR. ENGLUND: Steve Ebert?

DR. EBERT: Steve Ebert. To the question that is posed, my answer is yes. I will hold off on comments with the follow up.

DR. ENGLUND: Dr. DeGruttola.

DR. DeGRUTTOLA: Victor DeGruttola. I would say that this is a gray zone. It appears that there are patients who would benefit from this regimen. It also appears the answer to the question depends on the clinical importance of acute rejection which, I understand, has been used as an endpoint in some trials.

Given that concern, I would give this a qualified no but, again, emphasize that there does appear to be benefit in some populations and if that can be further specified, then I think that that fact should be taken into consideration when FDA makes its decision.

I know that is a long vote, but--

DR. ABERNETHY: Darrell Abernethy. No. I need more data and more analysis. So, at this point in time, I cannot say anything other than no.

DR. ENGLUND: Dr. Auchincloss.

DR. AUCHINCLOSS: Auchincloss. No. I think study 212 might as well be thrown out. I don't ever think it is going to be useful. I think they need longer and more analysis of the 310 study. I think they are going to need some additional data from an additional study. So, no;

I don't think that this is ready for a label change even though, as I have indicated, I will probably go home and do it on a patient.

DR. ENGLUND: Mr. Lawrence?

MR. LAWRENCE: William Lawrence. My vote would be yes but with the same reservations expressed by Dr. Suthanthiran and Dr. DeGruttola. I have serious reservations about applying this too broadly but I think the answer is more yes than no.

DR. ENGLUND: I am sitting hedging because what I am hearing is yes, not all, but we are hearing a lot of yes, buts and no, buts, which is difficult. But I think I would say no, but. The reason for that is that if I were having to say what would be the patient population to select, I can't do it.

If they are going to expect my help, our help, but my help, in designing who would benefit from it, I know it is good. I know it is going to work. But I don't know who to give it to and I feel that is, at this point--and, perhaps, further analysis could help us with that. So I am a no, but.

But, having said that, there are four yesses, five nos.

DR. ABERNETHY: So it was a tie-breaker.

DR. ENGLUND: The problem is I would say that questions 1a and 1b are actually closely tied in with question No. 2 in the sense that we need more studies. I don't care what they are called, but we need more studies.

For the yes people, how would you define the patient population, if we could just briefly go through the people who said yes. How would you define it based on the data available?

DR. SUTHANTHIRAN: I am strictly going by the data that I have. I know what patients to exclude from entering in the study which would include patients who had advanced to vascular rejection. It would include patients who have dialysis dependency. And it would include patients who have more than 400 micromoles of creatinine.

These four patients, the four groups of patients, cannot be entered into the study at this time because we have no data to support that these patients can be weaned off from cyclosporine. So those patients can be excluded from the study.

We have no data on African-Americans so those patients should not be included in the study.

DR. ENGLUND: I'm sorry; you mean--

DR. SUTHANTHIRAN: In cyclosporine withdrawal. I am listing the group of patients for whom we do not have data to make a recommendation. So I have five groups of people who should not be entered in a cyclosporine-withdrawal protocol at this time.

I also know that related and living-donor transplants are not--well, I am not that worried about that patient population because usually, if you can treat cadaveric patients, you can usually get away in a living donor. So that is not an exclusion criteria for me.

So, for my qualified yes, I would call all these patients as high-risk patients, these patients for whom I have no data, and I would allow other patients to be entered in this. Potentially, we can consider it for this protocol.

But I want to go back to what was said by Mr. Lawrence about--I wouldn't put the word "should." This is why I thought 1 and 1a are inextricably linked. I think "should" gives a very different connotation to the clinician. I think it should be "may" or "might" be considered and I would also add the line "in certain low-risk patients."

DR. ENGLUND: Mr. Lawrence?

MR. LAWRENCE: Dr. Hunsicker and I were discussing this point. This is who we thought should be included. You say who should not. "May be considered in low-risk patients," with an asterisk to define that. "No delayed graft function. No type III rejection. Adequate renal function. There is too little data to address blacks, Hispanics, Asians."

So, when I voted yes, I was voting yes based on these people. If I had a chance to vote no on the rest, I would vote no on the rest. But I want to encourage withdrawal of immunosuppressive drug. The flavor of that is a very attractive flavor to people like me.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: I wouldn't have much to add. First, maybe second, transplant patients who have kept their first kidney for a long time, low PRA, low panel-reactive antibody level, if they have had a rejection and easily treated, mild or mild-to-moderate rejection with complete reversal, preferably either no delayed graft function or minimal delayed graft function, I think those patients would fit into the category of patients

who might be candidates for a successful calcineurin inhibitor withdrawal.

I guess, like everybody else, I would be more concerned without more data.

DR. ENGLUND: I guess just as a response to you is I would be very concerned about putting something like--putting some of the things that people have said here on a label when there is actually nothing known about it. I agree, I think that is what people will do and will do it at my institution, but to put it on the label or to say that that is who we are giving it to without any data--we don't even have much living related data even though I believe it is good. So this is my comment.

DR. ENGLUND: I just want to echo what you just said in that--and part of my comment was just that. I tried to answer this as directly as possible whether the data support the effectiveness and that was the basis for my vote. But, as you said, whether you are going to try to put something--translate that into modifying the labeling, I think is a much slipperier slope.

Whether this is something that should be noted by practitioners and should be incorporated

into their daily practice as a "off-label" use in selected individuals or whether this should be, as you said, something that would be incorporated into the labeling. I think those are two very different actions.

DR. ENGLUND: We have two other questions actually that are not to be voted upon but really I think we should bring up for discussion.

DR. AUCHINCLOSS: Did the FDA feel like they got their answer to the question? Do they feel like they know what question we were answering? I was just struck by the comment that I heard over here because I think you were a yes vote.

DR. ENGLUND: Yes was "yes, but."

DR. AUCHINCLOSS: But you wouldn't rewrite the label?

DR. ENGLUND: Again, I agree with the chair in that I don't think that there is enough information available in a wide enough patient population that I would feel strongly enough to modify the labeling.

DR. AUCHINCLOSS: Because it was really sort of that question that I used as the way to hinge my vote one way or another.

DR. ALBRECHT: I think as I heard those last comments about perhaps uncertainty whether the information available was such that some of the members felt comfortable about putting them in labeling. The question that came to my mind is what would be the information that you would recommend or would like to see that would actually, then, make you comfortable about this kind of information being part of the label.

Again, not to go into the specific wording but some of the ideas that you were voicing about certain patient subsets or populations, what would be the data that you would like to see before you would be comfortable having this in the label? Again, I ask that really just for completeness of discussion, not to try to actually pin down the criteria because, again, this is a very hard issue.

DR. ENGLUND: I would just like to summarize. I think intention-to-treat data would be the echo of our committee, without having to call on everyone.

MR. LAWRENCE: Dr. Albrecht, I just have to ask you again. When you say what would you have to see before this would go in the label, I don't know what "this" is. I have been trying to clarify

what "this" is. If "this" is that this should be done generally, my answer is no, we haven't seen--if the answer is that this is that this can be contemplated by physicians based on the clinical picture of the patient that they see and in certain circumstances, then the answer is yes.

But you are not going to put that on the label. So question 1 is not actually crafted in terms of getting a yes or a no answer because the qualifications are so manifest that everybody at the table voted yes, but or no, but. I am not sure the vote that you got today is worth much.

Obviously, there are serious reservations. And, obviously, in some cases, it is appropriate and should be encouraged. If you are going to put that on the label, I will look for that.

DR. ALBRECHT: I think, as I said earlier, there are the two aspects of making a regulatory decision. The first is the burden of is the drug safe and effective and that is what is specified in the Food, Drug and Cosmetic Act.

Then the second aspect is how the information about the safety and efficacy of the drug is placed into the package insert so that it can be understood by the individuals that would be

using the product.

I think we really are just asking you to vote on the first issue of is the drug safe, is it effective, and then the details of the words that we will use to communicate that information, I think, is the next level and some of the comments that we are hearing, I think, indicate to me that that is going to be a very challenging area.

DR. ABERNETHY: In terms of the further information, I would suggest that--I think I need to see a U.S. study that reflects the U.S. transplant population. I would like to see patients randomized at the time of transplant so that we get a much better feel for where these risk stratifications should be with regard to benefit and then an intention-to-treat analysis.

DR. AUCHINCLOSS: Why is that? If the issue is cyclosporine withdrawal versus no withdrawal, why don't you randomized at the moment of withdrawal? Then you can do all the stratification you want at that point. It seems to me they terribly muddied their picture by randomizing up front and then withdrawing two months later. By then, a whole series of events had happened to the alternate population that

weren't comparable.

DR. DeGRUTTOLA: I would echo that. If you could randomize at the time you would withdraw, if that were a consideration, then I think that would get most directly at the question.

I think one of the issues we are struggling with is that, as Dr. Albrecht mentioned, the regulations talk about the effectiveness and safety of a drug, but we are really talking about the effectiveness and safety of a strategy to withdraw a drug which is a little bit more complicated. I think that Dr. Auchincloss' suggestion of randomizing at the time that you would reduce the cyclosporine, that choice is an interesting one to try and get most directly at the--

DR. ENGLUND: That was the 310.

DR. AUCHINCLOSS: It is the 310. But we are now asking for a United States study.

DR. ENGLUND: Right.

DR. ALBRECHT: May I actually add a few more comments about foreign studies because I think that this is an issue that is important to us. As you know, drug companies do conduct studies in the United States and abroad. As I indicated earlier,

the Code of Federal Regulations does allow foreign studies to be used.

But if I understand, your concern is that in the United States, there are a substantial number of patients who have living, related-donor transplants. In the studies that have been submitted--in fact, it was 90 to 100 percent cadaveric. So the concern is that we cannot extrapolate the data from those studies to U.S. patients--because I think it is just as important to recognize that, in the area of international drug development, we try not to stymie development across the world but, rather, the concern is when the patient population studied abroad cannot be extrapolated to the patient in the United States and, therefore, we cannot, then, effectively label products.

So was that the concern, that the patients being studied in these studies would not reflect the U.S. population?

DR. ABERNETHY: I think you are saying it in a, perhaps, too gracious way. The concern I believe is that it is clear that when this study was conducted, there was no commitment or no possibility of including a population that is of

great interest here. Then, secondly, the concern is is the practice pattern going to be the same in one setting versus another.

I understand what you are saying about harmonization on the one hand. On the other hand, we are talking about getting an appropriate practice for patients in the United States.

MR. LAWRENCE: A point of information. Last year was the first time in this country that living donors outnumbered cadaveric donors for kidneys. So that is a material question.

DR. AUCHINCLOSS: I agree that there are lots of potential concerns about an abroad population. I don't think that the living-donor issue is my primary one. I really would fairly strongly believe that if this kind of thing works for your cadaver-donor population, it is going to be okay for your living-donor.

DR. ENGLUND: I believe that. Wouldn't you like to see one or two patients?

DR. AUCHINCLOSS: Yes; I would like to see one or two patients but that is not, by any means, my primary concern about the patient population abroad.

DR. SHAPIRO: Actually, the living donor

would be sort of a positive in that those are patients who tend to do, as a group, better. I think there is a sense that the American transplant recipient population is more heterogeneous and that the need for doing a study in the United States to reflect that would be important.

DR. SUTHANTHIRAN: I think there is another issue we need to address in terms of randomization because we are going to be asked a question, whatever the regimen or whatever the protocol, is it safe and effective. The question is being asked is it safe and effective for transplant patients.

Now, at the time of randomization, certain groups of patients are excluded from randomization and they go into Arm C or nonrandomized. We are always going to have this problem. We always have this problem, it is safe but we cannot comment about population A, B or C who were not excluded in the randomization plan.

The only way to avoid the problem is to really enter all patients into randomization. Otherwise, we are going to revisit the issue all the time. It is kind of a Catch 22. If you start patients at zero time, all your transplant

patients, and then, let's say, at one month or two months, you randomize, but you are really not randomizing A B. You also have a group C because of whatever notion that group C is a high-risk patient population.

Now, when we are asked to answer the question, is this protocol fine for transplant patients, we are always going to say it is fine for the transplant-patient population minus group C.

DR. AUCHINCLOSS: But that is true of many studies. You have exclusion criteria and then the results apply only to those that were not excluded.

DR. SUTHANTHIRAN: Right.

DR. ENGLUND: But the problem here is we have not just those exclusion criteria but we also have the exclusion criteria for all the people that they didn't even--that weren't even enrolled in the first place.

DR. DeGRUTTOLA: I think the point is exclusion criteria, per se, shouldn't necessarily be a concern. If it is not appropriate to withdraw cyclosporine from some patients, then it is appropriate to exclude them both from the study and mention that in the label.

I think the issue is do you always want to

do the reduction of cyclosporine at three months so that is specified then, or could there be a more variable time at which you say, now is the time we might consider reducing the cyclosporine. It might be later, for example, in some patients. I think maybe you could get at the issue that way in allowing the randomization only to happen at the time that you want to consider withdrawing it, not necessarily fixed at three months by protocol but allowing some latitude with that.

DR. SHAPIRO: If I could just defend the selectivity on the part of the sponsor, you want--this is pretty radical to stop a calcineurin inhibitor and you want to load the dice to come up with a trial that is going to give you--one, that is going to give you a trial that is going to be relatively safe to do and one that is not going to fall on its face.

I think that they have succeeded extremely well in doing a study like that, at least at a first pass, in a relatively low-risk population. I think to have done an allcomer study at the beginning, one would have risked a result that would have been harder to understand and, two, would have been very difficult to do.

So I think that the rationale for looking at selected populations initially was the right one.

DR. ENGLUND: I would like us to move on to what additional studies would we want, would we ask for. I have heard from Dr. Abernethy.

DR. SHAPIRO: I would echo that. You would need to do a large-scale American trial with both living donor and cadaveric recipients and not restrict entry on the basis of ethnic group. You might want to restrict entry in terms of transplant number and PRA to at least give it a shot of being reasonable, just from a tactical point of view.

DR. ENGLUND: Would you consider randomization at time of transplant or at a period following transplant?

DR. SHAPIRO: The ideal thing would be to randomize pretransplantation. But you are going to increase your dropout rate enormously if you do that. At some level, that is the cleanest. The way to stack your trials so that they come out the way you want them to is to randomize after you know that you have got kidneys that are functioning in patients who are doing well.

The ideal thing would be to randomize

pretransplantation.

DR. ENGLUND: Dr. Johnson?

DR. JOHNSON: I am not sure that I would agree that they would have to redo the entire study in the U.S. population. I think that--you know, my main concern is that the African-American population represents such a large proportion here in the United States and I think that we need to have some data. That data may come back and say, yes, it is okay in certain conditions and they may say it is worse.

But that is the information that I would like to have because I think that, from the question that was asked, can we extrapolate this data, there is some extrapolation that I can do with this data but I can't, based upon prior data and based upon my knowledge of this group, extrapolate it to that subpopulation.

So, in my opinion, I am not sure they would need to redo the whole study. But I think that they need to provide supplemental data in African Americans in the United States in some fashion so that we can make a judgment one way or the other whether or not we need to provide a basis to exclude or include them in this labeling in some

degree.

DR. ENGLUND: Any other comments about the phase IV studies? I have heard that the pediatric studies--I have heard about those and I think those sound good and sufficient and I am pleased to see, actually, the numbers that are being discussed for the pediatric studies.

DR. SUTHANTHIRAN: I would add a biomarker to the study. I think it would be terrific if there is nice improvement in creatinine, there appears to be a nice improvement in renal function, it seems to hold out over time--I think it would be very nice of a biopsy is really part of the protocol and the patients get biopsied at defined times.

I know logistically there are some problems associated with it, but I think the study would be improved so much if a biopsy is done in all the patients and we can see a structural correlation and a structural counterpart to this improved renal function.

DR. ENGLUND: Dr. Shapiro?

DR. SHAPIRO: I would also point out that, while protocol biopsies are very nice and I have written about them and we have performed them and

we have published on them, and I have also been slammed for them, or our paper has been, as being of uncertain significance.

That is the problem with protocol biopsies in the world today. The transplant community has some people who are very interested in them and think that they are wonderful and a large number of people who think that they are nonsense.

DR. ENGLUND: I would just like to add, from my experience in clinical trials, that it makes recruiting in minority populations greatly difficult. It makes some of the recruiting more difficult in some of the populations, and I think that is something to consider.

DR. SHAPIRO: It depends how you sell it.

DR. ENGLUND: You are better at it than we are.

DR. ENGLUND: I don't really want to open a can of worms on this, but I think, if additional phase IV studies were going to be done, one might also want to consider having a subset of patients which, rather than doing prospective concentration-controlled dose modification may want to just start out immediately at a dose of, whether it is 8 milligram a day, 10 milligrams a day,

whatever have you, and try to see whether, in fact, doing dose titration really, in fact, does improve on outcomes compared with just arbitrarily giving a certain dose.

DR. AUCHINCLOSS: I know that the company is thinking about different ways of using their drug in combination with other drugs and they have thought, not just about cyclosporine withdrawal but they have thought about steroid withdrawal, et cetera, et cetera, et cetera.

But I do think it is worth their while to rethink again whether this is really their top priority, cyclosporine withdrawal. To me, as I looked at the 212 data which I found interesting even though I don't think it is a good study, it seems to me the message there is that high-dose sirolimus with very low-dose cyclosporine is a fantastic combination that is destroyed when you withdraw the cyclosporine.

So I just wonder whether they want to think again about whether their endpoint actually should be cyclosporine withdrawal or cyclosporine minimization.

DR. ENGLUND: Let me go, then, to question No. 3 which I think we have kind of addressed, but

let's make sure we have gone through all of our questions. Question No. 3 states, do we have any additional comments or recommendations regarding the study design and/or endpoints for controlled clinical trials intended to support the safety and efficacy.

In particular, one of the things which we have, I think, discussed, but for a maintenance and a maintenance withdrawal regimen which is going to be coming up before this committee again, one hopes, what comments do we, as a committee have? What would we like to be seeing in these trials?

Any comments in addition to what has already been stated? Perhaps our statistician?

DR. DeGRUTTOLA: I think points have already been made about longer-term follow up and the ability to relate some of the markers to longer follow up. I actually think that randomizing at the point when people would reduce the dose rather than up front is probably better for the reason that was mentioned, if you are going to have dropouts and people that can't be entered into the study. So I think that the design is actually more appropriate.

DR. ENGLUND: Any comments or questions

from the FDA?

DR. ABERNETHY: It may have already been said abundantly, but I think viewing this kind of a study as essentially an equivalence study, your new regimen of having one less medicine is really--you are testing equivalence to the currently accepted regimen and taking that point of view from day 1 and really understanding what that means would certainly make the interpretation at this end much better.

DR. DeGRUTTOLA: Yes; prespecifying what equivalence means. I guess it is as little confusing in that this study was intended to show equivalence for some outcomes but superiority for other outcomes, I guess prespecifying what the criteria are for equivalence or noninferiority, as was mentioned.

I also thought that Dr. Hunsicker made an interesting comment about doing intent-to-treat analyses of some of the toxicity results which is not standard. Typically, that is done on-therapy or as-treated. But, for the reasons that were discussed, I think that that is something that should be considered here as well.

DR. AUCHINCLOSS: You make a comment about

how you balance two what are, in effect, surrogate endpoints when we are not sure that either is okay. One is going to go up and one is going to go down. I think that the outcome here was pretty much as you might have predicted, a slight increase in acute rejections and an improvement in renal function. We are not quite sure how important either one of those things are.

DR. DeGRUTTOLA: I think that that is always a challenge in any study and there are a couple of ways to approach it. One is if you believe that you can predict or develop a predictive model, as I believe Dr. Neylan gave one example, so that you can essentially weight the improvement or lack of improvement by the expected clinical consequences.

What that presupposes is that you have information to allow to relate the markers to the clinical consequences and you know that that relationship is not affected by the drug that people are on because, in fact, that relationship could differ by drug. So, it is a challenging thing to do but I think that that is probably the only way, really, to evaluate what the consequence is going to be for the patient.

Other kinds of analyses that people might do in this setting are quality of life. But, because the surrogates that are being discussed don't seem to have a direct clinical impact. At least the acute rejection, from what I understood did not. The creatinine, I am not so sure. It wasn't discussed. Presumably not.

But, having some way to relate these endpoints to their clinical effect on patients I think is the only way to really address that question.

DR. ENGLUND: With that, I would--

DR. CAVAILLE-COLL: One moment please. I would like to get as much as we can out of this question 2. I know this is about the last time we are going to hear recommendations as well as clinical-study designs and endpoints.

This has been going on the past year at different meetings organized by AST and ASTS. But I would still like to, before we leave here, get the panel's opinion about whether they believe or not that bettering renal function is important in clinical studies in renal transplantation and should every effort be done to attain intent-to-treat information on renal function in

patients who discontinue study drug, for example, as well as patients who stay on study? This is for future studies.

DR. SHAPIRO: Yes.

DR. ENGLUND: Yes.

[Chorus of yesses].

DR. ENGLUND: With that, I would like to, once again, thank the committee, nonvoting guests. I thank everyone for their participation. Thank you for your presentation. And I adjourn this meeting.

[Whereupon, at 3:50 p.m., the meeting was adjourned.]

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