DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

Wednesday, November 16, 2005

8:00 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

William R. Hiatt, M.D., Acting Committee Chair
LCDR Cathy Groupe, RN, B.S.N., Executive Secretary

MEMBERS

David DeMets, Ph.D.
Frederick J. Kaskel, M.D., Ph.D.
Thomas Pickering, M.D., Ph.D.
John R. Teerlink, M.D.

CONSULTANTS (VOTING)

Darrell R. Abernethy, M.D., Ph.D.
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Susanna L. Cunningham, Ph.D., Consumer Representative
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Paul Oldam, Patient Representative
Michael Proschan, Ph.D.

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Mark Goldberger, M.D., M.P.H.
Renata Albrecht, M.D.
Marc Cavaille-Coll, M.D., Ph.D.
Karen Higgins, Sc.D.
Arturo Hernandez, M.D.
LT LaRee Tracy, M.A.
Joga Gobburu, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. HIATT: I would like to welcome everyone. I am William Hiatt from the University of Colorado and Acting Chair of the committee.

I think we would like to begin this morning with introductions. We will go around the table, and then Cathy Groupe is going to read the Conflict of Interest Statement. Then, Dr. Albrecht is going to give us an introduction.

With that, David, could you maybe start with telling us who you are.

DR. DeMETS: Dave DeMets, University of Wisconsin, Biostatistics.

DR. KASKEL: Rick Kaskel, Albert Einstein College of Medicine, Pediatric Nephrology.

DR. PICKERING: Tom Pickering, Columbia University, Hypertension.

DR. NISSEN: Steve Nissen, Cardiologist, from the Cleveland Clinic.

DR. CUNNINGHAM: I am Susanna Cunningham. I am a Professor at the University of Washington

School of Nursing in Seattle, and I am the Consumer Representative on the committee.

DR. VENKATARAMANAN: I am Raman Venkataramanan, University of Pittsburgh, Pharmaceutical Sciences and Transplant.

DR. ABERNETHY: Darrell Abernethy, Clinical Pharmacology, National Institute of Aging.

DR. TEERLINK: John Teerlink, University of California, San Francisco. Heart Failure.

DR. BURCKART: Gil Burckart, University of Southern California. Clinical Pharmacology.

LCDR GROUPE: Cathy Groupe. I am the Executive Secretary for the committee.

DR. MANNON: Roslyn Mannon, NIDDK, NIH Transplant Nephrology.

DR. PROSCHAN: Mike Proschan, Statistician, NBLBI.

MR. OLDAM: Paul Oldam. I am a Patient Representative from Milwaukee, heart transplant recipient 12 years and a kidney 2 1/2 years, and on the UNOS Board of Directors.

DR. GOBBURU: Joga Gobburu,

Pharmacometrics, Office of Clinical Pharmacology and Biopharmaceuticals, FDA.

DR. HIGGINS: Karen Higgins, Office of Biostatistics, Division of Biometrics III, FDA.

LT TRACY: LaRee Tracy, Office of Biostatistics, Division of Biometrics III.

DR. HERNANDEZ: Arturo Hernandez. I am the clinical reviewer for this application, Division of Special Pathogens and Transplant Products.

DR. CAVAILLE-COLL: Marc Cavaille-Coll, Medical Team Leader, Division of Special Pathogens and Transplantation Products.

DR. ALBRECHT: Renata Albrecht, Director, Division of Special Pathogen and Transplant Products.

Good morning. I wanted to mention Dr. Mark Goldberger, the Director of the Office of Antimicrobial Products, will be joining us within half an hour.

Conflict of Interest Statement

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the

appearance of such at this meeting.

Based on the submitted agenda 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 present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C. Section 208(b)(3), a full waiver has been granted to Dr. David DeMets. He serves as an Advisory Board member for the sponsor and as a consultant and Data Safety Monitoring Board member for a competitor. He receives less than $10,001 per year per firm.

In addition, Dr. Thomas Pickering has been granted a 355(n)(4) waiver for owning stock in the sponsor valued from $5,001 to $25,000. Because this stock does not exceed $25,000, 5 CFR 2640.202(a)(2) deminimis exception applies and an

(a)(3)(b)(3) waiver is not required.

A copy of the waiver statement may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 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 product they may wish to comment upon.

Thank you.

DR. HIATT: Thank you very much.

We are going to begin with a Welcome from Dr. Albrecht.

Welcome

DR. ALBRECHT: Good morning, everyone. On

behalf of our Division, as well as the Office of Antimicrobial Products, I would like to welcome everyone to today's meeting on everolimus for the prophylaxis of rejection in heart transplantation.

We would like to thank Dr. Hiatt, members of the Advisory Committee, and consultants for taking the time to come to Rockville and provide us advice on this application.

There are currently two products approved for heart transplantation by the FDA. These are mycophenolate mofetil and cyclosporine. So, we wish to acknowledge and commend Novartis for undertaking the development of everolimus for this indication, and also acknowledge their participation in today's meeting.

Finally, I would like to acknowledge the hard work of the FDA staff in reviewing the application and in preparing for today's meeting, and I would especially like to mention our Deputy Director, Dr. Steve Gitterman, as well as our Project Manager, Jackie Smith, for all the hard work that they have put into preparing for today.

[Slide.]

So, why are we bringing this application to this committee this morning? The Cardiovascular

and Renal Advisory Committee is a standing committee and there is no analogous committee like that for transplant products, so we determined that it was appropriate to present the Certican application before this committee because of the key issues that are important in this application: the indication, heart transplantation, and some of the safety issues which include renal toxicity and lipid abnormalities.

We have in attendance today committee members and invited guests who are experts in transplantation, cardiology, nephrology, statistics, and clinical pharmacology among others.

As noted in the Novartis background material, this application has received approvable actions previously, that is, the FDA was concerned that although efficacy was shown in the clinical studies, the risk of toxicity with the fixed dose everolimus and full dose cyclosporine regimen was

considered to outweigh the potential benefit.

Novartis, however, considered that Certican fulfilled an unmet medical need in heart transplantation and requested that the application be presented in a public meeting, a request we considered very reasonable, and so we are here today to discuss the application.

[Slide.]

During the morning, there will be presentations by both FDA and Novartis. Novartis speakers will give the first series of presentations starting with an overview of cardiac transplantation, then, a presentation on unmet medical needs in heart transplantation, results of efficacy with everolimus, findings on intravenous ultrasound, safety, renal issues, and a concluding presentation on the risk versus benefit of everolimus.

The Novartis presentations will be followed by three FDA presentations focusing on statistical issues, clinical issues, and exposure effectiveness issues that are germane to the use of

everolimus with cyclosporine in heart transplantation.

As you listen to the presentations, keep in mind the following four questions that we will be asking for you to deliberate and vote on. Actually, two of them we will be asking you to vote on Yes or No this afternoon, and two we will be asking for commentaries.

[Slide.]

To frame the first question, let me mention that the Certican development program included three prospective, randomized, comparative Phase 3 studies. One study was done in heart transplantation, B253, and two studies were done in renal transplantation.

The heart transplantation information is summarized in detail in both the FDA and the Novartis background material and will be highlighted during today's presentations.

These Phase 3 studies tested two fixed-everolimus plus full-dose cyclosporine regimens in combination with steroids. The

protocols were amended at 12 months because of toxicity and the amendment allowed for reduction in the dose of cyclosporine.

[Slide.]

The FDA, as I mentioned, issued an approvable letter after concluding that the risk of that tested regimen or those tested regimens outweighed the potential benefit, and Novartis actually had proposed labeling with the statement "Certican should not be used long-term together with full-dose cyclosporine."

[Slide.]

So, that leads to the first question that we would like you to keep in mind as you listen to the presentations, and let me read that to you.

Novartis has presented the results and extensively discussed the use of a "fixed-dose" everolimus regimen with "full-dose" cyclosporine in Study B253. Both FDA and Novartis agree that this exact fixed-dose regimen should not be used for the prophylaxis of organ rejection in cardiac transplantation.

We will ask you to discuss whether you believe or whether you agree with this conclusion.

[Slide.]

The second question deals with therapeutic drug monitoring. During the morning, Novartis will present a proposed dosing regimen in heart transplantation for everolimus, as well as for cyclosporine.

You will hear that there are no prospective randomized studies actually testing this proposed therapeutic drug-monitored regimen in heart transplantation, and that instead the information is derived from other sources, such as analyses of heart transplantation study using the full-dose cyclosporine regimen, it is extrapolated from noncomparative kidney studies, and finally, it is derived from clinical pharmacology modeling.

[Slide.]

So, that will lead to the second question that we would be interested in the committee's vote, and the question is:

Novartis has proposed an alternative

TDM-based regimen for the use of everolimus in combination with cyclosporine. The proposed regimen has not been prospectively tested in a cardiac transplantation study.

In the absence of a prospective study of this regimen, do committee members believe there is sufficient information available to conclude that the regimen as proposed by Novartis has been demonstrated to be safe and effective for use in heart transplantation?

[Slide.]

There are three caveats we would like you to keep in mind as you discuss this question.

The first:

(a) In your discussion, please be specific regarding what information supports the proposed TDM-based regimen.

(b) Please discuss in your answer whether you believe that everolimus has been shown to be safe and effective for all cardiac transplant recipients.

(c) Alternatively, please discuss whether

you believe there are certain subgroups where use should be specifically indicated or specifically restricted.

[Slide.]

Question No. 3. If your answer to Question 2 is Yes, that is, if you conclude that the proposed TDM regimen is safe and effective, then, please comment on what additional information should be obtained regarding everolimus post-approval.

In addition, we would actually be very interested in any comments and recommendations you would have about information to include in the labeling.

[Slide.]

The final and fourth question is: If your answer to Question No. 2 is No, then, please comment what additional information would be necessary for approval.

For example, please comment whether the currently ongoing European study or the planned U.S. cardiac transplantation study would be

adequate to demonstrate safety and efficacy.

Also, please comment whether additional data or studies would be necessary.

Thank you. I will turn it back to you, Dr. Hiatt.

DR. HIATT: Thank you very much.

I recognize that the first three questions are probably pretty straightforward. The fourth question might leave some ambiguity, but you are going to learn more during the presentations about these proposed studies.

We are going to move forward now and begin with a series of presentations by the sponsor. I realize that these are relatively scripted, but the committee tends to like to get things clarified during these conversations, so please be succinct and allow us a little bit of time after each talk to ask you some questions.

The first will be by Dr. Mark Barr.

NDA 21-628

Proposed Trade Name Certican (everolimus)

Novartis Pharmaceuticals Corporation

Novartis Pharmaceuticals Corporation Presentation

Current Status and Future Challenges

in Heart Transplantation

DR. BARR: Good morning, everyone.

[Slide.]

I have been asked to speak today regarding the status of the field of heart transplantation as an overview, so that everybody understands where this field has come from in the past 40 years, where it is currently, and what some of the problems are that we still have in this field in terms of long-term patient outcomes.

[Slide.]

Just by way of background, I am Associate Professor of Cardiothoracic Surgery at the University of Southern California, and I am Co-Director of the Heart and Lung Transplant Program there.

I am also President of the International Society of Heart and Lung Transplantation this year and sit on the Scientific Advisory Committee for the SRTR, the Scientific Registry of Transplant

Recipients.

Transplantation is a relatively new field compared to a lot of other diseases and procedures that all of us in the audience are used to seeing. The first transplant was performed December 3rd, 1967. You see the covers here of Life, Newsweek, and Time ballying the success of the original transplant that was done in South Africa by Dr. Christian Barnard. It has now been 40 years and 70,000 transplants later.

[Slide.]

However, the shine that we had in a positive light from the media didn't last very long. You can see just four later, this is the cover of Life magazine on the tragic record of heart transplantation. That is because all six of these patients you see photographed at the bottom of the slide, within eight months of this photograph being taken were all dead.

So, there were significant problems. The operation was successful surgically, but there were massive problems with the immunosuppression both

over- and under- immunosuppression.

[Slide.]

There are two reasons that the field has entered into the modern era. The first is this gentleman, Dr. Norman Shumway, who during those very dark years of that Life magazine cover continued to pursue the issues of detecting of rejection, as well as treatments for rejection, and all the surgical procedures--I am going to show you a few slides in a few seconds--come from Dr. Shumway's original lab, so even though Christian Barnard did the first transplant in South Africa, all that work was actually developed at Stanford prior to that time.

[Slide.]

The other reason that transplantation was successful was the introduction of cyclosporine, and as you will see, in terms of the numbers, this catapulted the field because we actually had the ability to not only operate on these patients, but keep them alive afterwards.

I am just going to show a few technical

slides, and there is a reason for this. I think it is important for people to realize that the physiology of a transplanted heart is a little different because of the nature of the operation.

[Slide.]

What you are seeing on this slide is what is remaining of the heart in the recipient when the heart is removed. This is the back wall of the left atrium. This is the back wall of the right atrium. The pulmonary artery is transected there. The aorta is clamped and transected, and the donor heart is sutured into basically the back wall of the left atrial and right atrial cuff.

This is important because this creates a denervated heart and also because of the fact that as opposed to what a lot of people think, the coronary arteries are actually coming with the donor heart. The coronary arteries are not left from the recipient's old coronaries.

[Slide.]

The suture lines are relatively large, baseball-like sutures, and this allows you to have

the heart, which is obviously creating a lot of stress on the suture line, to be intact without disrupting the suture line.

What you are seeing on this slide is the standard right atrial anastomotic technique that Dr. Shumway first described back in the '60s.

[Slide.]

This is just completion, then, after the left atrium and right atrium are completed. You see that the aorta and pulmonary artery are then sutured together.

[Slide.]

At the end of the case what you will have is a set of four suture lines and you will have pacing wires on the surface of the heart, and there is the pericardium which is left open. We do not close that because of the risk of tamponade, as well as the fact that there is no reason to do that, because of the fact that this will eventually seal over with time.

[Slide.]

The only difference in the surgery

technique that has occurred from the '60s to now is this minor modification. This is what is called a bicaval approach, and after the left atrium is completed, instead of a right atrial to right atrial cuff, the superior vena cava of the donor heart is sewn to the superior vena cava of the recipient, and the inferior vena cava is sewn to the inferior vena cava, and this minor surgical adaptation decreased the incidence of need for pacemakers after the surgery and also improved the integrity of the tricuspid valve with less tricuspid regurgitation.

Other than this modification, the operation is essentially unchanged from 40 years ago.

[Slide.]

Now, I mentioned already the importance of the introduction of cyclosporine. Back in the '70s, especially after that era of the Life magazine cover, there were very few transplants being done worldwide. Cyclosporine became clinically available in heart transplantation in

1981, and then there was a steady rise in the number of transplants.

Keep in mind, as opposed to other diseases like hypertension and hyperlipidemia, we are talking about a very small population overall. The total number recorded in the ISHLT/UNOS database, which is the largest of its type in the world, only just has exceeded 4,000.

This decreasing number that you see in the late '90s and early 2000s, doesn't actually reflect a drop in the number of transplants, it is actually due to a drop in reporting from European centers. The number of transplants in the United States have been relatively stable at about the 3,000 mark per year since the late '80s, early '90s.

[Slide.]

The data that I am going to show you today, as an overview, comes from the ISHLT Registry, and in that registry, as of 2001, over 60,000 transplants have been performed. As of 2004, the registry is now up to 70,000 heart transplants.

[Slide.]

There are some issues that have come up in recent years in terms of the types of patients that

we are transplanting and therefore being evaluated under any new studies.

Number one, we are doing older patients. In the early days of Shumway, the average age of the patient was in their 40s. The average age of the recipients now is very much older, in their 50s, and we are doing more and more patients who are over 65 years of age.

The patients are also generally sicker at the time of transplant with more patients being status 1A or urgent status 1B patients. We are also doing more women, and they are typically older at the time of transplant than again in the early days, in the '80s and '90s, and lastly, more patients are on mechanical support or a left ventricular assist device, artificial hearts, going into the transplant.

[Slide.]

This shows you long-term survival over two

decades from the ISHLT Registry with over 66,000 patients reflected. You can see that it is a fairly steep death curve in the first year that occurs and the T-half or 50 percent of patients will be dead at 9.6 years.

If you survive the first year, the conditional half-life is 12 years, but just notice the slope, which I am going to be showing you in some other slides, just as inexorable decline in terms of long-term outcome after transplantation.

[Slide.]

Now, we have gotten better. You can see if you break it up in eras from the ISHLT Registry, that, in blue, 1982 to 1988, followed by 1989 to 1993, 1994 to 1998, and lastly, 1999 to 2003, the curves have gotten better for survival, but most of it is made up in the early period of time when, due to improvements in the operating room, as well as improvements in monitoring for rejection and treatment, we have decreased deaths in the first year, but after that first year, these curves are very, very parallel and we still have that same

decline that I showed you on that 20-year slide.

[Slide.]

Pointing out the issue that we are also doing higher risk patients, but having better outcomes, this shows you patients who were transplanted from 1999 to 2003, broken out by whether or not they had a preoperative ventricular assist device.

The red line here is no LVAD before the transplant versus having an implantable LVAD, and you can see that these patients at multiple time points throughout their course have a higher incidence of death after the transplant, not just from the acute event, but there is even separation as they get out further, and that is for various immunologic reasons.

[Slide.]

As far as the overall outcomes after transplantation, in the first year, over 40 percent of patients are rehospitalized. The hospitalizations are generally due to rejection, infection and rejection, and infection alone. This

occupies at least 75 percent of the reasons why patients are hospitalized.

After Year 1, patients are still being hospitalized at a rate of about 20 percent per year.

[Slide.]

The patients that are survivors are doing extremely well fortunately. From a New York Heart Association classification, 90 percent of the patients have excellent functional status with no activities limitations and the minority of the patients in all the years of follow-up, after seven years, have some level of need for assistance, usually categorized in the New York Heart Association Class II area.

[Slide.]

So, although never subjected to a randomized, controlled trial, heart transplantation is currently the only therapy for advanced heart failure that observationally has been associated with excellent survival.

Advances in close follow-up and newer

immunosuppression have led to the improvements that I showed you, with one-year survivals now in excess of 90 percent at some centers.

The problem, as I showed you from those Kaplan-Meier curves, is in survival beyond one year which is still limited at 70 percent at three to five years, and 50 percent at 10 years.

[Slide.]

In terms of immunosuppressive maintenance phases, if you are low on your immunosuppression, then, the risk is breakthrough rejection, and if you are high, you pay the price with infections and malignancies, and if you are right in the middle, you are still going to have problems with nephrotoxicity, hypertension, diabetes, and neurotoxicity, and this is with adequate immunosuppression to prevent rejection and not over-immunosuppression to cause infections or malignancies, and you are still dealing with these problems.

[Slide.]

The most common immunosuppressive regimens

that are used in the United States in 2005 are either cyclosporine or tacrolimus based, and I just want to point out that these are utilized, these drugs are utilized in conjunction with therapeutic drug monitoring at all centers. Adjunctive therapy is usually with an antiproliferative and usually, most centers now use mycophenolate mofetil.

There is supportive immunosuppression with prednisone, and only 20 to 30 percent of patients are weaned off prednisone.

Then, lastly, additive immunosuppression, if you want to use that term, are the statins which have been shown to be immunomodulatory and have been associated with long-term improved survival, but in the classic sense, not an immunosuppressive agent.

[Slide.]

There are some interesting trends that have occurred over the past recent decade in terms of maintenance immunosuppression. You can see starting in 1995, that the vast majority of patients in heart transplantation were treated with

cyclosporine maintenance and very few were treated with tacrolimus. As of 2004, it's almost a 50-50 mix in terms of the baseline calcineurin inhibitor.

As far as antiproliferative agents go, in 1995, most centers in the United States were using azathioprine or Imuran, and that has had a steady decline with the approval of mycophenolate mofetil or CellCept with a rapid increase, so that the vast majority of centers are treating their patients with mycophenolate mofetil.

Interestingly enough, when sirolimus or Rapamune was approved, it started to have increasing use, and right now in the United States, at the time of discharge, approximately 10 percent of patients are treated with sirolimus as their antiproliferative agent.

[Slide.]

The major problems post transplant that we have to deal with, as mentioned, rejection, infection, cardiac allograft vasculopathy, which I will get to, and then the morbidities of hypertension, nephrotoxicity, and malignancy.

[Slide.]

As far as rejection goes, they are determined to occur based on invasive surveillance

biopsies, which is still the gold standard for determining if a patient has rejection.

The average patient, depending on the center, has approximately 13 to 15 biopsies done in the first year. These are done in the cath lab or in an interventional radiology suite. Each biopsy requires a minimum of three samples of the right ventricular septum from usually different sites to be meaningful for the pathologist, and a new biopsy grading system has just been recently developed, but has not yet been adopted, and I will show you that.

[Slide.]

This is how the biopsies are performed. This is actually an old cartoon picture from Dr. Shumway's group. This shows the Scholten bioptome, which was invented by Phillip Caves at Stanford, and it is inserted through an internal jugular catheter just like a Swann-Ganz catheter, across

the tricuspid valve, and a little snip of the right ventricular septum is obtained.

[Slide.]

In pediatric patients, or in patients who have an occluded right internal jugular vein, this procedure can be done from the groin, from the femoral vein.

[Slide.]

This is the ISHLT grading system. You are going to be hearing biopsy grading scores later today, and I just want to give you what the definitions are.

A Grade zero is no evidence of rejection. Grades 1A and 1B have various amounts of lymphocytes that are present without myocyte damage.

A Grade 2 is focal infiltrate with myocyte damage, and 3A, which is multifocal infiltrates with myocyte damage versus 3B, which is diffuse infiltrates with myocyte damage, and lastly, severe or Grade 4, which is diffuse infiltrates with extensive myocyte damage, edema, hemorrhage, and

vasculitis.

[Slide.]

This is what it actually looks like. This is Grade 1A with a little bit of perivascular cuffing there. You can see more diffuse lymphocytes here between the myocytes in Grade 1B and a Grade 2. There is your focal infiltrate with some myocyte damage. This is classified generally as mild rejection.

[Slide.]

More advanced rejection would be a Grade 3A where you now have multifocal infiltrates with myocyte damage, Grade 3B, more extensive infiltrates, and Grade 4 has extensive disruption of the architecture. These three grades are all considered threshold mandatory for therapy.

[Slide.]

Recently, the ISHLT had a task force that re-evaluated the issue of the current ISHLT grading system, and it was mostly because of discrepancies in determination of Grade 2 biopsies and discrepancies among pathologists, and I am just

going to show you very briefly for completeness what that system looks like.

[Slide.]

So, in the new system, a Grade zero will still be no rejection. That is unchanged.

A 1R now combines the 1A, 1B, and 2 classifications into this mild 1R classification.

A 2R is a former 3A, and the 3R is combining 3Bs and 4s, and screening box just highlights that 2R and 3R are mandatory treatment.

[Slide.]

Now, there has been a lot of discussion at the meetings regarding how much of a problem acute rejection is, and even though it has dropped quite a bit in kidney transplantation, heart transplantation in large trials, as well as in individual centers, still has a significant amount of rejection episodes.

If you take a look at four randomized trials, tac versus cyclosporine, mycophenolate versus azathioprine, tac versus cyclo again in the U.S. versus Europe, and Neoral versus Sandimmune,

you can see that instance of BPR, which is biopsy proven rejection, ranges anywhere from 73 percent to only as low as 42 percent, so the concept that acute rejection doesn't exist in heart transplantation, this is not analogous to kidney transplant where rejection rates are significantly lower. We still deal with acute rejection on a regular basis.

[Slide.]

Rejection without hemodynamic compromise is generally treated with oral prednisone, usually even at home, IV steroids are sometimes used, and that decision is dependent on the grading severity and the timing post transplant. If the patient has a rejection early after transplant, we generally tend to be more aggressive in the intravenous steroids.

Steroid-resistant rejection with or without hemodynamic compromise usually brings into play a whole host of alternative agents, and very commonly, these are used at most centers depending on what their local customs are, but cytolytic

antibodies, polyclonal or monoclonal anti-T cell agents, IVIG, intravenous immunoglobulin, plasmapheresis, photopheresis, anti-B cell therapy, rapamycin, methotrexate, cytoxan, and total lymphoid irradiation.

[Slide.]

So, cellular rejection remains an important issue. Although it has declined over the past two decades, at the least it still has about 40 percent incidence in the first year.

Antibody-mediated rejection is now recognized as an important entity, but has not been previously standardized and has therefore not been incorporated in terms of trials of immunosuppressive therapies. I think that is going to change in the future as we are trying to get our hands around antibody-mediated rejection more in the future, as we think that that is an important problem.

[Slide.]

Now, to show you some risk hazard functions, this is from the Cardiac Research

database, which is a very, very good database that is housed at the University of Alabama. It is multi-center and the data in this is extremely detailed.

This represents over 7,000 patients in this slide, and you can see that the risk hazard function of rejection, infections, nonspecific graft failure, or sudden death dramatically decreases over the first year, but what really plays into the survival issues are the instance of malignancy with time and allograft vasculopathy, which steadily increased in those patients who are survivors greater than one year.

[Slide.]

So, our long-term challenges are renal failure and metabolic adverse effects, which I am going to show you, cardiac allograft vasculopathy, which I would like to go into more detail, and then I am going to end on malignancy.

[Slide.]

As far as morbidities go, this is back to the ISHLT UNOS database. Just concentrate on the

five-year column here. The instance of hypertension is approximately 95 percent by five years.

The chance of having some degree of renal dysfunction is over 30 percent with 10 percent of patients having creatinines greater than 2.5, 2.5 percent of patients on chronic dialysis, and 0.4 percent of patients at five years after heart transplant actually needing a kidney transplant.

Eighty percent-plus of patients are hyperlipidemic, 30 percent or a third are diabetic, and a third have coronary vasculopathy by five years.

[Slide.]

As far as causes of death long term, just concentrate on basically the yellow highlighted areas. In the first month after transplantation, the number one reason you are going to die is going to be the issue of the graft itself not functioning correctly or infection.

After that first month, the big causes of death, 12 percent of deaths are due to rejection,

32 percent due to infection, only 4 percent are due to vasculopathy, and 10 percent is graft failure, which really is a surrogate for allograft vasculopathy, and these two are overlapping essentially in the database.

After the first year, at one to three years, the dominant reasons for death are 9.6 percent acute rejection, 13 percent infection, 14 percent vasculopathy, and 16 percent graft failure, so that is about 30 percent total from graft failure probably due to chronic rejection, and then malignancy starts to rear its head at this point, at about 15 percent.

These numbers and trends continue at three to five, and then greater than five years, where at this point, allograft vasculopathy and malignancy become the dominant reasons for death.

[Slide.]

This is Dr. Ojo's paper that was published in the New England Journal of Medicine in '03, just addressing the issue of renal function in solid organ transplantation, and I just am focusing on

this column on the data for the heart transplant patients.

You can see the cumulative incidence on the Y axis of Chronic Renal Insufficiency with Time Post Transplant on the X axis. 16.5 percent of patients after heart transplantation develop chronic renal insufficiency. Of this group of 16.5 percent, one-third required maintenance dialysis or renal transplantation.

Chronic renal failure was significantly associated with an increased risk of death with a relative risk of 5-fold, and this highly statistically significant.

[Slide.]

If you get a kidney transplant after heart transplantation, correcting for the time post transplant, you can see that those patients who then need a kidney transplant in and of itself don't do as well as the patients who have just got the heart transplant continuing, and this is somewhat common sense, but I just wanted to show you that the solution for renal failure after heart

transplantation getting a kidney is not without a price.

[Slide.]

In terms of cardiac allograft vasculopathy, this is the leading cause of death along with malignancy at five years post-transplant, accounting for a third of deaths.

It is characterized by a proliferation of the allograft vascular intima, which results in narrowing of the vascular lumen.

Because of that denervation that I showed you on those original surgical slides, these patients do not get classic chest pain when they have a myocardial infarction. Very often this presents a sudden death silent MI and heart failure or severe arrhythmia.

[Slide.]

There are multiple mechanisms that are felt to be involved in the development of cardiac allograft vasculopathy. There are immune issues, and we have already talked about acute cellular rejection and antibody-mediated rejection, well as

the level of immunosuppression, and then there are non-immune factors that have been shown in multiple studies to be involved in the disruption of the normal intima, which is the mode of brain death, ischemia reperfusion injury, hyperlipidemia, hypertension, CMV infection, and the age of the donor.

Now, what this lead to is two types of injury that can occur to the lining of the coronary arteries. One is the denuding injury where you get platelet, lymphocytes, and macrophages that come into this denuded endothelial lining, and the other is the non-denuding injury that basically is created by the lymphocytes and macrophages that then causes an inflammatory response.

The final common pathway is that you get upregulation of growth factors and cytokines, whether it is denuding type of injury or just a pure inflammatory response, and what this leads to is an upregulation of these growth factors that then creates a proliferation of the intima, which should only be one-cell layer thick, and this

histologic picture is shown characterized by this intravascular ultrasound picture where the intima should only be one-cell layer thick, this black lucency here is the media, and whitish gray area here is all intimal proliferation which correlates to that histologic finding.

[Slide.]

The intimal thickness does have prognostic significance. If you look at three studies, Mehra, Kobashigawa, and Dr. Tuzcu's study from Cleveland Clinic, the intimal proliferation, once it gets up to approximately 0.5 mm of thickness, is correlated with a higher chance of cardiac events, a higher overall plaque burden, and is prognostically relevant in terms of survival.

[Slide.]

Finally, to finish with malignancy, in patients outward of eight-year survivors, there is about a 26 percent chance of having malignancy. Fortunately, much of this malignancy are skin lesions - basal cell carcinomas especially, so these are easily treatable. However, there is a

real risk of lymphomas, as well as other solid tumors as time goes by.

[Slide.]

The relationship between different immunosuppressants and cancer risk is something that is still being studied, and the relationship between the duration and intensity of immunosuppression and cancer risk is unknown.

It is unknown if you have lower or minimal immunosuppressive regimens if that will decrease the cancer risk, and part of the issue in cancer screening of these patients is the frequency and the components of cancer screening. These patients may need to be screened at a molecular level more than just doing routine endoscopy type of screening.

[Slide.]

This is in vitro data, but this is very interesting, and this is my second to last slide. If you take a look at the inhibition of tumors based on different immunosuppressive agents, cyclosporine in yellow, sirolimus in blue,

mycophenolate in orange, and leflunomide in green, these are human cancer cell lines, hepatic cancer, colorectal, and myelodysplastic cell lines, and you can see that cyclosporine itself has no inhibition of tumors, whereas, as sirolimus, mycophenolate, leflunomide, depending on the tumor line, have various degrees of inhibition.

This is extremely intriguing. Again, this does not correlate at this point to clinical outcomes, but it is something that the entire transplant community is extremely interested in.

[Slide.]

So, in conclusion, we, at this point, need improved immunosuppression with less rejection, less cardiac allograft vasculopathy, and less side effects including the issue of malignancy.

We need to have better non-invasive methods to detect acute and chronic rejection, and the field is going toward the realm of genomics in the future.

We need to focus on improved survival and quality of life, and we need to do all of these

things with the increasing challenge of performing long-term, adequately powered multi-centered trials.

[Slide.]

I just have three brief, but very important acknowledgments. Dr. Mandeep Mehra, who is the head of Cardiology at the University of Maryland; Patricia Uber, who is a pharmacologist, also at Maryland; and lastly, Sarah Miller, who I work with at the SRTR, who is the Project Coordinator for the registry at the University of Michigan.

I thank you for your attention.

DR. HIATT: Thank you very much. That was a really nice, helpful clinical review.

I am going to take one prerogative, I want to ask you one thing. We would like to just have a brief moment of discussion.

In terms of events after transplantation, one of those that you discussed was biopsy-proven rejection, Grade 3A. My question is how often is that linked to another outcome, because you said

that often it is treated with a course of steroids, may be treated with more aggressive therapy, but if it's reversible, then, does it necessarily lead to hemodynamic compromise, complete rejection, or death, and if it's not linked to those things, should it be considered as a surrogate endpoint, or would you still consider it to be a primary endpoint?

DR. BARR: I would still consider it to be a primary endpoint because of the risk of death from the event. The questions you ask are good. There are various studies that have shown that if you have one rejection, you are more likely to reject again.

I think many of us view this to be a marker assuming they have good baseline immunosuppressive levels at the time of the rejection, i.e., it's not iatrogenic, that we haven't under-immunosuppressed them. It very often is a harbinger of things to come.

Hemodynamic compromise, in and of itself, may or may not be associated with the rejection

depending on the grade and the timing, and also that fuzzy area of antibody-mediated rejection.

You can have patients with lesser grade severity, but with bad hemodynamics, and that is felt by many to be due to humoral or antibody-mediated rejection.

DR. NISSEN: I have been behaving this morning, so, hopefully, my microphone got turned on.

You mentioned six different drugs that are used, and I need to understand either from the agency or from you what the regulatory status is of each of them in the heart transplant indication - cyclosporine, tacrolimus, azathioprine, mycophenolate, sirolimus, and corticosteroids.

Which of those are approved for this indication, or are all of them?

DR. ALBRECHT: As I mentioned, mycophenolate mofetil is specifically approved for heart transplantation, and cyclosporine is approved. The others are not.

DR. NISSEN: So, am I correct then that

the regimen that is now becoming the dominant regimen, the tacrolimus regiment is actually not an approved regimen, is that right?

DR. ALBRECHT: That is not today an approved regimen.

DR. NISSEN: Okay, so obviously, complicated issues.

DR. PICKERING: I have a question which actually relates to Slide 22. One of the issues that is going to come up is that the comparator drug for the key study was azathioprine, which is no longer used very much.

You referred to one study where azathioprine and mycophenolate seemed to be approximately similar in terms of the vasculopathy.

Can you explain why there has been this trend with decreasing azathioprine and the increase in mycophenolate?

DR. BARR: I think it is for two reasons. I think, first of all, because of the known incidence of cardiac allograft vasculopathy in the early era, all of us who grew up with

transplantation in the '80s, and so a lot of patients died, we would have used a drug that just was called not Imuran.

If you had a drug literally that was not that agent, we would have used it, so when mycophenolate mofetil came out, and because of a lot of data that would suggest from animal models that this might be antiproliferative, there was a strong push to shift over to the drug.

From a toxicity point of view, other than GI, it was fairly well tolerated. So, it is correct right now, to date, there is not convincing evidence although there are some studies from the post-hoc analysis of the mycophenolate, azathioprine original trial that Dr. Kobashigawa, who is here, was the PI for, that there is, in fact, some reduction in proliferation of the intima, but not as impressively strong as has been shown in other studies.

I forget your second question, sir.

DR. PICKERING: I guess the other thing was is it reasonable to generalize from an

azathioprine study to what would happen with mycophenolate with everolimus?

DR. BARR: I think the biggest problem we have got in doing any kind of studies are that we are limited to the comparator being something that is approved. I think Dr. Nissen just pointed the issue out by his question, that we are dealing with agents that are being used, in fact, the combination of mycophenolate and tacrolimus is probably the most common of those combinations, and that has totally not been studied.

So, we are limited by that, and that is in the control group, and that is still in Europe and in some centers, azathioprine, as you can see from the slide, completely vanished essentially in 2000. It was still being used in '99 fairly frequently, in fact, in '98, on this slide, you will see it is over 50 percent of the patients were on azathioprine in '98 and nearly the same in '99.

DR. HIATT: Are there any standard protocols for therapeutic drug monitoring currently today in clinical practice, standardized protocols?

DR. BARR: There are in terms of--well, standardized in the sense that there are certainly indications based on the labels for cyclosporine

and tacrolimus in terms of what target levels we should be going for, whether it's a trough or a Cmax level, and those C2 levels, and those are for specifically the calcineurin inhibitors. There is no recommendation and centers are very much based on local custom, deciding whether they are following mycophenolate mofetil levels. Some centers do, some don't.

DR. HIATT: And the guidelines haven't been developed, that you are involved in, to standardize that?

DR. BARR: The guidelines that I showed you as far as rejection goes were standardized guidelines, I think local practice. It is because of the adjuvant therapy you use. If you are going to push your mycophenolate mofetil up, or for those centers that are already using Rapamune, they are going to run their calcineurin inhibitor levels lower, and it is the same, if you will, local

practice that occurs with steroids.

Steroid dosing is totally empiric, but in cyclosporine and tacrolimus, we do have, based on renal toxicity and based on neurotoxicity, we have some idea where we should be running the levels, knowing you have to follow the renal function in these patients on an individual basis.

DR. HIATT: Are there any other questions before we move on? Steve.

DR. NISSEN: What is known about the pathophysiology of the renal dysfunction that occurs in post-cardiac transplantation patients? What do we know about it?

DR. BARR: There are people in the room who are more expert on that than myself. There is an acute issue that if the drug is too high, you actually can get a direct vasoconstrictive response, but the calcineurin inhibitors in general are known to be upregulators of TGF-beta, and that is definitely very fibroproliferative, so that you get both an acute injury, as well as a long-term chronic injury that is classic for calcineurin

inhibitors, but I would defer to people like Dr. Hunsicker in the audience.

DR. NISSEN: Thank you.

DR. HIATT: Good. Thank you very much. We will go on with the next speaker, Dr. Hukkelhoven.

Introduction and Regulatory Background

DR. HUKKELHOVEN: Thank you, Dr. Barr. Dr. Hiatt, members of the Cardiovascular and Renal Drugs Advisory Committee, Dr. Goldberger, Dr. Albrecht, FDA staff, members of the public, good morning.

[Slide.]

My name is Matt Hukkelhoven. I am the Global Head, Drug Regulatory Affairs, Novartis. On behalf of Novartis, thank you for the opportunity to present today. My colleagues and I look forward to reviewing the clinical development program for everolimus, proposed trade name Certican, in heart transplant patients.

[Slide.]

The clinical trial program for Certican

has been the most comprehensive program in organ transplantation to date. There have been 25 clinical trials enrolling approximately 3,000 patients. Over 1,800 patients have been treated with everolimus by 220 investigators worldwide.

Study B253, the Phase 3 study for Certican in heart transplantation has enrolled 634 patients with follow-up at 6, 12, and 24 months, and at 48 months for patients who elected to enter an open-label extension.

[Slide.]

In fact, Study B253 is the first successful superiority trial in heart transplantation.

In addition to Study B253, which we will focus on today, our core program includes multiple studies in kidney transplantation. The pivotal heart, two pivotal kidney studies, as well as one dose-ranging study in kidney, used everolimus in combination with full doses of Neoral, cyclosporine A.

A small study in pediatric renal

transplantation is ongoing with full dose Neoral.

In addition, an early exploratory study with reduced-dose Neoral was performed.

More recently, two large open-label trials utilized prospective therapeutic drug monitoring to evaluate concentration-controlled everolimus in combination with reduced doses of Neoral.

[Slide.]

To give you an idea of the global experience we have gathered with Certican, I will share the registration status to date. We have a total of 48 approvals in both heart and kidney transplantation including approvals in 25 European countries, and Certican is now commercially available in 27 countries.

There are approximately 1,200 patients taking commercial product, of which greater than 75 percent are in heart transplant.

Germany has the largest experience so far with more than 700 patients, of which 90 percent are heart transplant patients. This represents approximately 15 percent of the total de novo and

maintenance heart transplant population in Germany.

Additional country approvals have been obtained in Australia, South Africa, Switzerland, South and Central America, and Israel. Currently, we have a new drug application for heart transplantation under review in Japan. Three countries have not approved Certican.

[Slide.]

Let me briefly review the regulatory history of Certican. Our NDAs for heart and kidney transplantation were submitted in December of 2002, and following extended review period of 10 months, we received the first of two action letters.

The first approvable letter in October 2003 identified that Certican is efficacious in both heart and kidney transplantation. In this letter, FDA requested additional data to support safe dose recommendations with cyclosporine with regard to renal dysfunction.

Following a submission of data in response to these FDA comments, we received a second approvable letter in August 2004. Novartis met

with the FDA in November of last year to discuss next steps.

FDA indicated at this meeting that a sound dose recommendation could not be derived from our clinical trials in kidney and heart transplant, however, it was generally agreed that Certican has a more favorable benefit-risk profile in the heart transplant setting and that seeking Advisory Committee recommendations could be useful to move the application forward, and this is the indication heart transplant that we will focus on today.

Since that meeting, Novartis submitted additional documentation in March of 2005 to support today's presentation. Furthermore, we have reached agreements with the FDA regarding the design of another clinical heart transplantation trial plus we currently have a heart study ongoing in Europe as a post-approval commitment.

[Slide.]

Overall, our objectives for this meeting are to review the primary efficacy and safety data from the pivotal study in heart transplantation,

Study B253. We will present the results of additional analysis from our pivotal study and we will provide dosing recommendations for Certican in combination with Neoral.

We will also present a comprehensive review of the benefit-risk profile for Certican, focusing on acute rejection, cardiac allograft vasculopathy, renal safety, and the use of therapeutic drug monitoring.

Novartis believes that Certican has demonstrated efficacy in both heart and kidney transplantation. In fact, the Certican heart study has demonstrated superiority of everolimus in heart transplantation.

Renal safety remains an appropriate concern, however, as you will see, we have recommendations to manage renal safety. These recommendations are supported by pharmacokinetic, pharmacodynamic analysis of Study B253, experience from two prospective therapeutic drug monitoring studies in kidney transplantation, and postmarketing experience in Europe.

These dosage recommendations create a favorable benefit-risk profile for Certican in heart transplantation.

[Slide.]

Our proposed indication for Certican is for the prophylaxis of organ rejection in adult patients receiving a heart transplant. It is recommended that Certican be used concurrently with Neoral, cyclosporine A, and corticosteroids.

[Slide.]

To reiterate, Study B253 evaluated everolimus at fixed doses of 1.5 and 3.0 mg per day with full conventional doses of cyclosporine. As will be discussed later by Dr. Hunsicker, and based on the assessment of efficacy and safety, we are proposing that Certican be used in an additional regimen of 1.5 mg per day, adjusted then to achieve target trough concentrations from 3.0 to 8.0 ng/mL.

Certican should be used with reduced doses of cyclosporine after the first month.

[Slide.]

Momentarily, Dr. Howard Eisen will present

some of the challenges and opportunities that we face today in heart transplantation setting, as well as the basic mechanism of action of everolimus.

Dr. Jeffrey Hosenpud will present the efficacy results of Study B253. Dr. Jon Kobashigawa will present the intravascular ultrasound results, and this will then be followed by Dr. Ken Somberg from Novartis who will review the safety data.

Dr. Larry Hunsicker will address renal safety and dose recommendations. Finally, Dr. Eisen will return to summarize the favorable benefit-risk profile of Certican in heart transplantation.

[Slide.]

We are also joined today by Dr. Randall Starling from the Cleveland Clinic Foundation; Dr. Lee-Jen Wei from the Harvard School of Public Health, and Dr. Hans Lehmkuhl from the German Heart Center.

[Slide.]

At this time, I would like to introduce Dr. Howard Eisen, Professor of Medicine, and Chief, Division of Cardiology, Drexel University College

of Medicine.

Challenges and Opportunities in

Cardiac Transplantation

DR. EISEN: Thank you, Dr. Hukkelhoven for that introduction.

My name is Howard Eisen. Today, I would like to spend some time and share with you the state of the unmet medical need in cardiac transplantation.

[Slide.]

Over the past decade, the number of cardiac transplants in the United States has remained relatively constant, between 2,000 and 2,400 a year. In addition, the number of patients on the waiting list for a heart transplant is approximately 3-fold higher than the number who receive an allograft, and this ratio has not improved with time. Due to the shortage of organs, fewer patients receive heart transplants than need

them.

[Slide.]

A small number of heart transplants are performed at approximately 120 centers in the United States. Because of this, Phase 3 clinical trials in heart transplantation are small compared with the usual size of clinical trials in cardiovascular medicine and generally cannot be powered for mortality endpoint.

As transplant centers have their own customized treatment protocols, it is difficult to negotiate a standard protocol to test new medications in clinical trials. The net effect is only four randomized trials that have been conducted. The largest of these have enrolled about 600 patients.

The stakes for the individual patients are high. The treatment regimens require frequent alterations to ensure optimal outcome. This leads to frequent study medication discontinuation.

Approximately 30 percent of cardiac transplant patients drop out of clinical trials

annually. This and the relatively small number of patients available for enrollment limits the ability of clinical trials in cardiac transplantation to definitively address all important questions of long-term outcomes.

[Slide.]

Now, let's consider the major endpoint of each of these clinical trials which is acute allograft rejection. The table you see now shows the causes of death as a function of time after heart transplantation.

As you can see, in the first year after transplantation, acute rejection is the major cause of death in transplant patients. It is also important to note that cardiac allograft vasculopathy is a major cause of death in heart transplant patients when one goes beyond the first year after transplantation.

[Slide.]

We also need to appreciate that acute rejection, which is the basis of our efficacy for everolimus, is a relatively frequent complication.

It affects approximately half of patients after heart transplantation, and the diagnosis requires invasive monitoring.

Treatment requires high doses of immunosuppressive drugs. Treatment complications include high risk for infections, lymphoma, other malignancies, and sequelae of high-dose steroids.

If untreated, the result could be hemodynamic compromise and death.

[Slide.]

As this survival curve from the Cardiac Transplant Research database clearly shows, acute rejection is not a benign event. Indeed, patients alive at one year after transplantation and having no rejection have a significantly better survival compared to patients having one or more acute rejection episodes.

This graph starts in Year 1 following observation for rejection in the first year after transplantation. The survival rates between these groups begins to diverge only after Year 2.

[Slide.]

As Dr. Barr mentioned previously, acute rejection is not the only issue that confronts cardiac transplant patients. The entire

improvement in survival over the past 20 years can be attributed to advances in perioperative management, thereby accounting for better survival in the first year.

The long-term survival of cardiac transplant recipients has not improved, but has remained relatively constant with a median survival of 9 to 10 years. The long-term survival curves that you see here are parallel. There continues to be a significant loss of patients each year largely due to cardiac allograft vasculopathy.

[Slide.]

Cardiac allograft vasculopathy, or CAV, is the accelerated, obliterative coronary artery disease following heart transplant.

By intravascular ultrasound at 1 year, most patients develop intimal thickening to a greater or lesser degree, and in about half of these patients, the changes are moderate to severe.

Cardiac allograft vasculopathy is a major cause of mortality late after transplantation. Once cardiac allograft vasculopathy develops, there is no satisfactory long-term treatment. As with other cardiovascular diseases, the goal or treatment should be prevention.

[Slide.]

This slide shows angiograms obtained 1 and 3 years after transplantation in the cardiac transplant recipient. As can be seen, there is near obliteration of the distal coronary arteries and severe narrowing of the proximal vessels which all developed in a 2-year period.

This rate of progression is far more rapid and extensive than what is seen in non-transplant atherosclerosis. Given the diffuse nature of cardiac allograft vasculopathy, this disease is generally not amenable to revascularization either percutaneously or surgically.

[Slide.]

Here we see a histologic slide from a patient with cardiac allograft vasculopathy showing

the circumferential nature of the intimal proliferation characteristic of this disease. This slide illustrates the fact that cardiac allograft vasculopathy has accelerated the obliterative coronary artery disease following heart transplantation.

[Slide.]

I have already shown you the circumferential nature of the intimal hyperplasia characteristic of this disease. As opposed to native coronary artery disease, CAV is diffuse and distal in its involvement. Calcium deposition is absent, the internal elastic lamina is intact, and there is infrequent inflammation and vasculitis.

Most important, the rate of development of cardiac allograft vasculopathy is over a period of months as opposed to years for native coronary artery disease.

[Slide.]

Cardiac allograft vasculopathy is difficult to diagnose angiographically because of the diffuse extent of the disease. The most

sensitive and specific diagnostic modality for the early detection of allograft vasculopathy is intravascular ultrasound or IVUS.

IVUS has been demonstrated to be far more sensitive than angiography for the detection of cardiac allograft vasculopathy. In the case illustrated here, a matched angiogram and IVUS study in the same cardiac transplant recipient showed a normal left anterior descending coronary artery lumen on angiography, but a significant amount of intimal hyperplasia on IVUS.

[Slide.]

IVUS has been used to define the presence and extent of cardiac allograft vasculopathy, the four comparator clinical trials in heart transplantation. These include the open-label, randomized trials of statins and of sirolimus, and the post-hoc analysis of mycophenolate mofetil. However, the only study conducted as double-blind, randomized trial was the everolimus study we are talking about today.

[Slide.]

I will now present the relevant mechanisms of action and experimental efficacy of everolimus beginning with the mechanisms of action.

[Slide.]

Everolimus is an oral macrolide derivative of sirolimus. It is an inhibitor of the cell cycle protein mammalian target of rapamycin. After everolimus binds to it intracellular target FK binding protein 12, and blocks the activity of mTOR, ribosomal P70S6 kinase is inhibited.

This leads to the arrest of the cell cycle at the G1 to S phase, and thus inhibits lymphocyte and vascular smooth muscle cell proliferation in response to the cytokines and growth factors.

One result is prevention of allograft rejection, the other is direct attenuation of intimal thickening.

[Slide.]

Preclinical studies in various models of vascular remodeling led us to expect that everolimus would have a beneficial effect on the incidence and severity of cardiac allograft

vasculopathy.

Let us now look at the compelling effects of everolimus that were seen in preclinical studies. They are summarized here.

Everolimus inhibits cell proliferation in vitro. Everolimus has potent immunosuppressive activities in animal transplant models. Everolimus prevents remodeling in immune and nonimmune vascular injury models.

In the next few slides, we will examine the preclinical evidence in more detail.

[Slide.]

Here, we clearly see that everolimus compared to control reduces rejection and improves graft survival in mouse heart allograft and cynomolgus monkey kidney allograft recipients.

[Slide.]

The immunologic impact of everolimus is well established. I want to present some of the preclinical data for long-term vascular effects. The Apo E-deficient hyperlipidemic mouse is prone to develop accelerated atherosclerosis and is used

to study the effect of drugs on atherosclerosis prevention.

Mice with this genetic defect receive carotid allografts to determine the effect of everolimus on deleterious neointimal formation in the setting of severe hyperlipidemia.

The model is potentially analogous to the state of coronary arteries in patients after heart transplantation. The intimal occlusion progresses fairly predictably in untreated mice or in mice treated with cyclosporine which has no effect on the cell cycle per se.

In contrast, we can see that everolimus significantly attenuated the progression of intimal remodeling in this animal model. These data demonstrated that everolimus could prevent lipid-mediated vascular injury, as well as alloreactive injury.

[Slide.]

Extending these preclinical observations to research subjects, two, six-month analyses are reported from FUTURE I and FUTURE II trials. In

subjects treated with control bare metal stents, there was an approximate 0.8 mm loss in lumen diameter in both studies.

In contrast, subjects treated with everolimus- eluting stents experienced a negligible loss of lumen at the six-month evaluation. These data provided further rationale for evaluating the potential role of chronic administration of everolimus in the prevention of cardiac allograft vasculopathy.

It is important to point out that the hypothesis that everolimus would have a beneficial effect on the incidence and severity of cardiac allograft vasculopathy was developed based on the biological mechanisms of action and the results in various preclinical models, and is supported by the data from the related indications such as restenosis after stent deployment.

[Slide.]

So, in considering the efficacy and IVUS presentations to follow, it is important to remember these four concepts.

Acute rejection increases mortality after heart transplantation.

Long-term mortality remains unchanged over

the past 20 years.

Cardiac allograft vasculopathy is the leading cause of late allograft dysfunction and mortality.

The everolimus versus azathioprine study is the first blinded, randomized trial to show that an immunosuppressant can reduce both acute rejection and cardiac allograft vasculopathy.

While the FDA position is that the IVUS data from this trial are only hypothesis generating, in fact, they do provide important confirmation. While not providing definitive proof, the data you will see are entirely in keeping with what was expected based on the earlier preclinical work.

So, with this as background, let me turn over the podium to Dr. Jeffrey Hosenpud from the University of Wisconsin.

DR. HIATT: Before you do that, does the

committee have any questions? Tom.

DR. PICKERING: Could you compare everolimus and sirolimus? I mean are they interchangeable or why everolimus, and not sirolimus?

DR. EISEN: Sirolimus is approved for kidney, but not for heart transplant in this country. Sirolimus has been studies in a smaller study in Australia using intravascular ultrasound with similar results, and has been used off label in de novo patients in the United States in heart transplantation, but a number of the centers that actually used sirolimus stopped using it for reason of wound dehiscence, things that were not actually seen in the clinical trial that we are discussing.

DR. ABERNETHY: Isn't it correct, though, that when sirolimus drug-eluting stents were being studies, that systemic sirolimus was not effective in slowing the late occlusion with stenting, and there is an issue of systemic drug versus local drug, I think?

DR. EISEN: There is one study that I am

aware of which is actually from Norway, where they did not have a Cypher stent or the stent, sirolimus-eluting stent available, and actually used the systemic sirolimus with bare metal stents, and did see an attenuation of restenosis after stent deployment with the bare metal stents. So, there at least are some data. They have not been evaluated to the same extent. This is the OSIRIS study.

DR. NISSEN: It's like killing a fly with a sledgehammer.

DR. EISEN: Right. Again, the duration of using the agent would be relatively short after stent deployment compared to the life-long risk of developing cardiac allograft vasculopathy after transplant.

DR. ABERNETHY: I am just trying to understand how they extrapolate the finding, that's all.

DR. EISEN: This is the oral rapamycin study.

[Slide.]

This is actually a study from Argentina. It's the oral rapamycin study, so oral rapamycin was administered. Here, you can see that, in fact,

there was less instant restenosis and late lumen loss in patients with higher doses of rapamycin compared to lower doses.

DR. MANNON: Could you clarify something that you had mentioned on your third slide about the high stakes and the high rate of dropout in clinical trials in heart transplant, can you elaborate a little bit about what those stakes and why patients drop out?

DR. EISEN: Let me pull up the slide.

If you look at all the clinical trials regardless of the agent being studied, there was about a 30 percent dropout, so some of it may be due to tolerability, some of it may be due to issues of efficacy. Those don't just affect the investigational comparator, the investigational drug, but may affect the comparator, as well, which is often in these studies azathioprine.

Let me show you the discontinuation rate

for some of these studies.

[Slide.]

The two big ones are B253 and the mycophenolate study, and you can see the discontinuation rates here. The other study, the anti-IL-2 receptor study was really just five doses of anti-IL-2 receptor antibody given within the first five weeks of transplant, so it was less likely to have discontinuation, but it is, in part, based on side effects, and, in part, based on issues of efficacy.

DR. HIATT: Are there any other questions?

Okay. Thank you very much.

Efficacy Results of Study B253 in De Novo Heart Transplantation

DR. HOSENPUD: Good morning. My name is Jeff Hosenpud and I would like to present the efficacy results of this study.

[Slide.]

Following consultation with transplant experts and discussions with the FDA, Study B253 was designed primarily to compare the efficacy of

everolimus at 1.5 and 3.0 mg versus azathioprine in de novo heart transplant recipients in the first six months post-transplantation.

[Slide.]

Efficacy was defined based upon precedence from other renal and heart transplant studies as a composite. This composite included the absence of biopsy-proven acute rejection Grade 3 or greater, the absence of graft loss requiring a retransplantation or death.

Loss to follow-up was also considered a component of the primary endpoint, but its impact was limited with only one patient lost in the first six months.

[Slide.]

As shown previously by Dr. Barr, this is the standard biopsy grading scale initially proposed by the International Society for Heart and Lung Transplantation, and is used internationally.

Most centers will not treat rejection below a Grade 3A and hence, this is a reasonable and accepted outcome endpoint.

[Slide.]

There were several secondary study objectives including the analysis of the primary

efficacy endpoint at later time points, 12 and 24 months, an analysis of the individual components of the primary endpoint at 6, 12, and 24 months, and most importantly, the presence and severity of cardiac allograft vasculopathy at 12 and 24 months as assessed by intravascular ultrasound.

[Slide.]

Study B253 is the largest study of its kind involving over 600 patients at 52 centers. It was also important to remember that this is the only dose-ranging study conducted in heart transplantation to date.

It was a randomized, double-blind, double-dummy, multi-center trial. Everolimus and cyclosporine were both given twice daily. Azathioprine was given once a day. As you can see, it is a 3-arm trial with randomization on day 1 and everolimus being given at 1.5 mg with cyclosporine, at 3.0 mg with cyclosporine, or azathioprine given

at 1 to 3 mg/kg/day with cyclosporine.

The core study phase was 2 years with blinded analyses at 6 months and 12 months, and a subsequent analysis at 24 months.

Based upon the identification of a renal safety issue, the trial was amended to unblind the patients and allow for cyclosporine reduction. At the point of this amendment, over 85 percent of patients had already reached their 2-year endpoint.

[Slide.]

The everolimus dose chosen for the study was based upon dose finding in kidney studies. They were also based upon pharmacokinetic and pharmacodynamic modeling in primates. These tested doses of everolimus ranged from 0.7 to 10 mg. Doses up to 5 mg/day were found to be well tolerated.

Both everolimus doses were based upon dose-response relationships for sirolimus in kidney transplantation and then cyclosporine was used and adjusted to maintain trough ranges depending on the time post-transplantation.

As you can see in the lower part of the slide, target trough concentrations were 250 to 400 ng/mL in month 1, 200 to 350 ng/mL in months 2

through 6, and 100 to 300 ng/mL thereafter.

[Slide.]

Surveillance endomyocardial biopsies were standardized across treatment arms and were performed at every study visit. This frequency is consistent with prevailing standard of care. Eleven biopsies were performed in the first year. Additional endomyocardial biopsies were done for suspected acute rejection, and patients who discontinued study medication were followed up at 3, 6, 12, and 24 months.

[Slide.]

As all randomized patients were treated with at least one dose of study medication, the efficacy and safety populations are identical. Lab analyses were performed while on treatment.

The 12-month efficacy analysis included events through day 381. To be conservative with regards to safety, the 12-month safety analysis

included events through day 450. This resulted in small differences in graft loss and death between the efficacy and safety analyses.

Finally, the 24-month efficacy and safety analyses included events through day 810.

[Slide.]

This was a randomized study. Baseline demographics were well balanced among treatment arms with no significant differences between treatment groups, however, there were small differences particularly in number of patients at risk for primary CMV infection, patients whose underlying disease was coronary artery disease, and patients with pretransplant diabetes in the 3 mg arm.

[Slide.]

The protocol allowed investigators to adjust dosing at their discretion to manage side effects, such as leukopenia, thrombocytopenia, or hyperlipidemia, however, most patients took their treatments as assigned.

The median daily dose for azathioprine

averaged 1.7 mg/kg, everolimus at the 1.5 mg for the 1.5 mg study arm, and 2.8 mg for the 3.0 mg study arm.

[Slide.]

This slide shows you the trough levels of cyclosporine for the 3 arms, and you can see that basically, the cyclosporine dosing was equivalent among the 3 groups.

The dotted white lines represent the protocol-defined cyclosporine trough levels.

[Slide.]

Potential side effects or complications post-transplantation included hyperlipidemia, opportunistic infections including cytomegalovirus and cyclosporine-induced hypertension.

Accordingly, the medications listed here are all typical for this patient population. Approximately 90 percent of patients were on lipid-lowering therapy, 85 to 90 percent were on pneumocystis prophylaxis, 60-plus percent were on cytomegalovirus prophylaxis, and the vast majority were on antihypertensive therapy.

Importantly, the use of these agents was balanced between treatment arms.

At the time the study was conducted,

approximately half of the centers used lymphocytolytic induction therapy with either poly- or monoclonal antibodies as part of their standard protocol. Again, the use of these agents was balanced across treatment arms.

[Slide.]

Here now are the primary results. What is presented here are the percentage of patients who failed therapy in each of the 3 arms at the 6-month time points. Remember that failure was a composite of biopsy-proven acute rejection of ISHLT Grade 3A or greater, acute rejection associated with hemodynamic compromise, graft loss, retransplantation, or death.

The efficacy failure rate was 46.7 percent in the azathioprine group, 36.4 percent in the 1.5 mg everolimus arm, and 27 percent in the 3 mg everolimus arm. The P value for comparison of the 1.5 mg everolimus arm versus azathioprine was

0.031, and the P value for the comparison of the 3 mg group was less than 0.001.

Finally, both comparisons reached statistical significance favoring everolimus based upon the modified bonferroni procedure for multiple comparisons.

[Slide.]

Breaking down the components of the composite primary endpoint, you will see that the efficacy benefit in favor of everolimus was driven primarily by a significant reduction in biopsy-proven acute rejections.

Acute rejection associated with hemodynamic compromise was not significantly different across treatment arms, and survival in all 3 treatment arms was excellent, and there was no difference in graft loss or mortality.

[Slide.]

This slide shows the percentage efficacy failure at 12 and 24 months, similar to the previous slide I showed you at 6 months. The primary efficacy endpoint benefits of everolimus

demonstrated at 6 months are maintained through 2 years post-transplantation.

[Slide.]

Looking at these same data continuously over time using a Kaplan-Meier analysis, shows that the impact of everolimus on the primary endpoint is in the first 6 to 7 months post-transplantation, at a time when acute rejection is most frequent. Moreover, there is a clear and highly statistically significant dose-response.

[Slide.]

Importantly, there were no differences in mortality or graft loss between the 3 groups, with all groups having excellent survival.

[Slide.]

So, in conclusion, this study is the first blinded, randomized clinical trial in heart transplantation to show a significant efficacy benefit for a new immunosuppressive agent, specifically, everolimus.

Everolimus, as part of an immunosuppressive regimen in heart transplantation,

significantly reduces acute rejection. These efficacy benefits are durable and persist out to 24 months post-transplantation.

Finally, there were no significant differences in survival between the treatment arms with all groups having excellent survival.

[Slide.]

I will now turn the podium over to Dr. Kobashigawa to discuss the results of the IVUS study.

DR. HIATT: Before you do that, we might have a few questions.

DR. HOSENPUD: I surmised that.

DR. NISSEN: I am just going to offer an editorial comment and that is that the sponsor and the investigators are really to be complimented. Performing a 600-patient study in a disease where there are only 2,000 transplants in the U.S. a year is obviously an extremely difficult thing to do, and this provides more information than we get from almost any other study.

So, I think that needs to be said that

this is really an extraordinary effort in a population that is very limited.

DR. HOSENPUD: I appreciate that. Thank you.

DR. TEERLINK: Perhaps you will get to this later, but in your booklet, on page 59, table 5-2, you give the patient disposition at 12 months, kind of giving an outline of what is happening with the patients and how many are actually available for evaluation and things and on drug.

Do we have that 6 months in terms of how many patients are still on drug? That may be just being shown later with the Adverse Event section.

It's from the handout, page 59, Novartis briefing book, table 5-2.

DR. HOSENPUD: Dr. Teerlink, you are specifically interested in the discontinuation rate at 6 months?

DR. TEERLINK: Yes, and seeing where the patients are at 6 months.

DR. HOSENPUD: In terms of dropout, there was only one patient lost to follow-up, in terms of

the follow-up, and the others--

DR. TEERLINK: Who was actually still on drug?

DR. HOSENPUD: Do we have that data?

DR. SOMBERG: Ken Somberg, Clinical Research at Novartis. That is not one of our core slides, but we will get that produced. We may not have that until the lunch period.

DR. TEERLINK: That's fine.

DR. ABERNETHY: Could we look at Slide CE-12? I believe you said that 85 percent of the patients were at 24 months by the time the 12-month amendment was made.

DR. HOSENPUD: Yes.

DR. ABERNETHY: So, these cyclosporine concentration data would be based on 85 percent of people who did not have any dose adjustment and 15 percent of people who underwent dose adjustments related to the amendment, is that correct?

DR. SOMBERG: If I could speak to that, just to clarify, this amendment took place beginning at 21 months, and the amendment really

was introduced for safety reasons, that is, we recognized the problem and wanted to make sure there was an opportunity to unblind patients and allow cyclosporine to be reduced.

You actually can see, if you look earlier on, that although there are substantial overlaps.

[Slide.]

As we can see here, the average cyclosporine levels in everolimus-treated patients are a little bit lower, which probably do reflect some modification even on an unblinded basis in response to renal function.

Certainly, everything out to this point is fully blinded, and it is only here that you begin to have some patients that may have entered the amendment, but, in fact, only a minority of patients entered the amendment. I think that is for a variety of reasons. They were quite a ways out from transplant, and some did not probably want to return to the center very often, many had satisfactory renal function. Many had already had reduction in cyclosporine.

So, in fact, the renal amendment is not something we find very informative and certainly don't draw any real conclusions from. It is a

small amount of patients, very late, but again provide an opportunity to address the safety issue.

DR. ABERNETHY: Then, do we have data on the cyclosporine dosing regimens in that 85 percent who remained without the amendment? I am trying to understand the relationship of dose adjustments of cyclosporine, these concentrations, and the nephrotoxicity.

DR. SOMBERG: We do not have a specific slide that after 21 months, gives cyclosporine concentrations by amendment or non-amendment patients. However, when we talk about the renal function data throughout the first year, it certainly all represents the blinded data, as well as the renal function that accompanied that.

For the second year, again, the vast majority of the data remained blinded, but to your specific question, do we have data separating out cyclosporine levels in the 85 percent in the

amendment versus the 15 percent, no, we do not.

DR. ABERNETHY: What I am really trying to get at is the nephrotoxicity we are seeing really a function of cyclosporine exposure or some synergistic effect of everolimus and cyclosporine in the context of the same cyclosporine concentration?

DR. HIATT: I think it is more of an interaction, I would sort of characterize that, which has been characterized in the document.

DR. SOMBERG: Correct. Certainly, it wasn't just due to cyclosporine levels being higher in those patients. It is some interaction, the reason for which we really don't understand between those two.

DR. HOSENPUD: Just one additional comment from a clinical care standpoint. As we are following these patients and we see the renal function deteriorate, we will try to maintain the cyclosporine levels within the parameters of the study, but we will lower the doses based on what we are seeing clinically.

So those lower trough levels in the two everolimus arms, I am sure are clinically driven drops based upon the change in renal function.

DR. PROSCHAN: On Slide CE-9, you talk about safety analyses were conducted on all randomized patients receiving at least one dose of study medication.

I thought there was an issue about the fact that if they had gone off medication for at least 30 days, they were not counted, is that right?

DR. SOMBERG: Adverse events were no longer collected after 30 days. Malignancy, death, graft loss were collected.

DR. KASKEL: In your data on Slide 13, do you have a breakdown of the type of antihypertensive agents that were used regularly in these different groups?

DR. HOSENPUD: Do we have a breakdown of those? Yes, we do.

[Slide.]

You can see that the majority of patients

were on actually combinations of drugs, both ACEs or ARBs, and a large proportion of patients were on calcium channel blockers. Importantly, these percentages of patients are pretty comparable across groups.

DR. HIATT: I had a question about sort of the mortality data during the rigorously blinded phase of the study. Between the high dose of everolimus and azathioprine, at 6 months, there was an excess number of 4 deaths, and at 12 months, there was an excess 6 deaths, and then it washed out after that, but then the blind was broken after that, too.

My first question is, did the DSMB raise a concern about that? Even though it is not statistically significant, that is really not the question, because the numbers, the events are small.

DR. SOMBERG: No, they did not.

DR. HIATT: Were you at all concerned about that, because I realize that the endpoint is driven primarily by a biopsy-driven endpoint, and

you would think if that were sort of going to drive the harder events, that it would lead to maybe a reduced number of deaths or rejection, but it seemed not to, in fact, the opposite seemed to be occurring, mortality seemed to be slightly increased at least during the first 12 months.

DR. SOMBERG: It was certainly something that was considered and looked at carefully, and if actually one looks at causes of death, these were examined for patterns of increased infection or things of a specific nature. In fact, the causes of death were quite spread out over a variety of causes, so that issue was certainly addressed.

But DSMB did not raise a concern, but it does lead to the point that overall, the tolerability profile of the 3 mg dose was not as good, and that relates--and I will touch on this in the safety presentation--to the recommendation that the most appropriate starting dose is the 1.5 mg dose.

In spite of efficacy being better with 3 mg, the best balance between benefit and risk, we

feel is achieved with the 1.5 dose, and that plays into that.

DR. NISSEN: I wasn't as puzzled by that. I think it is recognized that there is a lag between these sorts of rejection events and then the ultimate cumulative effects, which are to lead to graft loss and death.

This is a relatively short-term experience. These patients are now living, as we now know, 7, 8, 10 years and longer, so without going out further, it would be a lot to expect to see a short-term mortality difference in any of these therapies particularly since the acute rejections are treated very intensively now.

DR. TEERLINK: Nonetheless, I still am interested in seeing what at 6 months and at 12 months, and you actually give this data in the briefing document, in your own briefing document, on page 37, table 4-4.

I am interested in seeing what, at 6 months, the endpoint looks like when you remove just the biopsy. If you get rid of the biopsy

portion of the endpoint and include just the graft loss, death, and rejection with hemodynamic compromise, what does that look like in terms of the comparison between the three groups.

DR. HOSENPUD: You have the survival data, which clearly is not different at 6 or 12 months. Where is the hemodynamic compromise data?

DR. TEERLINK: Obviously, all of these, if you add up the numbers of events, they add up to more than what is given in the total, because you can get--

DR. HOSENPUD: There were no graft losses and retransplantations, so really, the only two other endpoints that are relevant are either mortality or a rejection with hemodynamic compromise.

[Slide.]

Here is the data at 6 months, and you can see that the azathioprine group actually had a higher numerical incidence of acute rejection with hemodynamic compromise, so those are the individual endpoint numbers.

DR. TEERLINK: Right. The thing that I am looking at has graft loss, death, lost to follow-up at 12 months, 18 in the 1.5 group, 24 in the 3.0 mg

group, compared to 19 in the azathioprine group.

DR. SOMBERG: I think that is correct, and I think that, not surprisingly, if you take acute rejection out and are left with hemodynamic compromise, death, graft loss, lost to follow-up, the numbers will be very similar especially for the 1.5 mg everolimus and azathioprine arms, and I think that is consistent with Dr. Nissen's point that differences in mortality would become manifest at a later time point.

DR. TEERLINK: Although 12 months would be a point that would be reasonable to try to start seeing some of those differences, and, if anything, it is going in the wrong direction.

DR. HOSENPUD: Again, I think for the most relevant comparison, I think they are nearly identical.

DR. PICKERING: On that point, I think there was the same trend. Again, the numbers are

very small in the two renal studies. The 1-year mortality was just very slightly higher in the everolimus group.

DR. DeMETS: The question I would like to ask is a follow-up to Dr. Proschan's question about the ascertainment of your primary endpoint. Given that most of the activity is in the biopsy-proven Grade 3 or larger, what I am trying to understand is were you able to get ascertainment in all the patients that were randomized, because with a high dropout rate, I am trying to understand, do we have complete ascertainment or don't we?

DR. HOSENPUD: For all the patients who stayed on study drug, they had multiple biopsies. They had 11 biopsies that first year. In patients who didn't, who dropped out, we still had 3 month, 6 month, we had several biopsies plus we looked back at the clinical biopsies that were obtained in that patient population that were done at each center, which may not have been exactly at the same time point, but would have reflected rejection.

DR. DeMETS: So are you saying there was

essentially no or very few patients for whom you didn't have pretty good ascertainment?

DR. HOSENPUD: I think we had very good capture of these endpoint, yes.

DR. TEERLINK: Then, that is a little bit in contra distinction to what I saw in the FDA's document on page 36 where they suggest that 18 percent of the patients in your everolimus 3.0 mg group didn't have 6-month information compared to 12 percent in the 1.5, compared to 11 percent in the azathioprine, so one of the points that is actually brought up in the FDA briefing document is, is the beneficial effect in this reduced noticing of biopsy-proven rejection actually due to just an ascertainment bias where you are getting fewer biopsies at that time and patients who have already dropped out of the study, which also I was asking about the 6-month disposition of these patients.

I am just trying to see if this whole endpoint is being driven by something that is biased by dropouts and ascertainment.

DR. HIATT: There is a later table that looks at the same thing.

DR. TEERLINK: The actual number of

biopsies in the 3 mg group was numerically less than any of the two groups.

DR. SOMBERG: I guess a few points. One way we looked at this was a sensitivity analysis that looked at if you missed any biopsies, and I think from the clinician's point of view, even if a biopsy doesn't fall in a visit window, it's not likely that Grade 3A rejection would just disappear and not be found maybe a little bit later, but nonetheless, I think in a rather conservative sensitivity analysis, when anybody who missed a biopsy was included along with the composite endpoint, you still see the everolimus treatment arms above with a less frequent failure with azathioprine below in blue.

For the 1.5 mg group, you do just lose significance. It is certainly still there for the 3 mg group, so we did try in different ways to address this. Overall, the average number of

biopsies across patients in the study was quite similar, so we think that ascertainment bias, although an important thing to raise, is not a significant contributor to the efficacy.

DR. NISSEN: I just feel compelled to point out to the committee that interpretation of the mortality data with the confidence intervals being what they are, we are talking about a very, very small number of events, and I would be extremely careful not to--I don't read anything into the data at all at this point given the confidence intervals.

DR. HIATT: Shall we move on? Thank you.

Intravascular Ultrasound (IVUS)

Results of Study B253 in De Novo Transplantation

DR. KOBASHIGAWA: Good morning. My name is Dr. Jon Kobashigawa. I am from the University of California, Los Angeles. I would like to present the Certican intravascular ultrasound results from the B253 study in de novo heart transplant recipients.

[Slide.]

I will begin my review by speaking on the background of IVUS technology and discuss the recent clinical studies involving IVUS and cardiac

allograft vasculopathy in heart transplant recipients.

I will then discuss the results of the IVUS B253 study in regards to the primary analysis, bias assessments, and sensitivity analysis, and then I will summarize this presentation.

[Slide.]

This slide was shown by Dr. Eisen, demonstrating that angiography is rather insensitive to detect cardiac allograft vasculopathy as compared to intravascular ultrasound. If you look at the yellow and orange arrows, you will see figures of the intravascular ultrasound to the right.

In the bottom portion, you see the orange arrows that designate that the lumen is 3.1 mm and very little intimal thickening. The white circle in the middle is a catheter artifact.

Now, if you look at the yellow arrow, and

both arrows point to what we would call normal coronary angiography, you will see that the lumen again is 3.1 mm, but now you see the very thick crescent of intimal thickening.

What happens in that to picture is that you get compensatory vasodilation, and that is what happens when you get intimal thickening. Therefore, the artery may look normal because the lumen is indeed the same, and the angiographic dye merely fills the lumen, and that is why at least angiography you will see the same lumen diameter, but yet the intravascular ultrasound will pick up that very thick crescent of intimal thickening.

[Slide.]

Let me show you now the IVUS measurements that we used in the study, and that is used in most study protocols.

In red is the lumen area, in yellow is the media adventitia, what we call the external elastic membrane. In green is the intimal area, and then we do two measurements that are very important. Actually, we have the minimal intimal thickness to

the right and then to the left, at 7 o'clock, we have the maximal intimal thickness, and that appears to represent outcome.

[Slide.]

We perform intravascular ultrasound by putting a catheter down the left anterior descending coronary artery. We have a motorized pullback that pulls back at 0.5 mm/second, and we can do longitudinal measurements.

As you can see here in the left anterior descending artery, this is a schematic. We have 18 images, a millimeter apart, between two septal branches, and you can see all 18 images that we see here.

[Slide.]

Now, we do the measurements by site-to-site analysis. We perform intravascular ultrasound analyses by, first of all, taking a baseline image. This way, we can make sure that there is no pre-existing coronary disease in the donor heart.

We take the baseline 4 to 6 weeks after

transplant and we find a side branch that we can use as a reference, what you can see in the yellow line here. We move 5 millimeters over from the branch, and we take that image, and that is what you see by intravascular ultrasound on the bottom.

Again, you see the catheter artifact and basically, no intimal thickening.

Then, one year later, we find that same side branch, denoted in the yellow area, we again move 5 millimeters over, and take that image, and now we can see some intimal thickening in a concentric format in the bottom there, and that is more than 0.5 mm in diameter.

[Slide.]

The maximal intimal thickness has been accepted as the standard method for cardiac allograft vasculopathy measurements. The change in the MIT, greater than or equal to 0.5 mm, represents an increase beyond 2 standard deviations for the mean MIT in normal individuals, has been associated with increased major adverse cardiac events, what we call MACE.

These are represented by acute myocardial infarction, congestive heart failure, percutaneous cardiac intervention, coronary artery bypass graft

surgery, implantable cardiac defibrillators, sudden death, cerebrovascular accidents, and new peripheral vascular disease.

Again, this change in first year MIT greater than or equal to 0.5 mm has been associated with reduced cardiac and overall survival. Many of my colleagues have published this in the literature in the references listed below.

Finally, the first year MIT, greater than or equal to 0.5 mm, represent an important intermediate outcome.

[Slide.]

Now, to further validate the use of the MIT, maximal intimal thickness, as a prognostic indicator, we performed a retrospective multi-center study. This included 125 transplant patients transplanted before 1997, and we collected data through five years post-transplant to assess their outcome.

In green, the green line represents those patients with CAV, defined as first year change in maximal intimal thickness greater than or equal to 0.5 mm, and in purple, represents those patients without CAV, again defined as MIT less than 0.5 mm in the first year.

Now, let me focus your attention to the graph on the left. Patients with CAV, in green, had significantly less freedom from death at 5 years compared to those patients without CAV, in purple. Of note is that the survival curves begin to diverge at 4 years post-transplant, but become statistically significant at 5 years. The P value is noted.

In the graph to the right, patients with CAV, in green, had significantly less freedom from major adverse cardiac events and/or death compared to those without CAV, in purple.

[Slide.]

We also looked at a study from the Cleveland Clinic which showed similar results. Their study consisted of 143 patients with 8- to

10-year follow-up. In the graph to the left, those patients with CAV, in green again, defined by IVUS first year MIT greater than or equal to 0.5 mm, had significantly less freedom from death compared to those patients without CAV, in purple.

Again, we note the survival curves begin to diverge in this study at 5 years.

On the graph to the right, patients with CAV, in green again, had significantly less freedom from nonfatal myocardial infarction and/or death compared with those without CAV, in purple.

This study, and the multi-center IVUS validation study, demonstrate that first year IVUS, maximal intimal thickness greater than or equal to 0.5 mm, does predict poor outcome within 5 to 10 years after transplantation.

[Slide.]

Now, let us turn our attention to the B253 study. The IVUS efficacy assessments were performed at baseline and 12 months for patients remaining on study drug.

The IVUS analysis was conducted centrally

by an experience core laboratory at the Cleveland Clinic by cardiologists blinded to the treatment assignments.

[Slide.]

The primary assessment was a change in mean maximal intimal thickness from baseline to 1 year. We analyzed the left anterior descending coronary artery known as the LAD. The right coronary artery was used if the LAD was not feasible. We did a minimum of 11 matched sites.

Now, most of the other studies that have been performed in the past have looked at 3 to 5 matched sites, so the current study is actually a much more vigorous study, looking at 11 matched sites.

The secondary assessments were the incidence of CAV, defined as the MIT, maximal intimal thickness, greater than or equal to 0.5 mm increase from baseline in at least 1 matched site, similar to the other studies that have been published, and, of course, the multi-center IVUS validation study I just spoke of.

We also looked at other IVUS parameters of intimal area, intimal volume, and cross-sectional area of stenosis of the mean and maximum change

from baseline.

[Slide.]

Here, we see the patient disposition in the IVUS analysis. All randomized patients consisted of 634 patients. A baseline IVUS was performed in 419 patients. A 12-month IVUS was performed in 262 patients, and at 12 months, there were 211 patients who had both baseline and 1-year matched sites.

This last group represents one-third of the patient population. The percentage of patients involved in the IVUS is similar to other multi-center, randomized trials in heart transplantation.

[Slide.]

These were the reported reasons for the IVUS that are not being performed or lost at the 12-month mark. These reasons were rather comparable in all three groups except for two

reasons. Number one, due to renal problems, and two, IVUS tape not analyzable.

There was imbalance in the patients who did not receive IVUS evaluations due to renal problems. There were 16 patients in the low-dose everolimus group, 12 patients in the high-dose everolimus group, versus only 4 patients in the azathioprine group, and we do know that serum creatinines were elevated mostly in the everolimus group which caused investigators not to proceed with the angiography or IVUS procedure.

Now, IVUS tapes were not analyzable. That is due to imaging artifacts that prevented further analysis of the tapes. There were low numbers in the low-dose everolimus group, but since the core laboratory was blinded to treatment randomization, I believe that this difference probably represents a chance finding.

[Slide.]

Since the IVUS population represented one-third of the whole population, we looked at baseline demographics to see if these two groups,

the intent to treat population, and the IVUS population, were comparable.

On the lefthand side, we have the intent to treat population, which is all 634 patients. On the right are the 12-month IVUS population that represents the 211 patients that had matched baseline and 1-year procedures.

We looked at the baseline demographics of age, male, gender, race, diabetes at baseline, pre-transplant diagnosis of coronary artery disease, and patients with severe renal disease, GFR less than 29.

In the ITT versus IVUS population, in the azathioprine group, the first column on the both sides, there were no significant differences. In the low-dose everolimus group, there were no significant differences again between the intent to treat population and the IVUS population.

In the high-dose everolimus group, there were more diabetics than the IVUS versus the ITT population. In fact, this might bias against the IVUS population as diabetes may be a risk factor

for the development of cardiac allograft vasculopathy.

We looked at the baseline laboratory characteristics that are not up here on the screen including mean creatinine, mean LDL, cholesterol, mean triglycerides comparing the intent to treat population to the IVUS population. There is no significant difference.

So, in general, the IVUS population appears to be comparable to the intent to treat population, and therefore appears to be representative of the population as a whole.

[Slide.]

Here are the intravascular ultrasound results. The primary endpoint was a difference in mean maximal intimal thickness, and that you see in the first line, in yellow. As you can see, the everolimus groups, the low dose and high dose groups, had less intimal thickening compared to the azathioprine group, and this was highly significant.

When we looked at the mean intimal area,

the mean intimal volume, again, the everolimus groups and low-dose/high-dose groups had significant less increase in intimal thickening over the first year compared to the azathioprine group.

Now, as a secondary endpoint on the bottom here, we looked at those patients who had a maximal intimal thickness increase in the first year, greater than or equal to 0.5 mm, and that is what we call vasculopathy, that is what we use in the IVUS validation study.

It was markedly lower in the low-dose and high-dose everolimus group compared to the azathioprine group, and this also was highly significant. I will get back to that graph shortly.

[Slide.]

We also looked at 95 percent confidence intervals around the differences between the treatment arms and the change from baseline. Now, anything left of the vertical dotted line at the zero mark represents a statistically significant

benefit for everolimus. Anything to the right of the dotted line would represent a benefit in favor of azathioprine.

The primary IVUS endpoint, mean change in maximal intimal thickness, was in favor of everolimus, and is completely to the left of the vertical hatched line.

We also looked at the mean intimal area in this figure here, and that also was in favor of the low-dose and high-dose everolimus groups compared to azathioprine.

Now, this is the first time we observed such consistency of effect across IVUS parameters in heart transplant studies. Let me show you some other data.

[Slide.]

This slide shows the other IVUS parameters, the maximal and mean change in cross-sectional areas, again both in favor of the low-dose and high-dose everolimus groups compared to azathioprine.

Intimal volume is very important because

it represents truly plaque burden across a section of the left anterior descending coronary artery. It's a 3D image, if you will.

This data shown in the slide represents a significantly lower plaque burden in the low-dose/high-dose everolimus groups compared to the azathioprine group, the line on the bottom.

[Slide.]

Let's take a look back at the incidence of CAV. We showed this graph to illustrate the absolute differences in CAV as defined as first-year change in maximal intimal thickness greater than or equal to 0.5 mm.

In the azathioprine group, 52 percent of the patients had this rapid development of intimal thickening. Now, there were 35 percent of patients in the low-dose everolimus group, 30 percent in the high-dose everolimus group who developed this rapid intimal thickening greater than 0.5 mm in the first year, and both were significantly lower than the azathioprine group, and the p values are noted.

[Slide.]

We looked at the strengths and limitations of the IVUS study. The strengths included a prospectively planned study that met the planned

sample size. We used a blinded central core laboratory.

Baseline and 12-month IVUS studies were evaluated while treatment groups were blinded. The majority of centers participated at baseline and at 1 year.

Demographics and clinical characteristics of the IVUS subgroup were similar at baseline to those without IVUS, as were concomitant medications.

The limitations of the study included the fact that only one-third of the patients were included in the IVUS study, and that it was not intent to treat analysis. Patient participation was determined by the investigator.

The IVUS required survival to 12 months to have the baseline and 12-month IVUS procedure performed, and only patients on therapy were eligible.

[Slide.]

Recognizing that the IVUS subpopulation represented only one-third of the whole population, we performed an assessment of the potential bias in the IVUS subpopulation.

The purpose of this assessment was to

identify selection bias favoring everolimus. We reviewed baseline demographic and post-transplant clinical characteristics, and we planned to identify items of bias in favor of the everolimus arms.

We also planned to perform sensitivity analyses to investigate the impact of potential biases.

[Slide.]

The potential sources of selection biases are listed in this slide. The lefthand column represents baseline demographic characteristics that have been reported in the literature as risk factors for the development of CAV.

The righthand column represents clinical characteristics of post-transplant, also reported

in the literature as risk factors for cardiac allograft vasculopathy.

Now, of all the characteristics analyzed here, only 2, in yellow, were imbalanced with potential for bias, diabetes as a baseline demographic characteristic was greater in the high-dose everolimus group, as I had mentioned previously, compared to the azathioprine group. This would tend again to bias against the high-dose everolimus group as diabetes is reported to be a risk factor for CAV.

The 12-month creatinine clearance was higher in the azathioprine group compared to the everolimus group. This difference will be addressed when we do the sensitivity analyses.

[Slide.]

We performed a sensitivity analysis to assess the impact of the missing IVUS data. Imputation method used for missing the 12-month values could be done in two ways. First of all, we assigned missing data with age-matched azathioprine patient outcome.

For example, we took maximal intimal thickness from the age-matched azathioprine patient and inserted that data into missing data in both

groups. Now, this would tend to bias against the everolimus groups as the azathioprine group, intimal thickness in general is greater compared to the everolimus group.

Now, the second imputation method, we assigned a CAV outcome defined as MIT, maximal intimal thickness, greater than 5.5 mm by IVUS.

Now, this would be a very conservative scenario as these patients are designated with CAV. Now this would also tend to bias against the everolimus group more so than the azathioprine patients because more of the azathioprine patients had IVUS-defined CAV in the study. This would more or less dilute the data, if you will.

Now, these imputations were performed for two sets of missing data. This included patients with no IVUS due to reported renal dysfunction, and to patients with no 12-month IVUS.

[Slide.]

Now, here are the results. In the top section here, this is the primary IVUS endpoint of mean maximum intimal thickness where there is no imputation data. Again, this shows statistically significant benefit of everolimus compared to azathioprine. It is completely to the left of the

hatch mark.

Now, let's look at the second section in the middle. We imputed data that were missing due to renal dysfunction. This is 32 patients, so the N now is 243 patients. Now, if we assigned age-matched azathioprine values, we do lose statistical significance, but not so actually in the high-dose group, but the trend is still quite strong in favor of everolimus, more or less to the left of the hatch mark.

When we assign a CAV diagnosis of MIT greater than 0.5 mm to all patients, we again lose the statistical difference, but the trend is still in benefit of the everolimus group.

Let's focus attention to the bottom section here. Looking at this area, we imputed data

for all missing 12-month values. Now, the total population is 419 patients, two-thirds of the patients as a whole.

If we assign age-matched azathioprine values, we do lose statistical significance, but again the trend is strongly in favor of everolimus. If we assign a CAV diagnosis of MIT greater than 0.5 mm to all patients, we again lose statistical significance, but the trend again is strongly in favor of everolimus.

I think you can see that almost all groups of lines on this slide are more or less to the left of the zero hatch mark. There is overall consistency in these data to support would suggest that everolimus is beneficial to reduce cardiac allograft vasculopathy.

[Slide.]

Let us now turn from the IVUS data to the clinical results of the B253 study. As you may recall from the multi-center IVUS validation study, there was more nonfatal major adverse cardiac events and/or death at 48 months in patients with

CAV as defined as first year IVUS.

We are now able to review 48-month data of the B253 study, which was available to us in regards to the 48-month major adverse cardiac events data. In the 48-month follow-up of the study, there is a strong trend for greater freedom from graft-related MACE, from 1 to 18 months in the low-dose everolimus group compared to the azathioprine group.

The high-dose everolimus group had numerically graft-related MACE compared to the azathioprine group, which was not statistically significant. You can see the P values up there.

The first month MACE data was censored as these events were to perioperative complications, and not due to immunosuppressive choice.

[Slide.]

This slides shows all the MACE data that now is reviewed. In each category, the everolimus group have numerically decreased events compared to the azathioprine group, again demonstrated in the graft-related MACE is a decrease in this

graft-related MACE in the low-dose everolimus group compared to the azathioprine group. The P value is not quite significant at 0.52.

[Slide.]

In summary, patients treated with everolimus had smaller increases in maximal intimal thickness versus azathioprine patients, a lower incidence of cardiac allograft vasculopathy versus azathioprine patients, a smaller increase in other IVUS parameters versus the azathioprine patients, and sensitivity analyses for renal dysfunction and in all missing data support the beneficial effect of IVUS for cardiac allograft vasculopathy.

Forty-eight month MACE data suggest a potential for long-term benefit.

Now, the IVUS portion of the B253 study is the first to demonstrate significant benefit of any newer immunosuppressive drug in all measured IVUS parameters, and that included maximal intimal thickness, intimal area, percent luminal stenosis, and intimal volume.

In my opinion, there is conclusive

evidence to suggest that everolimus is a very potent antiproliferative drug and significantly does decrease IVUS-defined cardiac allograft vasculopathy.

Thank you.

DR. HIATT: Do we have questions?

DR. PICKERING: Again the comparator drug was azathioprine. Is there any reason at all from animal or human data to consider the possibility that it might actually accelerate vasculopathy?

DR. KOBASHIGAWA: You mean to say that azathioprine would accelerate?

DR. PICKERING: Yes.

DR. KOBASHIGAWA: It is more likely that the calcineurin inhibitors, cyclosporine accelerates cardiac allograft vasculopathy. If you look at data before cyclosporine and after cyclosporine, even though rejection is decreased, you still have the same amount of cardiac allograft vasculopathy.

There is animal studies, in vitro studies, in vivo studies to suggest that calcineurin

inhibitors do cause endothelial cell damage, and it is probably the calcineurin inhibitors, and not so much the azathioprine.

DR. NISSEN: I need some clarification on the primary endpoint of the IVUS study. Was it the absolute value for the maximum intimal thickness, or was it the percent of patients exceeding a 0.5 mm threshold?

DR. KOBASHIGAWA: The primary IVUS endpoint was the mean maximal intimal thickness, and as a secondary endpoint, it was those percentage of patients that exceeded the 0.5 mm.

DR. NISSEN: The reason I asked that is the sensitivity analysis is based upon the percent exceeding 0.5 mm. So, the sensitivity analysis was based not upon the primary endpoint.

Did you make any attempts to do a sensitivity analysis based upon the primary endpoint? I can suggest a methodology that might be applied. I mean it would make some sense. You could, for example, impute the renal dysfunction patients as some, say, 1 or 2 standard deviations

above the mean for the group that they are in.

You could say, well, let's assume that the renal failure patients had more than typical amounts of--and we would actually put that into the primary endpoint. This percent imputation is hard for me to interpret, because it is not the primary endpoint.

Do you guys understand what I am trying to get at here?

DR. KOBASHIGAWA: We did it in two ways, Dr. Nissen. We impute the CAV greater than 0.5. That was one imputation method. The other imputation method that we used was to take age-matched assignment for MIT. That was the mean maximal thickness. We imputed that, and so we actually did look at the primary endpoint, which was the MIT.

[Slide.]

You can see here that's the top line. Then, we looked at CAV greater than 0.5, which is the bottom line here. So, we did use both the primary IVUS endpoint, which is the mean maximal

intimal thickness, and then greater than 0.5 in these two areas.

Is that what you meant?

DR. NISSEN: That is not really what I meant.

DR. KOBASHIGAWA: Okay, I am sorry. May I ask our statistical colleague to comment on that?

DR. HIATT: I think the question is the major concern around bias are the patients excluded from IVUS who have renal disease, and the FDA background made a big deal about that. The question is if you assigned them the worst IVUS score by millimeters of thickness, not a categorical definition, how would that change this analysis if you assumed they had the worst vasculopathy.

DR. NISSEN: For those of you that know the stuff that I have published with atherosclerosis, in the reversal study, I actually assigned a numerical value to the patients who were non-completers to show in a sensitivity analysis that you don't lose significance when you do that.

That is what I am trying to understand. I actually think it is going to be more favorable for the drug to do it the way I just suggested, but we

will see. We will see.

While they are getting that, obviously, everybody here knows that intravascular ultrasound is something I do for a living. This concept of not having every patient that gets a baseline study get a follow-up study is true for every one of our trials. For a whole host of reasons, you are not able to assess 100 percent of people that enter a trial.

The typical rates for atherosclerosis trials in the ones we published are about 25 percent. Some of them have been up as high as 30 or 35 percent. It is a big higher here, and the reason it is higher I think should be apparent to everybody. These are sicker people. They tend to be more unstable.

Heart transplant recipients are viewed by their physicians as amongst the most valuable, I mean they get the most TLC of any patient group I

know of, because they are very precious. You know, there are only so many people that you get to transplant, and we try to take really good care of them, and so you have to stand in the shoes of the people doing these studies.

They are not going to put a probe down the coronary if there is any question about getting into any kind of trouble, because they are not going to put the patient at risk.

So, just to make sure everybody understands, these lost to follow-up rates are not unreasonable. They are actually pretty reasonable for the population that you are looking at given the fragile nature of them.

What we refer to when we report these is we call this a modified intent-to-treat population recognizing that you simply can't do a highly invasive assessment in 100 percent of people that enter such a study.

DR. GALLO: I am Paul Gallo from Novartis Biostatistics. Just a very brief answer to a question you had raised. Obviously, we did a lot

of sensitivity analyses, presented a small number. We did do the continuous versions of the binary one.

[Slide.]

So, this basically is the imputation of the continuous values, and as you had surmised, they looked more favorable than the CAV results did.

DR. NISSEN: But I want to know what you imputed your renal patients, what value did you assign them?

DR. GALLO: They were imputed with selected AZA patients. Let me let Professor Wei answer that question.

DR. WEI: That is an excellent question. I am Lee-Jen Wei, Professor of Harvard.

In fact, we exactly did what you suggested. We used ranks.

DR. NISSEN: Are these normally distributed values or are they not?

DR. WEI: It doesn't really matter. I used the highest rank to penalize the missing data.

DR. NISSEN: So, these are means, though, so why would you use ranks?

DR. WEI: We used Wilcoxen.

DR. NISSEN: But that is not what you are showing here. You are showing mean, not median.

DR. WEI: No, no, no, with P values based on the Wilcoxen.

DR. NISSEN: I see, okay, but if you are going to do the P values based upon a non-parametric analysis, you ought to show us the non-parametric values.

DR. WEI: Absolutely.

DR. NISSEN: So, you are showing us mean, but then you are calculating the P values with non-parametric statistics.

DR. WEI: Absolutely.

DR. NISSEN: So, let's be consistent. This is important because I actually think that the analysis presented in the sponsor's slides is overly conservative, it really isn't the way to do it. This is actually the way to do it, and as I surmised, it actually doesn't dilute the efficacy

very much, but this isn't consistent statistically is the problem.

DR. WEI: Well, as you said, this is more impressive than the CAV imputation.

DR. PROSCHAN: The problem, though, with imputing a value like, you know, 1 standard deviation above, you know, the problem with that is that doesn't just change the mean, that also changes the variance, so that is why it is a little bit easier to impute when you have the categorical variable, it is a little bit more tricky, or to do what L.J. Wei said, you know, giving it the worst rank rather than assigning an actual.

DR. NISSEN: I hear you. I would have been just fine with that method based upon ranks, but I would have liked to then have seen the median value since if you are going to use a non-parametric method, then, you ought to be consistent and show us the median values for the intimal thickness. That was my only criticism there.

If you could come up with that, that would

be very interesting and very helpful here I think for everybody to understand, because, you know, again, this issue about how robust is the IVUS data has been raised, and since this is something I do a lot of analysis of, I really want to make sure I am clear that I understand it.

DR. WEI: Yes, you are absolutely right. Thanks.

DR. HIATT: We should maybe take one or two more.

David.

DR. DeMETS: Just a comment about the issue of comparability between the 3 arms in the study, as well as a comment about representative of the larger study.

Just because we don't see differences in the variables, we know how to measure doesn't mean there aren't differences in those measures, and furthermore, there is a lot of things we don't even know about that we have kind of lost control of because there is no longer randomized comparisons. I am not saying that it invalidates everything, it

is just an issue we need to keep in mind.

DR. PROSCHAN: I guess what I am bothered by most about this is the fact that you don't do the IVUS if they are not on treatment. I mean the numbers you presented in that table where you show reasons for not doing it don't include that, and that is much more troubling to me than anything else.

So, I wonder why you did that, why you didn't include patients who are off treatment.

DR. SOMBERG: That was a design issue at the time the protocol is actually put together, and clearly, with that information, it would have been much more of an intent-to-treat analysis and more valuable.

I think that limitation is consistent with our view of the data in that they are not definitive proof. I think it has been clear that we recognize what the limitations are, and I think that is part of why at the outset we were trying to indicate that as opposed to sort of a surprise, you know, P value at the end of a study, the hypothesis

really came from the biological mechanism of action.

The stent data are consistent with that biological mechanism of action. The treatment effect is large, and it is a large study, but the issues that you bring up are real, so again we think it has some confirmatory value because it was prospectively defined and there is a consistent mechanism of action, but there are weaknesses that you point out that prevent it from being fully definitive in terms of proof.

DR. HIATT: John, I will take one more question.

DR. TEERLINK: I would like to just, first of all, say, you know obviously, there are limitations to this, but you are really to be congratulated on pursuing what is looking at kind of pathophysiologic investigation of what is an incredibly important issue in this patient population, so kudos along those lines.

Yes, we would have liked it to be more intention-to-treat, so let's do that next time.

But the other thing is obviously, Slide CV-8 and 9 develop a very interesting hypothesis, and that is, that if you reduce your MIT, you

should get improvements, and marked improvements, in MACE at 24 months, at 48 months.

Interestingly, in this study, and I don't agree with getting rid of the first 28 days, but whichever way you want to slice it, there is not a significant difference in MACE at 24 months or at 48 months in this.

So, does this actually call into question the hypothesis given that this study is three times, four times larger than these other studies, is followed to time points that are relevant, so that is the first question.

The second question is how are we supposed to interpret these findings when, according to this document at least, MACE information was not collected once patients stopped taking study medication.

So, once again, the MACE is incredibly biased in patients who don't take the medicine, and

if there is a higher dropout rate among your everolimus group, that is a problem.

DR. KOBASHIGAWA: Let me answer your first question and then I will ask Dr. Somberg to answer your second question.

When you look at MACE, MACE, it does occur early, early on, as you can see from the graph on the right. All this data here was done before the statin era. These patients were transplanted before 1997.

I did publish the work on pravastatin in heart transplantation that demonstrated improved survival by decreased rejection, and that is part of it, too, I believe, but we all know statins are anti-inflammatory, they do knock down these major adverse cardiac events.

I think that is a lot to do with it, because in this study here, statins were not the rule of thumb. In fact, they were used in very few patients early on in the first year. Clearly, over 90 percent of the everolimus patients were on statins. I think that has a lot to do with

attenuating the major adverse cardiac events.

Perhaps we will see that further on, maybe a delayed response, if you will.

DR. NISSEN: I am going to jump in for just a second because I think maybe you misunderstood where this population comes from. This is not from the everolimus study.

DR. TEERLINK: No, in fact, that is why I am saying this would suggest that in the everolimus study--

DR. NISSEN: You should have seen this.

DR. TEERLINK: You should have seen a bigger one, and the fact that you don't, I am wondering, and especially when, sure, the statins have reduced events and things, but you are using the same categorical variable. So, presumably, what you are comparing as statins have already done their work in terms of reducing MIT, and what you are seeing is the MIT that was reduced in addition by everolimus.

What we are seeing is that the extra effect of reducing everolimus, and MIT didn't have

any clinical benefit in terms of MACE.

DR. KOBASHIGAWA: Yes, I agree. What we do know in non-transplant studies, statins do decrease cardiovascular morbidity and mortality by as much as 30 percent. So, I think we are seeing some of it, as well.

[Slide.]

This is just a quick slide to answer your question about the additive effects of everolimus on top of statins. On the right is the pravastatin that I published in 1995, and that shows intimal thickening. In green is statin, azathioprine, and cyclosporine, which is basically, the same in both groups, the control group, and the intimal thickness is about the same, and that is with statins added.

The blue line again is without statins at all.

Now, the orange-brown line, the table here shows the added effects of everolimus to decrease intimal thickness even further beyond statins, so it is not purely just the statin effect.

DR. TEERLINK: But that further decrease had no clinical benefit. The second question is how are we supposed to interpret this when we don't

have any MACE information on the patients who discontinue drug, which was higher in the everolimus group.

DR. SOMBERG: Just two comments to that. One, I think that is a limitation, but I do want to again point out, you know, this was a dose finding study, and for the dose we are recommending, the 1.5, the dropout rate was essentially identical to that of the azathioprine group, but you do present an important limitation to the data.

DR. HIATT: I think we should probably move on. Do you want to ask a question?

DR. BURCKART: I just wanted to ask Dr. Kobashigawa to find out if you had any experience with IVUS mycophenolate mofetil treated cardiac transplant patients that you can share with us.

DR. KOBASHIGAWA: Yes. The original trial looking at mycophenolate, we did do IVUS, as well. I was the lead author on that paper, as well. We

used morphometric analysis, which is different from site-to-site analysis, and when we use morphometric analysis, basically, we take 10 segments at evenly spaced intervals and we average them.

The problem with doing that is that if you have one area that has a lot of intimal thickening, if you average all 10 segments, you basically dilute the real critical finding. That is what I believe we did on the mycophenolate trial.

We re-analyzed it recently using site-to-site analysis, and we did find differences in intimal thickening. Mycophenolate actually decreased maximal intimal thickness, but at a level of 0.3 mm.

We went up to 0.4, the P value went to 0.1 instead of less than 0.05. We went up to 0.5, and the P value was 0.1, so we lost it all together. I think it is about the small numbers. There were some differences, though. When we looked at other parameters, yes, MIT was decreased at the 0.3 interval mark. When we looked at intimal area, there was no difference across the board.

So, there were some differences between both studies.

DR. HIATT: Thank you. We have two more

safety presentations before the break, so why don't we keep going.

Safety of Everolimus

DR. SOMBERG: Thank you. As I mentioned earlier, I am Ken Somberg. My background is in clinical liver transplantation and I am responsible for clinical research and development in transplantation at Novartis.

I will now direct the discussion to the safety aspects of the program.

[Slide.]

By way of agenda, we will begin by discussing patient disposition, followed by deaths, serious adverse events, and discontinuations.

I will then continue with overall adverse events, followed by infections, malignancies, and a focus on certain relevant adverse AEs.

I will then turn to laboratory assessments focusing on hematology and lipids, and then ask Dr.

Hunsicker to come up to address the issue of renal safety.

[Slide.]

This slide depicts patient disposition over the first 12 months post-transplantation. As you will see throughout the presentation, and consistent with my prior comments, the safety profiles of the azathioprine group and the 1.5 mg everolimus group are generally reasonably comparable, with the everolimus 3.0 mg group being less well tolerated.

This contributed to our recommendation that Dr. Hukkelhoven stated at the outset, that the starting dose for everolimus should be 1.5 mg/day. So, most of my comments will focus on this most relevant comparison of azathioprine to 1.5 mg of everolimus.

As you can see here, the overall rate of treatment discontinuation of 29 to 30 percent was similar between these two groups, and this rate is not only consistent, but as you saw earlier, actually, better than that seen between MMF and

azathioprine in its pivotal trial.

The reasons for treatment, as well as study discontinuation, were also balanced between these treatment groups, however, as you can see, for the 3.0 mg group, both treatment and study discontinuation rates were higher.

[Slide.]

To provide an overview of safety, this slide depicts death, nonfatal serious adverse events, and discontinuation of study drug due to adverse events at both 12- and 24-month time points.

The rate of death at 12- and 24-months was nearly identical between the azathioprine and 1.5 mg everolimus groups, and a few percentage points higher in the 3.0 mg group as pointed out earlier.

In terms of nonfatal serious adverse events, looking at 24 months, but the pattern is similar at 12, the 3.0 mg group is highest at 77 percent versus 65 percent and 72 percent for azathioprine and lower dose everolimus groups respectively.

If we look at patients who had to be discontinued from treatment due to adverse events, a pretty reasonable overall view of tolerability,

this was nearly identical at both 1 and 2 years between azathioprine and the 1.5 mg everolimus groups at 19 to 21 percent. The 3.0 mg group was higher at 28 percent.

[Slide.]

Then, moving to causes of death. The rates of death for a cardiac transplantation were overall low and considered quite good across all the treatment groups, and were not significantly different at 12 months.

If one looks at the causes of death seen in the early first year, these tend to be typical ones, such as infections, cardiac disorders, immune disorders which represent rejection, or multisystem organ failure.

The slight excess of cases seen especially with the 3.0 mg group come from the, quote "Other category." These include a mix of gastrointestinal bleeding, respiratory or nervous system disorders,

or procedural-related complications.

[Slide.]

Total adverse events were presented in your briefing book, so we will move here to serious, but nonfatal adverse events and look at those that occurred in at least 3 percent of the population in any of the treatment groups.

We see that the occurrence of any SAE was relatively balanced between the azathioprine and 1.5 mg group, but highest in the 3.0 mg group.

For convenience, relevant events that I will discuss are grouped by color. You see in the purple color, pericardial effusion, cardiac tamponade, or pleural effusions were more common with everolimus treatment, with the latter two occurring in a dose-dependent fashion.

Cytomegalovirus, as a serious adverse event, was notably lower in both everolimus groups compared to azathioprine, however, pneumonia, not otherwise specified, was a more common SAE in both everolimus groups compared to AZA. This will be discussed on a subsequent slide.

Renal impairment, not otherwise specified as a category, showed a predominance in the 3.0 mg everolimus group, and as mentioned, the topic of

renal function with the everolimus/cyclosporine combination will subsequently be discussed in detail.

[Slide.]

To understand the impact of immunosuppressive treatment on infection, we look here at the key categories of infections. Viral infections were significantly more common in the azathioprine group driven by a higher rate of CMV infection. This is potentially important due to the association of CMV with vasculopathy as noted by Dr. Barr.

As reported by Dr. Valentine at Stanford and others, CMV viremia, even without tissue invasion, has been associated with the development of diffuse vasculopathy.

On the other hand, as you can see, bacterial infections were significantly more frequent with everolimus treatment in a

dose-dependent manner, and this was spread out over a large number of organisms.

Fungal infections, at the bottom of the slide, were similar across all three groups.

[Slide.]

One particular type of infection worth further discussion is that of pneumonia. As you can see here on this slide, this includes both infections in which a specific identifiable organism was seen, as well as a number of patients in whom no organism was identified.

We see a modest increase in bacterial pneumonias with both everolimus treatment groups. Viral and fungal pneumonias were uncommon. There were, as I noted, substantially more pneumonias without an identifiable organism in the everolimus treated groups.

The cause and significance of this type of pneumonia is not clear. There is a hypersensitivity pneumonitis that has been reported with this class of drugs, but that typically leads to drug discontinuation, which was not the case in

this trial.

In terms of trying to put the pneumonias in perspective, it is important to note that both the discontinuation rate of drug due to pneumonia, as well as death due to pneumonia, were low and actually lowest in the 1.5 mg everolimus group.

[Slide.]

Let me now turn to neoplasms, which along with infectious diseases, really represent two of the hallmark adverse events that are seen with immunosuppressive therapy. The rate of malignancy in a transplant population was low across all treatment groups.

The incidence of post-transplant lymphoproliferative disorder, sort of the hallmark malignancy after transplant, was nearly identical and less than 2 percent in all groups.

The most common malignancies were non-melanoma skin cancers. The highest rate was in the 1.5 mg everolimus group, but this was still generally quite low, and solid tumors, such as prostate cancer or cervical cancer, were low across

all groups. There were a small number of benign neoplasms seen in a balanced fashion, as well.

[Slide.]

Wound complications, which have been mentioned earlier, are known to be an issue with this class of drugs. Lymphocele, which is typically in the groin at the site of instrumentation, was more frequent in everolimus-treated patients. Although the numbers are quite small, wound dehiscence and wound drainage were more frequent with everolimus, as was incisional hernia, which was typically a ventral hernia.

[Slide.]

Turning now to laboratory values beginning with hematology, this slide presents data based on threshold values that are clinically meaningful. If we look at the occurrence of a hemoglobin less than 7 grams/dL in the first year, this was similar between the 1.5 mg everolimus and AZA group, but higher with 3.0 mg.

Then, looking below, the occurrence of leukopenia or neutropenia were both significantly

more common with azathioprine treatment. Thrombocytopenia, defined as a platelet count less than 50,000 in the first month, or 75,000 thereafter, was numerically more common with everolimus, but not significantly different.

The next two slides turn to lipids.

[Slide.]

Triglycerides are known to increase with this class of drugs, and that we did indeed see here. The difference becomes evident over the first several months, and if we look at both 12 and 24 months, the everolimus-treated patients do have higher triglyceride values.

[Slide.]

This slide depicts total cholesterol, LDL, and HDL. We see a modest increase in total cholesterol in everolimus-treated patients, which is driven by the higher triglyceride values predominantly, but when we look to LDL in the middle or HDL in the bottom, we see that these parameters are not different between the treatment groups, but it is important to recall that

per-protocol and standard practice in cardiac transplantation, the vast majority of patients were treated with statins.

[Slide.]

I do want to revisit the major adverse cardiac events in light of this increase in triglycerides and modest increase in cholesterol. Given the provisions about the data, I think it is worth again pointing out that numerically, there were less MACE events seen in the patients for whom we have data.

[Slide.]

To summarize safety, the incidence of adverse events and serious adverse events overall were similar between the 1.5 mg everolimus and azathioprine groups, but higher for the 3.0 mg everolimus group compared to AZA, and as noted, this is an important part of our reasoning on why we focus on the 1.5 mg dose.

Everolimus is associated with a lower incidence of cytomegalovirus infection, but a higher incidence of bacterial infections,

especially for the 3.0 mg dose.

The incidence of pneumonia, both infectious and potentially noninfectious, was also higher with everolimus although discontinuation of drug treatment or death due to pneumonia was uncommon and least frequent with the 1.5 mg everolimus group.

The incidence of malignancy was comparable across all groups.

[Slide.]

Similar changes in LDL and HDL were observed in all treatment arms, but there were higher triglyceride levels observed with everolimus treatment. As noted, fewer major cardiac events were seen amongst everolimus-treated patients.

Let me stop at this point. I assume there will be questions, and then last, Dr. Hunsicker could address renal safety.

DR. HIATT: Questions? Tom.

DR. PICKERING: On Slide 8, about the pneumonia with no organism identified, could you tell us a bit more about that? Was that something

that just got better or was it a big problem?

DR. SOMBERG: That data we have to answer that are limited, and I think probably the best way to answer it is it was not leading to study discontinuation. Patients in a transplant setting, in whom infections are suspected, are typically treated fairly aggressively and often investigated fairly aggressively, so I really can't speculate on the pathophysiology other than to say it was extremely rare to take somebody off of treatment.

DR. HIATT: Remind me again how many of these serious adverse events do you think were dose related and how many were not. I have got a long list of them here, but in those that you think are dose related, do you think therapeutic drug monitoring would alleviate those events?

DR. SOMBERG: It is an interesting question and it is one we spent a lot of time addressing after discussions with FDA about potentially defining an upper end to the therapeutic range. We did a number of investigations looking at patient's average

everolimus exposure up to the time of an event and we looked at a fairly exhaustive list of all the relevant laboratory parameters, malignancy, aspergillus, sepsis, drug discontinuation, and the like, and really did not see significant correlations.

For thrombocytopenia, as one got up above 10 or 12, the incidence became a bit more common, approximately 10 percent versus 5 percent, testosterone values tended to be a little higher above that time, but when we looked at those major infections, for example, we did not see a correlation with exposure.

DR. HIATT: So, obviously, going forward, therapeutic drug monitoring would be a critical component.

DR. SOMBERG: Absolutely.

DR. HIATT: So, again, the question is how much of that would be mitigated by therapeutic drug monitoring? Do you think you would change any of those outcomes if you really tightly controlled dose and concentration in the blood?

DR. SOMBERG: I guess there is two parts to answer that. There is two things that would change with the recommendation for the combination

of everolimus and cyclosporine going forward. One is concentration control for everolimus, and the other is lower exposure of cyclosporine, so overall, the immunosuppressive burden would be lowered.

For things like infection, for example, both types of drugs would be contributing, and, in fact, in two prospective renal trials in which we used concentration controlled everolimus with lower cyclosporine, the tolerability was improved and actually quite similar between the two everolimus groups.

DR. HIATT: I guess what I am wrestling with, and we will come to later in the day, is how much certainty we have about that concept around therapeutic drug monitoring, and is that really a testable hypothesis, or do you feel you have enough data to adequately ensure safety based on that. I think that conversation will be relevant with renal

toxicity that comes up next.

DR. NISSEN: With this reduced-dose cyclosporine and the concentration controlled approach, what loss of efficacy do you expect?

DR. SOMBERG: We don't expect a loss of efficacy. If I could possibly hold that to Dr. Hunsicker's presentation.

DR. NISSEN: All right, but you see this is obviously going to be a central issue for the committee, because we need to understand. I mean I recognize you can reduce drug toxicity by giving lower doses, but then will you lose the efficacy advantage.

DR. SOMBERG: Sure, and the theme that Dr. Hunsicker will present is that within the range of exposures we studied, efficacy was related to everolimus exposure, and after the first few weeks, that cyclosporine exposure is not critical. It is in the first 8 days or the first 15 days, but thereafter within the range we studied, cyclosporine was not contributing to efficacy.

DR. VENKATARAMANAN: It is related to a

previous question, but in so looking at the dose as a classification for the side effects, taking the 3.0 to 8.0 ng/mL, which is proposed to test the therapeutic range, if you just look at those patients, what is the incidence of lipid abnormalities in that group?

DR. SOMBERG: This slide looks at predominantly laboratory parameters and looks at patients who have levels less than 3.0, 3.0 to 8.0, or greater than 8.0, comparable azathioprine values on the right, so as I mentioned, for example, thrombocytopenia does become modestly higher, about 10 percent versus 6 percent, hypertriglyceridemia not much different, and total cholesterol not too much different, elevated creatinines, again since we do not believe everolimus directly contributes to the nephrotoxicity, not much different.

The same analysis was done again looking at sepsis and drug discontinuation and a variety of things of that nature.

DR. PROSCHAN: On the topic of dose-related events, I mean it certainly looks from

your Table 8, CS-8, that pneumonia isn't dose related. I mean it is substantially higher even in the 1.5 mg.

I worry about whether the therapeutic dose monitoring is going to do any good for pneumonia.

DR. SOMBERG: I am not sure it would. If I could ask Dr. Eisen to come up and address that, because I think one of the core issues gets to the fact that, you know, the population has a large number of side effects that the clinician is trying to wrestle with and manage.

I cannot tell you that I would necessarily expect that to get better. I think the real key benefit of the therapeutic drug monitoring will be to allow us to make sure we have adequate exposure to everolimus and allow safe reduction of cyclosporine, but I think that is a fair statement.

In terms of sort of putting pneumonia in perspective, if I could ask Dr. Eisen to comment as a clinician.

DR. EISEN: I don't want to minimize pneumonia as a serious problem, but usually, it is

pneumonia with organism identified, and pneumonitis, at least in the heart transplant experiences, both the anecdotal and in the Australian study, it did not seem to be a significant cause this pneumonia without an identified organism seemed to be a significant problem in terms of mortality.

I think you have to weigh that against everything else and against all the other side effects. The other thing you have to remember once again about this study is that there was absolutely, I mean all the levels that we see are retrospective, there was no therapeutic drug monitoring, and the approach that we would use prospectively would be very different.

DR. TEERLINK: If I could just clarify the last statement that you made about fewer MACE events, do you think it's an appropriate statement to say that there is no real difference between MACE events between any of the groups at 48 months?

DR. SOMBERG: Let me see if I can say this as clear as possible. I think recognizing there

are limitations in how the data were collected, numerically, there were fewer MACE events, I believe, in the everolimus-treated patients, although this did not reach statistical significance. Is that--

DR. TEERLINK: That's an okay one, although the data that you are showing only includes--do you have one that includes from beginning of therapy to 48 months? Could you show that?

DR. SOMBERG: We sure do. Yes, we have a backup that shows that. The events in the first month were similar between the groups. MA-13. Hold on.

[Slide.]

The events that occur in the first month were balanced across the groups and typically include perioperative type things. I am looking for the actual numbers from day 1 through month 48. Just a moment.

DR. TEERLINK: It is Table 5-16 in your briefing book. Anyway, I don't want to belabor

that, but I don't think it is nearly as impressive. That is different than the one we have, but okay. I don't see a major difference there at all, and I would be hard pressed to tell a patient that they could do better from a MACE event with this drug.

DR. SOMBERG: And I don't want to overstate those data. I think it is consistent.

DR. TEERLINK: And I am no saying you are. I just wanted to make that clear.

The second thing is, though, as I mentioned before, and we won't belabor it, but it looks like over a third of the patients aren't actually followed for MACE events by month 48, so there is a major challenge there.

One of the things that we saw in the primary endpoint is it is clearly driven by the increased biopsy-proven graft rejection. So, what is the down side of that? Well, the down side of that is you should see more deaths, more graft loss.

Well, we don't see that here, and granted, maybe we are not looking long enough, although we

are looking out 48 months and further than that, we don't see. So, another thing that you could tell the patient of why is it bad to have graft rejection, well, you would see that perhaps it would cause worsening angiopathy, so you would say, well, there should be, you will improve MACE.

Well, we don't see that here either. So then you say, ah, but we are going to reduce the number of times that you have to get all those evil, you know, immunosuppressive regimens, so we will decrease the risk of infections, because all those things cause that.

So, I was looking for that and hoping to see that to say, okay, we are going to have some benefit that I can go to the patient with here, and then when I look at infection risk, if anything, and pneumonias has increased, yeah, it's balanced out by CMV, but certainly there is no benefit there in terms of SAs.

So, I am trying to look at the combination here of from the SAEs, is there something that we are improving in terms of bad effects. We aren't

seeing any improvements in terms of good effects anywhere in this study. Are there any bad clinical effects that we are actually positively influencing with this new drug?

DR. SOMBERG: If I could ask Dr. Kobashigawa to come up and address that, both in terms of the benefits of reducing rejection, as well as the potential benefits of reducing CMV, and in putting it in light of managing the side effects.

DR. KOBASHIGAWA: Cardiac transplantation has improved over the decades. We have seen actually increase in survival, as well. This is a rather healthy patient population, first of all, and when you look at--we randomize after transplantation--when you look at the survival curves, many of the deaths are occurring early on in the perioperative phase. In fact, anywhere between 5 and 8 percent can actually perish in that first month, if you will, from perioperative complications, and those are the ones we don't randomize. In fact, we randomize patients who can

take study medications. So, they are more of a healthier type population.

I think that is why we are seeing less of these complications that do occur, and perhaps that is why we see less of these MACE, too, in these populations.

Again, I truly believe, though, statin therapy has helped to attenuate many of these problems that we do see.

Let's take into account the issue of decreasing rejection per se. The mechanism of cardiac allograft vasculopathy is immune mediated, and the more rejections you have, in fact, we have done studies looking at IVUS, as well, looking at smoldering rejections, any type of rejections, mild and moderate, we find that those rejection episodes do have increased intimal thickness, and I think in the long term, much longer than we are looking at right now, we are going to see a benefit in survival.

None of these studies are powered to show survival benefit. In fact, it would take literally

more than 1,000 patients to show survival benefit significantly at the 15 percent mark. We have done those analyses in all of our studies, and so I don't really think we are going to see that here, at least not for a longer period of time when you take into account that, quote "good" patient population in terms of survival benefit.

But I think we will still, even based on the IVUS data and the fact that now 90 percent were on statins, I think we will see it further out. Even from the Cleveland Clinic data, really, it took more than five years to show the curves diverge, and we just started seeing them diverge at 45 years. Again, this is pre-statin therapy.

So, I think in the long term, decrease in rejection is a good benefit and it will have effects later on.

DR. HIATT: I think we should move on, but I think the committee is struggling a bit with trying to link those kinds of surrogate measurements with these hard outcomes and whether we should even be asking for that kind of evidence

i the context of this kind of trial or not.

DR. HOSENPUD: Could I just make a brief comment? I guess to follow up on that, again, you are dealing with a very small study in terms of the relative world of clinical trials. You are dealing with a quite variable population. These are not all the same patients. The intragroup variability is huge.

So, to try to target the issues that Dr. Teerlink has brought up are going to be very difficult when we are constrained with the types of studies that we can do, so we are forced to look at these endpoints as surrogate endpoint and relay them to large registry data showing that if you have rejection, you have a poor outcome when you can look at 7,000 patients. When you have intimal thickening or coronary disease, by our registry analysis, you are going to die sooner.

So, we are forced to relate the endpoints that we have to the larger registry data with all of its flaws to try to make sense of this.

DR. HIATT: I think we really are gaining

a sense of appreciation of that.

DR. NISSEN: Let me just sort of think out loud with the committee a little bit.

You know, what we are talking about is a therapy that perhaps reduces the development of transplant vasculopathy, which fundamentally tends to be the late, the dominant late cause of mortality, so it is not unreasonable to expect, given the fact that we know there is a link, that there is going to be a significant lag phase between a therapy that reduces transplant vasculopathy and benefits on survival of such a therapy.

So, you only really answer that question by taking several different regimens and studying them over an 8- to 10-year period of time, and what you are really trying to do for these patients is, you know, you want to keep them alive for as long as you possibly can, and you want it to be 10 years or 15 years, and not 5 or 6 or 7, but it is very hard in this kind of a clinical trial setting to get there.

So, you have to then ask yourself the question do you accept the transplant vasculopathy is the dominant cause of the late loss, later lack

of survival.

DR. HIATT: Yes, I think we all appreciate that.

Renal Safety and Efficacy Extrapolation,

Dose Recommendations

DR. HUNSICKER: Good morning and thank you for the opportunity to speak with you. I am Dr. Hunsicker. I am Professor of Medicine and Medical Director of Organ Transplantation at the University of Iowa.

[Slide.]

There are four main points that I want to make with my presentation.

First, use of everolimus, together with cyclosporine in usual doses, is associated with a significant reduction in kidney function.

Second, this nephrotoxicity is closely related to the trough levels of cyclosporine, but it is essentially unrelated to the trough levels of

everolimus.

Third, use of everolimus with reduced-dose cyclosporine results in calculated creatinine clearance levels, which reflects renal function, similar to those seen in patients treated with full-dose cyclosporine and either azathioprine or mycophenolate.

Fourth, pharmacodynamic analyses demonstrate that everolimus with cyclosporine, at a reduced dose after the first month, is effective in preventing cardiac rejection.

[Slide.]

To help orient you to my discussion, let me first present what will be our recommendations about the dosing of everolimus and cyclosporine in heart transplantation.

Everolimus should be used in an initial dose of 1.5 mg per day in 2 divided doses, but dose adjusted to achieve target trough levels of 3 to 8 ng/mL.

We recommend traditional target trough levels of cyclosporine 250 to 400 ng/mL for the

first month following transplantation, but cyclosporine should be used at a reduced and progressively lower dose after the first month.

[Slide.]

Now, let me first review with you the renal safety data from the B253 heart study.

[Slide.]

This slide presents the data on renal function in the patients assigned to the three groups: the two everolimus dose groups in the brighter and darker orange, and the azathioprine group in blue.

You can see that there is a difference in the Cockroft-Gault estimated creatinine clearance over time with significantly lower creatinine clearances in the everolimus patients. This difference appears early and it persists for the duration of the study. It is somewhat reassuring that it does not diverge further after 12 months.

[Slide.]

Because 12 months was the end of the fully blinded treatment period, I have chosen to show you

here the data with respect to that time point. At the top, you will see that the estimated creatinine clearance in the patients assigned to azathioprine was 65 mL/minute, whereas, in the two everolimus arms, it was 52 mL/minute, not different for those in those two groups.

Correspondingly, at the bottom, the serum creatinine in the azathioprine arm, 1.7 mg/dL was lower than in the two everolimus arms, 2.1 mg/dL. Long-term use of everolimus with full-dose cyclosporine clearly results on average in reduced renal function.

The impact of the everolimus/full-dose cyclosporine regimen on renal function was recognized in the course of the study and it led to the renal amendment which permitted investigators to reduce cyclosporine dose when serum creatinines had risen.

This amendment occurred late in the study and was used after 20 months in each case, 21 months in each case. We have complete results on relatively few of these patients and we agree that

no meaningful conclusions can be drawn from the creatinine data following these changes.

[Slide.]

Now, to examine the renal impact of everolimus with the reduced dose of cyclosporine, let me first review the renal outcomes from some other trials that Novartis has carried out for other indications.

[Slide.]

This first slide showing the renal function outcomes of everolimus used without any calcineurin inhibitor for the treatment of rheumatoid arthritis reminds us that everolimus is not, in itself, inherently nephrotoxic.

Patients were treated with everolimus for 12 weeks, followed off treatment for 12 additional weeks. You see that there is no difference at all in any time point over the 24 weeks between the serum creatinines of the patients assigned to everolimus at 6 mg/day and those of patients assigned to placebo.

Reduced renal function only occurs when

everolimus is used with a calcineurin inhibitor. This suggested that the adverse renal impact of everolimus, when used for transplantation, might be ameliorated if the dose of calcineurin inhibitor were reduced.

[Slide.]

This possibility was tested in trials of kidney transplantation. This slide shows you the design of two pairs of studies, B201 and B251, in which the two doses of everolimus were compared with mycophenolate mofetil together with full standard dose cyclosporine, and two other pairs of studies, A2306 and A2307, in which the two doses of everolimus were used together with reduced-dose cyclosporine.

There was no mycophenolate arm in the latter two studies, so a direct randomized comparison of patients treated with everolimus and reduced-dose cyclosporine and patients treated with mycophenolate and full-dose cyclosporine cannot be made, but the patients entered into these two pairs of studies were similar in most respects and the

comparisons informative.

[Slide.]

You can see within the dashed line box at the bottom of this slide that patients receiving everolimus at either dose with reduced-dose cyclosporine, in the two righthand columns, had levels of renal function comparable with the patients taking mycophenolate with full-dose cyclosporine, the left two columns at the bottom.

Perhaps more importantly, patients taking everolimus with reduced-dose cyclosporine achieved levels or creatinine clearance around 65 mL/minute that are typical for the well functioning kidney allograft.

Kidney transplant doctors universally recognized this as an excellent level of kidney function for a patient on calcineurin inhibitor-based immunosuppression. Thus, everolimus can be used safely in kidney transplantation, but that is not today's issue, so I ask what about renal outcomes at varying levels of everolimus and cyclosporine exposure in the

heart study.

[Slide.]

This slide shows data from the B253 heart study on the impact on renal function of different achieved levels of everolimus and cyclosporine exposure.

You have in your briefing books an earlier version of this graph in which the same data on decreases in renal function are modeled as linear functions of everolimus and cyclosporine.

We have chosen today to show you these data in a more granular way to permit you to recognize directly the variability in the model and to show you the fine structure of the relationships in a non-parametric way.

The quartile of trough everolimus levels is given on the X axis, and the quartile of cyclosporine exposure on the Z axis, while the Y axis shows the occurrence of renal dysfunction defined as the fraction of patients in each category experiencing a 30 percent or greater decline of creatinine clearance following the first

month of treatment.

Remember that some decline of renal function is expected with the initiation of any form of calcineurin inhibitor-based immunosuppression.

You can see that the incidence or renal dysfunction is higher in the upper two quartiles of cyclosporine exposure, the back two rows, irrespective of the level of everolimus exposure.

Conversely, the frequency of renal dysfunction is quite low in the lower quartiles of cyclosporine exposure, the front two rows, especially, in the middle two everolimus quartiles that represent our recommended target range of everolimus trough levels.

It is possible, although not statistically robust, that the frequency of renal dysfunction is slightly higher among patients in the lowest and the highest quartiles, but the optimum combination for renal toxicity appears to occur with reduced-dose cyclosporine at the recommended levels for everolimus with the renal event occurring in

only 15 to 21 percent of patients.

Thus, the same pattern of renal safety is seen among the cardiac transplant recipients as among the kidney recipients.

[Slide.]

Now, it would be meaningless to document the renal safety of the everolimus/reduced-dose cyclosporine regimen if it were not still effective in preventing cardiac rejection, so I shall now review the pharmacodynamic analyses of everolimus and cyclosporine exposure on cardiac rejection, again from the B253 heart transplant study.

[Slide.]

First, this slide shows the fraction of patients experiencing a biopsy-proved cardiac rejection episode of Grade 3A or greater as a function of average everolimus trough levels without regard to cyclosporine dose.

You can see that the rejection rate begins to drop at 3 to 4 ng/mL. it reaches a minimum at levels of 4 to 5 ng/mL with little or no further effect at higher levels.

[Slide.]

Indeed, if we divide patients into groups achieving levels of 8 ng/mL or higher, the dotted

line, 3 to 8 ng/mL, the dashed line, less than 3 ng/mL, the solid orange line, or assigned to azathioprine, the blue line, you can see that superior outcomes occurred at levels of 3 to 8 ng/mL, our recommended target, whereas, those below 3 ng/mL of everolimus were not different from azathioprine-treated patients. There is no additional benefit from everolimus at levels above 8 ng/mL.

[Slide.]

Now, on this slide, we divide patients both by levels of everolimus exposure and level of cyclosporine exposure starting from day 15, but then through the end of the trial.

Focusing on the two front rows, patients achieving lower than median levels of cyclosporine, one can see that even with these low levels of cyclosporine, achieved everolimus levels within our recommended target of 3 to 8 ng/mL, the middle two

quartiles, had very low rejection rates, 4 to 15 percent even with low cyclosporine exposure.

[Slide.]

But what about those first 15 days? This slide shows the incidence of rejection within the first month in the 3 randomized arms of the study now on the Z axis at 4 quartiles of cyclosporine exposure now on the X axis.

You can see that reduction of rejection to levels better than with azathioprine require either the higher dose of everolimus in the second row, or higher achieved levels of cyclosporine at the right or top quartile in the front row.

[Slide.]

This pattern disappears after the first month, indeed, after the first 15 days. For all successive periods of the study, very low rejection rates are seen with everolimus, the lower 1.5 mg/day dose, the front row, irrespective of cyclosporine exposure.

This slide shows months 2 to 3.

[Slide.]

Months 4 to 6.

[Slide.]

Months 7 to 12.

Thus, after day 15, it appears that everolimus at a recommended level, together with reduced-dose cyclosporine, retains its effectiveness in preventing rejection even as it minimizes renal toxicity.

The FDA modeling presented in their briefing book comes to essentially the same conclusion.

[Slide.]

Now, with the above as background, I should like to explain our specific recommendations for the safe and effective use of cyclosporine in combination with everolimus for prevention of cardiac rejection.

This slide shows for periods of 2 to 3, 4 to 6, and 7 to 12 months post-transplant, the rates of rejection for each quartile of cyclosporine exposure in the different colored bars.

Consistent with what I have shown you

before, the rates of rejection are low, and not clearly related to cyclosporine exposure. Specifically, the results in the lowest quartile at the lefthand of each group of bars are at least as good as those in the upper 3 quartiles.

Thus, we have focused on the lowest quartile of cyclosporine exposure which provides excellent efficacy and the least nephrotoxicity. Note that the levels of cyclosporine exposure at the bottom of the slide drop over time, so that the boundaries between the quartiles also drop.

The median values for the lowest quartile at these 3 time periods were 151, 126, and 95 ng/mL.

To reach our final target recommendations for cyclosporine trough levels, we rounded these levels up to 175, 135, and 100 ng/mL respectively, being a bit more conservative in the first few months.

[Slide.]

In summary, the combination of everolimus with standard dose cyclosporine is associated with

reduced renal function compared with cyclosporine with either azathioprine or mycophenolate.

But reduced-dose cyclosporine with either dose of everolimus is associated with excellent renal outcomes, similar to those with full-dose cyclosporine in either azathioprine or mycophenolate.

The use of everolimus with lower doses or cyclosporine after month 1 is equally effective in preventing cardiac rejection.

[Slide.]

In conclusion, renal toxicity is primarily associated with the blood levels of cyclosporine, whereas, anti-rejection efficacy is primarily associated with blood levels of everolimus.

It is possible to dose these agents so as to avoid renal toxicity and maintain anti-rejection efficacy.

Therefore, in the hands of transplant experts, the use of everolimus as we have recommended is effective in cardiac transplantation and is safe with respect to the effects on the

kidneys.

[Slide.]

I am repeating now our final dosing recommendations.

The initial dose of everolimus is 1.5 mg/day.

We recommend the use of everolimus to achieve trough concentrations of 3 to 8 ng/mL for the entire post-transplant period.

As implied above, therapeutic monitoring of everolimus levels is appropriate.

[Slide.]

The recommended target exposure of cyclosporine in the first month is 250 to 400 ng/mL.

Exposure to cyclosporine beyond month 1 should approximate the median of the lowest exposure quartiles observed over time in Study B253:

175 ng/mL for the months 2 to 3.

135 ng/mL for months 4 to 6.

100 ng/mL beyond month 6.

Thank you for your attention.

DR. HIATT: Thank you. I might not to everyone it's 11 o'clock. We are supposed to be

done with our break by now. We have one more to go.

But I want to pick up some time this afternoon, so I suggest we continue on with these presentations until we are done, and then we will take a break.

Let me just ask one question then. You said everolimus is not associated with nephrotoxicity and cyclosporine clearly is, and that when they are combined, all the nephrotoxicity is explained by cyclosporine.

But the question has come up in some other material, the FDA material, that there is truly an interaction between the two drugs. I guess I am puzzled by that, because if you are proposing therapeutic drug monitoring should just be the cyclosporine for nephrotoxicity, I don't think so.

Could you explain the concept of an interaction here?

DR. HUNSICKER: Yes. Everolimus by itself is not nephrotoxic. Cyclosporine by itself is nephrotoxic. But the interaction of everolimus with calcineurin inhibitors is to reduce the levels at which the calcineurin inhibitors become nephrotoxic, so you see more nephrotoxicity at

lower levels--let me say that again.

At the same dose of cyclosporine, you get more nephrotoxicity when it is done with everolimus than without. So, you have to reduce the dose of cyclosporine to achieve the levels of nephrotoxicity you have seen beforehand.

Now, I would not imply that any regimen that includes a calcineurin inhibitor will not be nephrotoxic. I think there is some nephrotoxicity in all of these regimens, but you can minimize that nephrotoxicity by reducing the cyclosporine levels, and you can maintain efficacy.

Now, clearly, we use concentration monitoring for cyclosporine, everybody does, so what we are proposing is that you need to use concentration monitoring for both cyclosporine

throughout the course of the study at different levels and everolimus also.

DR. HIATT: Right. So, the question is what is the role of the everolimus levels on cyclosporine toxicity.

DR. HUNSICKER: It is not clear. If you look at the data, it is not clear once you have everolimus on that higher doses of everolimus are that much worse than lower doses of everolimus, so the real issue here for recommending the lower doses of everolimus has to do with the tolerability in other areas that you have heard from Dr. Somberg.

DR. ABERNETHY: If we could go to Slide CN-11. I am just trying to understand the numbers in the various everolimus exposure groups, so that we will have some idea of the robustness of those distributions.

[Slide.]

DR. HUNSICKER: This is, over here, the cyclosporine exposures. That is the actual average trough levels - less than 180, 180 to 230, 230 to

280, and greater than 280. The four everolimus quartiles, less than 4, 4 to 6, 6 to 9, and greater than 9.

These two, 4 to 6, and 6 to 9, approximate very closely. They are quartiles. They were divided by anything, they are just quartiles, but you see that these two medium ones approximate the recommended levels.

DR. ABERNETHY: So, you are saying that 25 percent of the group was below 4, and 25 percent of the group was above 9?

DR. HUNSICKER: Yes.

DR. ABERNETHY: And then that is further divided by the stratification and cyclosporine exposure.

DR. HUNSICKER: That's correct.

DR. ABERNETHY: I guess I just feel more comfortable. N equals over each one of those boxes.

DR. HUNSICKER: Well, since they are quartiles in both directions, you can divide the N in the study by about 16, and you will be close to

that. There was about 40 patients in each group roughly.

DR. VENKATARAMANAN: When you look at the interaction between sirolimus and cyclosporine, at least there is some documentation that sirolimus concentrations are significantly increased--I am sorry--cyclosporine concentrations are significantly increased by sirolimus especially in the kidney tissues.

DR. HUNSICKER: The interrelationship between the levels of--

DR. VENKATARAMANAN: Comparing sirolimus/cyclosporine with everolimus/cyclosporine, there doesn't appear to be a interaction, everolimus doesn't significantly alter cyclosporine clearance. If at all, it is only 10 percent difference.

I am trying to understand the mechanism, if you know of any reason why, without changing any pharmacokinetics, we have potentially some other mechanism of this interaction, and would that be avoided by changing the drug levels.

DR. HUNSICKER: You asked two questions, and I can see Dr. Somberg up here trying to speak to you. Let me give you a first answer, and then

you can hear from Dr. Somberg.

First of all, the basis for this renal impact of both of the mTOR inhibitors on toxicity of both of the calcineurin inhibitor levels is not understood. It is not explained by blood levels. You can't make it go away with blood levels. What you can do is show that you can lower the blood level of cyclosporine, and that minimizes the nephrotoxicity.

So, I guess the first question is we don't understand the mechanism, and the second is that it is not dependent entirely on blood levels.

Do you want to say something at this point?

DR. SOMBERG: Two brief points. There is a modest interaction, such that you can achieve the same cyclosporine level with about 10 to 20 percent cyclosporine, but again that tends to wash out in routine monitoring. We really don't know what

causes this interaction--excuse me--which causes the renal insufficiency.

One area that has been looked into is the possibility of altered concentrations within the tissues, and there is really conflicting evidence - a salt-depleted model that says yes, other studies that say no, but I mean I think the short answer is we really do not understand.

DR. TEERLINK: Just to get at I think one of the points that Darrell was trying to make, we are going to have to make some decisions about how confident we are about this modeling in terms of what recommendations, if any, later on we make.

So, if you look at Slide CN-20, here, we have all these nice quartiles divided up by percentages and everything, and by back-of-the-hand calculations type thing, it is looking like actually that first yellow column represents 1 patient, the orange one is probably 5 patients, the darker orange one--

DR. SOMBERG: If I could clarify, these are quartiles, so each group represents 50.

DR. TEERLINK: Fifty patients, but in terms of the difference between event rate--

DR. HUNSICKER: Two percent of 50 is only

1.

DR. TEERLINK: It is 1 patient, you know, where we are seeing 1 patient versus 5 patients--

DR. HUNSICKER: These are small numbers.

DR. TEERLINK: So, the confidence intervals in terms of how confident we can be that we are really seeing that this represents what we are all looking for, that capital T, Truth.

The N above each of those numbers, as Darrell was saying here, is helpful and I think needs to be remembered.

DR. HUNSICKER: There are two things that you can say. First of all, this is BPAR, this is the rejection rate of less than 10 percent. You remember in the study, the good outcome was 30 percent. So, this is very good outcomes.

We are not arguing that these are different. We are arguing only that they are all very low and that there is no evidence that the

lowest quartile of cyclosporine is any less good than anything else. That is all we are arguing.

Second, with respect to the question of how confident are we that this is going to represent the truth beyond here, there are really three sources of information we come on.

The first is the precedent in the rest of what we understand about calcineurin inhibitor and mTOR interactions. In the area of nephrology, it is well recognized that if you maintain an adequate mTOR level in the case of sirolimus, that the calcineurin inhibitor level, whichever one you are using, becomes relatively irrelevant and you can lower the dose and reduce renal toxicity. This is entirely consistent with that.

The second is the evidence, not from this trial, but now from the renal trials, if you will put up--remember I have shown you in the two renal trials--it's the one that we said I would probably need.

[Slide.]

If you look in the renal trials, these are

the renal trials, which, in fact, we used everolimus--this is the royal "we" I am talking about--we use this pretty much exactly as we have described.

I have already shown you the renal safety in that group of patients, it was very good. What you see here in efficacy again, that if you look at biopsy, acute rejection episode, in everolimus in these two groups, the biopsy-proven acute rejection episodes were smaller or equal to what they were in the mycophenolate with full dose, so the efficacy is retained and the safety is retained.

In the renal trials in which we are using this, in fact, the way we have talked about, with concentration monitoring.

The third piece of evidence comes from the earliest data that we have from the postmarketing stuff of everolimus in Europe for cardiac transplantation, we have, for instance, a report that was presented at the ISHLT meeting this past spring of 30 patients who were treated pretty much exactly as we have described here, 30 patients in

whom rejection rates were 10 percent, and there was no evidence of renal toxicity.

So, if you put all of these things together, the burden of the data strongly suggests that what you see in this modeling is going to be reflected when we use this in manufacturing, when we get to the full release of this for cardiac transplantation.

DR. PROSCHAN: Just related to your earlier point about the small sample size, I did just a back-of-the-envelope calculation, and I get that when you are seeing an event rate of 10 percent, and about 40 people in each quartile, it is about 0.09, plus or minus 0.09 if you tried to do a confidence interval.

DR. HUNSICKER: Sure, but again, remember that what we are starting from is a rejection rate of 30 percent in the good group when we look at it, so I mean however you cut it, these are good outcomes.

DR. PROSCHAN: Right. I am just talking about trying to compare the different bars to each

other.

DR. HUNSICKER: Oh, I don't think the different bars on Slide CN-20 are significantly different.

DR. HIATT: David, and then I think we should go on to the last presentation.

DR. DeMETS: One of the challenges of dose outcome modeling is to try and understand which comes first. In other words, you can imagine that something is going on and the dose is modified, therefore, you would see a lower trough level or a serum value, and therefore, it looks as though--which is cause and which is effect.

So, there is lots of examples where we have gone down the wrong pathway. I am trying to understand how that impacts--

DR. HUNSICKER: You are absolutely right, Dr. DeMets, and therefore you could not make the argument that the causation was going from the dosing to the effect in the cardiac study that I presented to you, but in the renal study, it was the other way around, and in the postmarketing

experience, it's the other way around.

DR. HIATT: I am sorry, but the consensus now is to take a break. So, let's do about a 10- to 15-minute break.

[Break.]

DR. HIATT: One thing that wasn't discussed in the real toxicity issue was the early versus late toxicities. Some of the questions that I guess can't be answered by the current data, because therapeutic drug monitoring really kind of occurred as a late event, is to whether the late reductions in creatinine clearance would have ever been modifiable had drug monitoring been instituted.

DR. HUNSICKER: We don't know the answer to that from this study for the reasons that you have said, however, there are parallel data. Don't bother to look, there is nothing you are going to be able to find.

If you consider the Johnson study of sirolimus, which is a congener, in kidney transplantation, they, in that study, randomized

patients to cyclosporine and sirolimus, and then at 3 months, the cyclosporine was either continued or removed.

In the patients who were on the sirolimus-only arm, there was a substantial increase in clearance subsequently, so that it appears that at least after 3 months of cyclosporine therapy, you can have substantial increase in renal function once you take away the calcineurin inhibitor.

Now, whether that gives you a total answer for this, I am not sure, but at least it is the best answer I can give you at the moment. That is to say I believe that at least some fraction, well, 50 percent of cyclosporine is associated with stabilization of renal function. I think that is a little different.

DR. HIATT: I guess if you played out a thought experiment and you did the therapeutic drug monitoring, and used, you know, those curves on creatinine clearance with the 2 doses going down and the comparator staying the same, if that

outcome wasn't changed at all, how would you feel about the safety of this drug?

DR. HUNSICKER: There are a couple of things to be said. First of all, if there were no further drop in creatinine clearance or if the renal function did, in fact, stabilize forever, it becomes fairly irrelevant compared to the benefits that you have seen from the cardiac point of view.

What we know for kidney transplants, but don't know for heart transplants, for obvious reasons, what is the rate on average of decline of creatinine clearance over time, so I can't tell you how many years difference, if there is a consistent decline, that difference in serum creatinines would mean.

DR. HIATT: We have all conceded that the long-term events that we really care about--

DR. HUNSICKER: Are cardiac.

DR. HIATT: Are cardiac and that the IVUS data may be associated with improvement, we would never expect this database to show us that kind of improvement. To be consistent with that logic,

wouldn't you also have to say we don't know how many end stage renal disease patients are going to occur, because if the creatinine clearance is stabilized, I agree with you.

DR. HUNSICKER: We do know that, as you have seen somebody else present, I don't remember which one of you, that it was something like 7 to 8 years, Ojo looked at this and found that perhaps 15 percent of patients went on to one form or another of chronic renal disease.

I think how you interpret this depends in large measure on how you value the IVUS data. I am a nephrologist, I am not a kidney doctor, but let me answer this if I might. I am not uncommonly asked by my colleagues whether somebody can do a dye study and the patient has got renal insufficiency, and I said, well, it depends upon what you are trying to do. If you are trying to save his heart, go ahead and do it and we will pick up the pieces, because the fact is kidneys almost never work well when the heart has stopped beating.

So, the heart obviously trumps. So, if

you think that there is a benefit in the likely long-term outcome based on the IVUS, then, really, that trumps everything else.

DR. PICKERING: I would just like to ask about the blood samples on which all these analyses were based. This was before--

DR. HUNSICKER: Before discontinuation.

DR. PICKERING: --therapeutic drug monitoring.

DR. HUNSICKER: There was no therapeutic drug monitoring for everolimus in this study.

DR. PICKERING: Right, but you showed a lot of everolimus drug levels. These were taken throughout the course of the study, but blinded?

DR. HUNSICKER: Yes, and analyzed.

DR. PICKERING: How many samples per patient are we talking about?

DR. HUNSICKER: How many samples per patient were done?

DR. SOMBERG: Let me ask John Kovarik, our pharmacokineticist, to address that, because I do not know that number off the top of my head.

DR. KOVARIK: John Kovarik from Clinical Pharmacology, Novartis. Usually, in the first month, we got 4 samples about once per week, and

then at month 3, 6, 9, 12, 15, 24. So, if a patient stayed in the trial for 2 years, there was between 10 to 13 samples.

DR. MANNON: Dr. Hunsicker, I have a couple of questions. I think that the committee is sort of struggling with the extent and the impact of what this reduction is renal function is. So, maybe from a practical perspective, did any of these patients that had significant drops in GFR undergo a biopsy? I mean it wasn't required by the protocol, but was there any clinical information gathered on those patients in the extent of biopsy data or proteinuria that you are aware of?

DR. HUNSICKER: Do you mean kidney biopsies?

DR. MANNON: Kidney biopsies in this trial.

DR. HUNSICKER: I think that is quite variable. I would have to ask the PIs how often

native kidney biopsies were done in the patients with dysfunction.

NOVARTIS REPRESENTATIVE: I am not aware of any.

DR. MANNON: Not at all.

DR. HUNSICKER: Probably very few.

DR. MANNON: So, I guess it's difficult. You know, the question is how much of this reversibility after the 20-month amendment, when that took place, whether you would expect any additional improvement and how severe was this reduction if you go from the baseline.

It is difficult for me to say in the absence of significant proteinuria or an ongoing continued decline, if this is significant that they dropped by that percentage.

DR. HUNSICKER: We concluded that the data that were available for patients who had, in fact, had a drop in response to the renal amendment, were so few and so patchy that it was almost impossible to interpret them.

Again, I might put it into a different

way. If you are taking care of a renal patient, you might consider stopping the cyclosporine entirely, right, and put them on a different regimen.

If you are dealing with a heart transplant, there is absolutely no precedent for that. So, the choice, you know, if you ask what do you do when you see renal insufficiency, as some of the members of the panel know, you charge ahead and you do the best you can.

DR. MANNON: I mean I can't respond to what they would do. I think that when you are a nephrologist on these kinds of patients, you do have to work up with a compromise about appropriate therapy in the context of being concerned about cardiac output and such, so I can't comment about whether I would recommend stopping one of the other drugs.

DR. SOMBERG: If I can suggest, we have an analysis that I think may get to both of your questions. I will ask Kevin Mange, who is an epidemiologist/nephrologist in our group, to

explain a look at what happened to patients who had reduction in cyclosporine within the trial. So, this does not depend on the amendment, this is actually looking on the in-trial experience.

DR. MANGE: Good morning. I am Dr. Kevin Mange from Novartis. I am a nephrologist/epidemiologist and an adjunct scholar at the University of Pennsylvania School of Medicine.

[Slide.]

To answer this question here, we focused on the first year post-transplant, a time during the trial when study treatment assignment we blinded and also when the protocol itself allowed for cyclosporine reduction to occur.

We focused on cyclosporine reduction at a minimum of 50 percent anytime throughout the first year. Using an analytical procedure called "repeated measures analysis," what we did was we compared the rate of change of creatinine clearance prior to that cyclosporine reduction and the rate of change of creatinine clearance after

cyclosporine reduction within patients.

One can see here that in a third of the patients, again during the first year, the cyclosporine reduction was compared to, as a reference, was the trough level at the end of the first month, so 50 percent reduction referring to the trough level of cyclosporine at the end of the first month.

One can see here that for all three groups, there was deterioration of renal function albeit larger in the everolimus groups, however, after the cyclosporine was reduced, for the Imuran group, as well as the everolimus group 1.5, there was no further change in renal dysfunction through the end of the 12th month.

DR. HIATT: I remember seeing that data. I think that is actually helpful in support of the concept that TDM would actually preserve renal function.

DR. MANGE: And it goes to the fact that there is reversibility here. Renal function is, as Dr. Hunsicker said, and others have said, that

there is an acute effect here that is very much reversible.

DR. KASKEL: I would just like to make a comment about the measurement of renal function. We are using the best estimate that is available in the outpatient setting, but for some studies, it might behoove investigators to think about doing a more sophisticated measurement at different points in time, i.e., the Iohexol infusion or comparing this to cystatin C measurements.

DR. ABERNETHY: Just a point of clarification. You said "reversibility." Unless I am reading that slide wrong, it is simply stopping the rate of decline.

DR. MANGE: I would agree with that.

DR. HIATT: Are there any other questions about renal toxicity?

If not, why don't we go to the last presentation.

Benefit/Risk Assessment

DR. EISEN: I am Dr. Howard Eisen still.

[Slide.]

I would like to turn our focus now to a discussion of benefit/risk in the context of the unmet need and the available agents and the data

which you have seen today.

As the FDA has noted in their briefing materials, the toxic effects of immunosuppressants may be acceptable in order to decrease rejection rates and improve patient and graft survival. However, toxicity is not acceptable if it exceeds the supposed benefits, i.e., rejection-free patient and graft survival.

I am in agreement and I believe that the heart transplant community is also in agreement with this position.

[Slide.]

There remain, as you have heard, significant unmet medical needs in heart transplantation, specifically, acute rejection and cardiac allograft vasculopathy. As you have also heard, only cyclosporine and mycophenolate mofetil are approved in heart transplantation.

Azathioprine, as we know, was the first

widely available adjunct used in heart transplantation. Mycophenolate mofetil gained approval based on non-inferior efficacy relative to azathioprine.

As Dr. Barr had mentioned, sirolimus and tacrolimus are increasingly being used, but they are being used off label and without guidance on how they should be used and on their safety. To be honest with you, sometimes they are being used in desperation.

In fact, there has been no new chemical entity approved for heart transplantation since 1998. Everolimus is the first drug in the proliferation signal inhibitor mTOR class for which there are extensive data demonstrating its efficacy in heart transplantation.

In addition, the safety of everolimus has been extensively documented. Finally, everolimus is the first adjunct in which efficacy has been unequivocally demonstrated relative to an active comparator.

[Slide.]

It is important to remember that the use of all immunosuppressive agents evolves over time. Therefore, Novartis has indicated their commitment

to further refine the everolimus regimen.

This includes conducting a post-approval commitment trial in Europe. This is a concentration-controlled study in heart transplantation, and we will compare trough-controlled everolimus dosed to 3 to 8 ng/mL, administered together with tapering cyclosporine to 50 to 100 ng/mL by month 7 versus a comparator arm of 3 grams of mycophenolate mofetil administered with standard or full-dose cyclosporine.

The primary endpoint of this trial is renal function at 6 months, and the secondary endpoints are acute rejection of ISHLT Grade 3A or greater rejection at 6 months and 12 months.

The study will enroll 176 patients through March 2006, and the results of the 12-month analysis are anticipated in the second quarter of 2007.

[Slide.]

In addition, a large, predominantly U.S. study of 630 heart transplant patients is starting this month. This study will compare two concentration-controlled everolimus dose ranges of 3 to 8 ng/mL and 6 to 12 ng/mL administered with tapering of cyclosporine to 50 to 100 ng/mL by

month 7 versus a comparator arm of MMF and full-dose cyclosporine.

The primary endpoint is the same composite endpoint at 12 months that was studied in B253, and the secondary endpoints include renal function and IVUS parameters at 12 months.

The study will enroll over 24 months and the results of the 1-year analysis are anticipated no sooner than 2009, but if you think about it, the results of later outcomes that may be even more important in this patient population won't be available until well into the next decade.

These studies will provide further data in the use of everolimus in transplantation, however, on the basis of the information that you have heard in this presentation, I believe that a substantial

majority of our transplant community shares the opinion that we have sufficient information to justify the use of everolimus today as part of current immunosuppressive therapy.

[Slide.]

Let me summarize what you have heard today. Acute rejection accounts for substantial morbidity and mortality during the first year after transplantation, and actually accounts for mortality when one gets past the second year after transplant if one looks at the CTRD data that was shown previously.

To summarize the results that Dr. Hosenpud discussed with you today, everolimus 1.5 mg and 3.5 mg doses significantly reduced acute rejection compared with azathioprine throughout the whole study period.

[Slide.]

The next outcome that we looked at was cardiac allograft vasculopathy. CAV is a major, if not the major cause of mortality late after transplantation. It affects approximately half of

all heart transplant recipients within 5 years of surgery, and further, there is no recognized treatment to prevent CAV or to reverse it once it is established As with other cardiovascular diseases, the goal of treatment should be prevention.

To summarize the study previously presented by Dr. Kobashigawa, both doses of everolimus significantly reduced the incidence and severity of cardiac allograft vasculopathy as defined by intravascular ultrasound compared to azathioprine at 12 and 24 months.

In addition, the incidence of at least non-fatal graft-related MACE at 1 to 48 months, a potential outcome of cardiac allograft vasculopathy was also significantly lower at least in the low dose everolimus treatment arm.

[Slide.]

One of the potential risks of immunosuppression is malignancy, however, we observed a comparable incidence of malignancy with everolimus compared with azathioprine. In

addition, although infections occur including dose-dependent increase in the risk of bacterial infections, the infections were manageable and there was no increase in deaths among everolimus-treated patients due to infections.

In contrast, cytomegalovirus infections were more common among azathioprine-treated patients than everolimus-treated patients. Total triglycerides and cholesterol were increased, however, the magnitude of the increase in triglycerides was modest and HDL and LDL values were similar across the treatment groups.

Further, these lipid abnormalities were not associated with an increase in major adverse cardiovascular events compared with azathioprine.

[Slide.]

The renal safety of everolimus and cyclosporine was among our primary concerns during the trial. There was significantly lower mean creatinine clearance values and higher creatinine levels among patients treated with a combination of everolimus with full-dose cyclosporine, however, no

further reductions in mean creatinine clearance was demonstrated beyond 12 months in particularly with the low dose everolimus group, indicating that by and large, patients did not experience progressive renal dysfunction due to this regimen.

Exposure-response analyses demonstrated the critical role of cyclosporine in risk for renal dysfunction. In contrast, anti-rejection efficacy is primarily associated with blood levels of everolimus. As shown by Dr. Hunsicker, it is possible to dose these agents so as to minimize renal toxicity and maintain anti-rejection efficacy.

I feel confident that with the information available to us now, and also the experience of some of our colleagues in Europe who routinely use this drug for clinical purposes, and who presented their experience at the International Society of Heart and Lung Transplantation meeting in 2005, we could avoid the renal toxicity and maintain the beneficial effects in terms of prevention of rejection.

The overall assessment of benefit-risk can be further improved by optimizing everolimus treatment through application of therapeutic drug

monitoring. Exposure outcome assessments suggest a therapeutic range for everolimus would be expected to benefit the vast majority of heart transplant patient recipients.

[Slide.]

Indeed, adjusting whole blood trough concentrations of everolimus to a range of 3 to 8 ng/mL allows physicians to ensure adequate everolimus exposure and beneficial outcomes.

The expose-response analyses further support reducing cyclosporine dosing, allowing improvement in renal function, yet maintaining efficacy, and as Dr. Hunsicker indicated, this is already being done in some of the renal transplant trials.

[Slide.]

So, in conclusion, everolimus has demonstrated a significant benefit versus azathioprine in the reduction of acute rejection

and in the reduction of both the incidence and severity of allograft vasculopathy.

These outcomes are known risks for survival in heart transplantation, and we really don't have therapies that have effectively eliminated these, nor have the off-label therapies that we use so commonly affect these, as well.

Everolimus, like all immunosuppressive therapy used clinically in transplantation, has significant side effects that are manageable by transplant professionals.

Given the unmet needs in preventing acute rejection and reducing the incidence and severity of cardiac allograft vasculopathy, improved outcomes justify a tradeoff for acceptable risk.

I would like to thank the committee for allowing me to speak and for your attention.

Committee Questions to Novartis

DR. HIATT: Thank you very much.

In the last few minutes, I would like the committee to recognize that these two trials, the one that is ongoing in Europe, and the proposed one

to start up in the U.S., particularly the second one, will be topics of discussion around the questions that we have later in the afternoon.

I am wondering if you all have any questions about them, this would be one opportunity, although there will be others, and I do have a couple of questions. I understand a non-inferiority design around the European study, because the primary is renal toxicity. I would be curious what the margins are around non-inferiority.

I was also curious to note that it was a non-inferiority design for the U.S. study, which I also agree with, but I am wondering if you could justify why you selected that.

DR. EISEN: Dr. Somberg.

DR. SOMBERG: You are talking about the non-inferiority margin in terms of the creatinine clearance?

DR. HIATT: That's the first question. I would like to know what the non-inferiority margin is for the primary and the U.S. study, as well, and

your thought on why you chose a non-inferiority design for the U.S. study.

DR. SOMBERG: I believe the creatinine clearance of 7 mL per minute was the bounds for non-inferiority for the renal study, and 10 percent is the confidence interval around the composite primary endpoint for the U.S. study with again the primary endpoint in the U.S. study being the composite of rejection. That is in agreement with the agency.

DR. HIATT: And the rationale for non-inferiority around the U.S. study?

DR. SOMBERG: The comparator here is MMF, and although the modeling suggests and the sample size calculation does expect that numerically, everolimus would be better. To actually demonstrate superiority would take an extremely large number of patients, and what we are talking about with this study, similar to 253, is essentially 10-plus percent of patients in the U.S. will have to be entering into this trial.

So, to actually have a superiority design

would take an inordinate number of patients, and essentially, prolong enrollment to three years or maybe even more.

DR. HIATT: Do you think MMF might neutralize some of the differences between groups, as well?

DR. SOMBERG: That the difference in efficacy may not be as large?

DR. HIATT: Yes, correct.

DR. SOMBERG: That is possible.

DR. HIATT: But, again, I think that all sounds appropriate.

Does the committee have any questions?

DR. PICKERING: I had a question about the 2411. You say that the everolimus group is going to have tapers cyclosporine, but that is with therapeutic drug monitoring, is that right?

DR. SOMBERG: That is correct. This was a post-approval commitment to the French Health Authority that wanted a study that was consistent with--

DR. PICKERING: But the other group will

presumably have standard cyclosporine, does that mean they will get a bigger dose, and wouldn't that sort of predispose them to get more nephrotoxicity?

DR. SOMBERG: I think you bring up an important issue, which is in transplantation, we are really talking about regimens versus regimens. So, the cyclosporine dosing with everolimus is lower. With MMF, it is typical or higher, and that is different, but, in fact, the evidence would suggest you need that degree of cyclosporine with MMF to have acceptable efficacy, so it does become a comparison of regimens and regimens.

DR. EISEN: In essence, also, comparison of new regimens, the regimens with everolimus to what essentially has become one of the standards of care, which is full-dose cyclosporine with MMF.

DR. TEERLINK: This is giving you a chance to also address one of the earlier questions. In the 2310 trial, obviously, the thing that is really going to drive it once again is the biopsy in terms of the endpoint.

So, one thing I would like you to address

is can you address the issue of ascertainment bias in the current study in terms of the biopsies, and secondly, how are you going to deal with it and make sure that doesn't drive the study in perhaps in an inadequate way in 2310.

DR. SOMBERG: Certainly. Let me answer a few point and I would also like Dr. Kobashigawa to come up and address whether he thinks the way we ascertain biopsies was reasonably consistent with practice.

Let me just mention one thing, that IVUS is also part of the 2310 study, and one of the things that is being done in that study, which again would not become--when we say the data would become available in 2009, an approval would be at the end of that year or 2010.

One of the things we are doing is whether patients stay on therapy or not, we are going to be trying to ascertain both all the biopsy information and the IVUS information. We will attempt to do it in an improved fashion this time.

I think it is worth--Dr. Eisen may mention

also--the difficulty in obtaining some of those procedures in patients who are no longer on treatment from an IRB point of view.

Let me get to the issue of ascertainment bias that both you and Dr. DeMets talked about. First, if I could show the slide of disposition at 6 months. I think it's OB-27.

[Slide.]

At six months, the incidence of dropout, it was 20 percent in the azathioprine group and 22 percent in the everolimus group, so the numbers are quite comparable and higher in the 3 mg group.

[Slide.]

If we look at time to discontinuation, I think that is SM-72, we see that the lines essentially overlap in terms of time to discontinuation between the azathioprine and 1.5 mg everolimus group.

Then, you see these two lines, the azathioprine in blue, and the everolimus in yellow, essentially overlapping, and obviously more discontinuations with the 3 mg arm.

Then, I believe it's SM-69, and maybe, Dr. DeMets, this gets more specifically to your question, biopsies are missed, and maybe one of the

clinicians could talk about the fact that because of intercurrent illnesses or other issues, a biopsy may be delayed compared to the planned timing, but if we look at the bottom half of this slide, it indicates numerically the number of biopsies that were missed at any given time.

Again, I would direct you to what I believe is the most relevant comparison, the azathioprine and the 1.5, so this is patients who did not have a biopsy at this visit, you know, at day 7, 14, 28, et cetera, for azathioprine and 1.5. These are the number of patients still alive and in study whether they were on drug or not, but potentially available patients.

I think what you see is the numbers are nearly identical, and actually identical at the 6-month time point between azathioprine and everolimus for patients who did not have a biopsy at that time point.

DR. DeMETS: I think the concern I have is not that the numbers are the same, because while that is interesting, that is not what I am looking for.

The question really is how many patients never had one, it is truly unknown. If you missed

a window, can you catch up next time? But the question is how many just don't show up, because then it really is unknown.

DR. SOMBERG: Let me let one of the clinicians talk about it, but I will make the point whether you had rejection or not, the average number of biopsies per patient in the first year was 12 to 13 in all groups, but if I could ask Dr. Kobashigawa to comment on those aspects of ascertainment.

DR. KOBASHIGAWA: Just to let you know, biopsies are performed by either protocol biopsies or by patients are related in terms of hemodynamic compromise.

The protocol biopsies are quite standard - once a week for 4 times, every two weeks, and once

a month, et cetera, and that is what we use when we do all these clinical trials, and that has been standardized fortunately by all involved transplant centers.

But then you do have patients who have rejection, and incidentally, rejection was more so in the azathioprine group, but what we do is we do follow-up biopsies two weeks later, so naturally, you are going to have more biopsies in patients who have had rejections, because we will do them more frequently just to make sure that the biopsy is showing resolution of rejection.

I don't think that there was more biopsies missed in the azathioprine group. As you can see, they are more or less, you know, overall they were pretty much comparable, but if you look at increased rejections in the azathioprine group, it will appear that you are having less biopsies in the everolimus groups, when, in fact, you are having more biopsies to follow up, to make sure that rejection is resolved.

DR. HIATT: I might charge ahead here. I

apologize to the agency that their time is past. It was at 11 o'clock, and I think it is important that we hear from them, and I am just logistically thinking that we could potentially take a lunch break now and start at 12:30, if that would be feasible.

I think we are going to be able to gain some time this afternoon, so that we can keep it all consolidated. Would that be all right with you all? It would be about a 35-minute lunch.

I think we will have time to come back and talk about these two studies, which I think there is more questions that will come up in the discussion period later this afternoon.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to be resumed at 12:30 p.m.]

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

[12:30 p.m.]

DR. HIATT: It looks like everyone has been great to come back around 12:30, I appreciate that very much. If you are all getting somewhat prepared, maybe we can start to get organized for the FDA presentation.

Food and Drug Administration Presentation

Statistical Overview of Study B253

LT TRACY: Now that you are full, I will try not to put you to sleep.

[Slide.]

Good afternoon. My name is LaRee Tracy. I am the primary statistical reviewer for the Certican application for prophylaxis and heart transplantation being discussed today.

[Slide.]

My presentation will be restricted to the review findings of Study B253, the single pivotal Phase 3 study conducted in de novo heart transplantation.

I intend to summarize the efficacy results

while addressing the concerns regarding premature treatment discontinuation, notably those due to adverse events.

I will briefly summarize observed renal toxicity and other notable safety events.

Also, I will discuss the secondary analysis of intravascular ultrasound performed in a subset of Study B253 patients.

Lastly, I will summarize the statistical concerns associated with the sponsor's exposure-response analyses.

Again, this presentation pertains only to Study B253.

[Slide.]

In brief, Study B253 was a pivotal Phase 3 study originally submitted in December of 2002 for NDA 21-628, as basis for the indication of prophylaxis in heart transplantation.

This study was originally designed as a 24-month double-blind study, but due to safety concerns, the study was amended at month 12 leading to treatment unblinding.

A total of 634 patients were randomized to receive either everolimus 1.5 mg/day, 3.0 mg/day, or azathioprine given as 1 to 3 mg/kg/day in

combination with full dose cyclosporine and steroids.

The primary endpoint the composite to biopsy proven acute rejection of ISHLT Grade 3 or greater, acute rejection associated with hemodynamic compromise, patient to graft loss, or lost to follow-up, whichever occurred first, was measured at 6 months.

These failure events were also measured at months 12, 24, as secondary analyses, and although not specified in the original protocol, patients were followed for up to 48 months.

The comparator azathioprine is not FDA approved, as we have discussed, for heart transplantation, and therefore the primary objective of Study B253 was to demonstrate superiority of either everolimus groups over azathioprine at 6 months.

[Slide.]

As summarized here, the primary endpoint at 6 months, shown in the top row, occurred less frequently in both everolimus groups compared to azathioprine, resulting in a superiority finding.

These differences were solely driven by the lower rates of biopsy-proven acute rejection in

both everolimus groups. No statistically significant differences were observed in the rates of acute rejection associated with hemodynamic compromise, death, or graft loss, or the composite of death and graft loss, which are endpoints considered more severe in this patient population.

Note that the sponsor utilized appropriate methods to address for these two pairwise comparisons, and therefore there is no concern regarding multiplicity.

[Slide.]

Differences observed at month 6 continued through month 12, which were again driven by the lower incidence of biopsy-proven acute rejection in both everolimus groups. Results after 12 months will not be discussed due to changes in the study

protocol that led to treatment unblinding and a switch to TDM after all patients had completed their 12-month visit. Amendment 3 will be discussed, which was the basis for that protocol change.

[Slide.]

Now, there was a significant rate of premature treatment discontinuation throughout this study. Rates were similar between the everolimus 1.5 mg group and azathioprine, however, rates observed in the everolimus 3.0 mg group were statistically significantly higher than those in the azathioprine group.

The primary reason accounting for approximately 50 percent of premature treatment discontinuation was adverse events. Renal and urinary disorders were the most frequent common adverse event, leading to treatment discontinuation, and were consistently higher in both everolimus groups compared to azathioprine.

At 6 and 12 months, unsatisfactory therapeutic effect leading to premature treatment

discontinuation occurred at similar rates in the everolimus 1.5 mg group and azathioprine, but less frequently in the everolimus 3.0 group.

[Slide.]

The purpose of this slide is to summarize one sensitivity analysis performed by FDA to examine the effects of the high rates of premature treatment discontinuation on overall efficacy.

This sensitivity analysis considered premature treatment discontinuation as a failure event among the composite primary event. This analysis therefore looked for the occurrence of premature treatment discontinuation, biopsy-proven acute rejection, acute rejection associated with human dynamic compromise, death, graft loss, or lost to follow-up, whichever occurred first.

At 6 months, difference between everolimus 1.5 and azathioprine is not statistically significant. At 12 months, both everolimus groups appear to result in a statistically significantly lower rate of efficacy failure.

This analysis is a sensitivity analysis

only, and not intended to negate the primary efficacy findings of Study B253, but rather to point to the fact that the statistical significance between everolimus 1.5 and azathioprine is not maintained.

It is also to point out that the large number and disproportionate reasons for premature treatment discontinuation should not be ignored while interpreting the overall study results.

[Slide.]

To briefly summarize the findings of the primary efficacy analysis, the primary efficacy objective was achieved by demonstrating that the incidence of biopsy-proven acute rejection was statistically significantly lower in both everolimus groups compared to azathioprine.

The incidence of acute rejection associated with hemodynamic compromise, graft loss, patient survival were, however, not statistically different among all three groups.

Treatment discontinuation occurred statistically significantly more often in the 3 mg

group compared to azathioprine, with the majority of the reasons due to adverse events.

The sensitivity analyses including treatment discontinuation led to a loss of statistical significance between the everolimus 1.5 group and azathioprine at 6 months, but does not negate the protocol specified primary analysis findings.

[Slide.]

I will now briefly discuss key findings from the safety review for which Dr. Hernandez will present next in greater detail.

The protocol specified safety population consisted of all randomized patients who received at least 1 dose of treatment and had at least 1 safety observation.

Two important points should be kept in mind while interpreting safety. Firstly, safety events were reported only in patients still on treatment or who had just discontinued treatment within the last 30 days.

An exception to this was for a minimal

number of renal assessments in some patients who were off of treatment, but by and large, most patients off treatment were not assessed.

Secondly, the high rates of premature treatment discontinuation just discussed may lead to an underestimation of safety events particularly in the everolimus 3.0 mg group since again safety was reported only in patients still on treatment.

[Slide.]

I will briefly summarize the renal toxicity that was observed in both everolimus groups beginning as early as month 3. These graphs illustrate the early onset of renal toxicity that persisted throughout the study.

Shown on the left graph is mean creatinine measured in micromoles per liter, and shown on the right is creatinine clearance measured as milliliters per minute using the Cockroft-Gault formula. Time is represented on the X axis, and everolimus 1.5 is shown in red, the 3.0 mg group is shown in black, and azathioprine is shown in blue.

The graph on the left shows statistically

significantly greater creatinine values in both everolimus groups at all post-baseline time points compared to azathioprine.

Similarly, creatinine clearance values, shown on the right, were statistically significantly lower in both everolimus groups compared to azathioprine at all post-baseline time points.

Again, it is worth noting that given the disproportionate rates of premature treatment discontinuation, it is likely that the laboratory measurements are underestimated or overestimated depending on parameter, especially in the everolimus 3.0 mg group, however, this is speculation that cannot be tested since data is only available on patients still on treatment or who had just recently discontinued treatment.

[Slide.]

This slide illustrates the percentage of patients observed with creatinine value greater than or equal to 2.5 mg/dL, the cutoff indicative of severe renal failure.

Note that percentages are not cumulative from time point to time point, but rather reflect the percentage of patients at the specified time

point.

As you can see, the percentage of patients with severe renal failure in both everolimus groups is statistically significantly greater than azathioprine at months 3, 6, 12, 18, and 24.

The percentage of azathioprine-treated patients is similar to that reported in the ISHLT Thoracic Registry, which is approximately 7.8 percent at 1 year follow transplantation.

[Slide.]

This notable renal toxicity prompted protocol amendment 3, which led to treatment unblinding and switch to TDM for patients still on assigned therapy who had notable renal impairment.

A total of 170 patients, or 58 in everolimus 1.5, 51 in the 3.0 group, and 61 in the azathioprine group entered this open label phase, and were thus switched to the TDM regimen. Of these, less than half had follow-up renal values

measured. These limited data prevent any qualitatively meaningful comparisons.

[Slide.]

In addition to the persistent renal toxicity, other notable safety events occurred more frequently in both everolimus groups compared to azathioprine. These included pericardial effusion, cardiac tamponade, pneumonias, and thrombotic microangiopathy.

The incidence of viral infections was statistically significantly higher in the azathioprine group compared to everolimus. Conversely, the incidence of bacterial infections was statistically significantly higher in both everolimus groups compared to azathioprine.

Changes from baseline in cholesterol and triglyceride levels were statistically significantly greater in both everolimus groups compared to azathioprine.

These findings, albeit not all statistically significant, should raise concern given that there was a common trend of increased

adverse events in both everolimus groups throughout the study as compared to azathioprine.

[Slide.]

I will now discuss the intravascular ultrasound secondary analysis. From a reviewer's perspective, it appears that the analysis of IVUS data were exploratory for several reasons.

For example, comparing IVUS results among groups was listed as 1 of 10 secondary objectives. Typically, if a sponsor considers a secondary objective highly important, that objective is listed as the primary second objective. This one was listed as the sixth.

The analysis was performed on a subset, approximately one-third of the study population. Also, there were various analyses stated for more than one IVUS endpoint and no method to account for missed follow-up in patients who had an initial assessment.

[Slide.]

As previously discussed by the sponsor, the sponsor's analysis of the incidence of

allograft vasculopathy, defined as an increase of at least 0.5 mm from baseline in maximum intimal thickness suggests a lower incidence in both everolimus groups compared to azathioprine at 12 months. These results are shown in the first row of the table.

The purpose of the remaining rows is to highlight two sensitivity analyses performed by the sponsor and submitted as part of the pre-Advisory Committee packet, which attempted to account for missing data.

The first, performed in the population of all patients who had an initial IVUS assessment within the first 6 weeks following transplantation, imputing failure for patients who had a missed 12-week assessment, shows a lack of significant difference between either everolimus group and azathioprine in the incidence of allograft vasculopathy. This is shown in the second row.

Similarly, when the population is defined as all patients who had an initial and a 12-month assessment plus those who had missed their 12-month

assessment due to renal dysfunction, again, no difference between treatment groups is shown. This is reflected in the third row.

[Slide.]

To summarize these findings, they suggest a positive trend favoring everolimus in reducing coronary artery thickening compared to azathioprine, but that these results should not be considered definitive for the following reasons:

These results are based only on a subset of patients who were selected at 12 months into the study, which could introduce bias. Also, treatment tolerability or renal impairment was a major reason for patients not having IVUS, which again can introduce bias.

The ongoing issue of premature treatment discontinuation, particularly the disproportionate rates and reasons causes concern.

Additionally, the influence of statins on these variables cannot be fully determined due to the limitations in data collection. Specifically, only statin drug, the name of the drug is reported

in the case report forms, not dose or durations or attempts to optimize therapy. This could add potential bias, as well, given that more patients in the everolimus groups had increased lipids, therefore, potentially requiring more statins.

[Slide.]

Lastly, and most importantly, is that there was no overall benefit in the rate of survival in the IVUS subgroup, nor in the overall study population.

The month 48 overall survival rates were similar between treatment groups - 15.3 percent in the everolimus 1.5, 16.1 percent in everolimus 3.0, and azathioprine had a mortality rate of 14 percent.

Forty-eight month survival rates in the IVUS subgroup were 4.3 in both everolimus groups and 2.8 in azathioprine.

So, in conclusion, patients treated with everolimus seemed to have less coronary artery thickening compared to azathioprine, but that these results should not be considered definitive.

[Slide.]

Due to unacceptable renal toxicity known to be due to the use of everolimus with full dose

cyclosporine, the sponsor attempted to model more appropriate regimens using whole blood everolimus and cyclosporine levels that were obtained during the first six months of Study B253.

The objective was to model a regimen that would allow cyclosporine reduction while maintaining adequate efficacy. It is not my objective to discuss the methodology used, nor the conclusions drawn, but rather to address some general statistical concerns when considering exposure-response results as definitive proof of safety and efficacy.

Firstly, and perhaps most importantly is the issue regarding loss of original treatment randomization in these retrospective analyses. Specifically, due to patient regrouping as a function of measured whole blood drug concentrations, the original randomization of B253 is no longer preserved.

This is of concern given that measured concentration levels are dependent on multiple variables measured during the study or not measured during the study.

Also, the disproportionate rates of premature treatment discontinuation observed in the

everolimus 3.0 mg group could bias outcomes being measured in these exposure-response models.

[Slide.]

Additionally, these models are limited due to their inability to predict both safety and efficacy outcomes during the first month follow transplantation, a period of time crucial for long-term morbidity and survival.

Specifically, these models do not definitively predict how low cyclosporine levels can be titrated downward without precipitating acute rejection. These analyses are further burdened by sparse PK sampling as specified in the study protocol.

So, in other words, the protocol's limited assessments after month 3 led to insufficient

amounts of data for modeling purposes.

There is also the concern that the selected concentration ranges may be subjective and biased due to the estimation and calculation of average concentration values, missed concentration measurements near events of interest, infrequent concentration sampling and unequal spacing between samplings are data measuring concerns.

There is also the concern of potential bias associated with which method was used to estimate average concentration, i.e., the arithmetic mean, the geometric mean, or the time average mean.

Considerable variability exists in the measured concentrations, as well.

Lastly, these models only model renal toxicity and fail to model other notable safety events, and are limited by only what was observed in Study B253, and therefore cannot predict what may have occurred with the modified regimen. Specifically, these models cannot predict what new toxicities may occur with an increased everolimus

exposure or a decreased cyclosporine exposure.

[Slide.]

In conclusion, the FDA review of Study B253 with a confirmatory study in heart transplantation for the Certican NDA found that fixed doses of everolimus, when given the full dose cyclosporine and steroids, were superior to azathioprine with full dose cyclosporine regimen in reducing the rate of biopsy-proven acute rejection at months 6 and 12 following transplantation.

This study also showed that there was no difference in incidence of patient or graft survival or acute rejection associated with hemodynamic compromise between randomized treatment groups. Disproportionate rates of premature treatment discontinuation were observed throughout Study B253 with statistically significantly more occurring in the everolimus 3.0 mg group.

The primary reason for premature treatment discontinuation was adverse events.

[Slide.]

Study B253 also demonstrated unacceptable

safety including renal toxicity associated with fixed doses of everolimus given in combination with full dose cyclosporine, which occurred as early as month 3 and continued throughout the study, which led to a modified regimen.

The secondary analysis of intravascular ultrasound, which measured coronary artery intimal thickness, showed promising trends favoring everolimus, however, these results cannot be considered definitive due to potentially biased patient selection and disproportionate rates of premature treatment discontinuation.

Study B253 did not demonstrate that the fixed doses of everolimus, when given with full dose cyclosporine, are both safe and effective in a heart transplantation.

[Slide.]

In addition, the sponsor's exposure-response analyses are tremendously useful as hypotheses generating, however, they are not hypothesis testing.

To demonstrate safety and efficacy of the

model-derived regimens, it is essential that these regimens are prospectively tested in a future Phase 3 trial to confirm efficacy and safety.

Also, it is important to study the clinical feasibility of such regimens to determine if target concentrations are indeed attainable and sustainable.

This concludes my presentation. Thank you for your attention.

DR. HIATT: Thank you. We will take some questions.

DR. NISSEN: I wonder if the statistical group at the FDA did any other sensitivity analyses. As you I am sure heard earlier, I just don't like doing a sensitivity analysis based upon what is a secondary rather than a primary endpoint.

I just don't think that this particular sensitivity analysis is an appropriate one. So, I wonder if you guys have explored that at all.

LT TRACY: Again, it is due to the issue with the data being continuous and how do you impute those data, what do you impute for patients

who had missing values, and we are looking at mean values.

So, no, we did not do any additional sensitivity analyses. Again, we considered that endpoint as a secondary one.

DR. ABERNETHY: I would ask I guess anyone, but obviously, this amendment that occurred was a big deal, so I would like some understanding as to the drivers of that. Was that a DSMB directive? How did that come about, because it strikes me that there were two possibilities when one had those sort of findings.

One was to stop the study and the other one was to try to rescue whatever was possible.

LT TRACY: I will answer from what I have learned from the review, and if the sponsor wants to add to it, they can. It was driven basically by DSMB findings. They recommended that the regimen be modified and at the time it was near the 12-month period meaning at the point where most patients had reached their 12-month assessment.

DR. SOMBERG: I think the timing Ms. Tracy

described is accurate. The DSMB noted an imbalance in SAEs of renal function pretty much at the same time we were getting the 12-month dataset and agreed that for patient safety, the amendment should take place.

They felt the study did not need to be stopped, but that this modification was reasonable.

DR. PICKERING: I am a bit confused. Earlier this morning you said, somebody said that 85 percent of patients had completed their two-year period when amendment 3 actually came into being, is that right?

DR. SOMBERG: That is correct. The enrollment in the study was quite on, and then from the time that the decision was made that we have to amend it to the time the amendment was written, and then accepted or approved at the various institutional IRBs, that time period allowed 21 months to have passed at a minimum. Eighty-five percent of patients had 24 month follow-up by the time the amendment was enacted.

DR. PICKERING: So, the 170 patients, I

mean it was only a relatively brief period in the trial, is that right?

DR. SOMBERG: The 170 patients are those who actually chose to enter into the amendment, recalling that to enter into an amendment a few years after follow-up, means coming to a center more often, I think in many cases the clinician had already lowered the cyclosporine when the renal function was satisfactory.

So, again, it was 170 patients who entered into the amendment, a minimum of 21 months after they started the study.

DR. NISSEN: We heard from the sponsor some analyses related to this reduced cyclosporine dose regimen and renal toxicity from other studies. Were any of those submitted to the agency for review?

LT TRACY: The data that the sponsor presented, the kidney data, that was presented to the FDA. We did review that. I have slides to discuss some of the concerns we have with that, mainly being the concern regarding across-organ

comparisons.

It is my understanding, and certainly the clinical group could add to this, that conclusions drawn from one organ cannot necessarily be extrapolated to another organ, and additionally, there were across-study comparisons performed using those data, the uncontrolled data which used the TDM regimen study in the kidney were compared with the original studies in the kidney that were controlled using the MMF regimen.

There were multiple concerns with that data, but, yes, the sponsor did present that data to us in the amendment.

DR. NISSEN: But isn't it the same organ? I mean we are talking about renal safety, right?

LT TRACY: I would defer the rest of that to our clinical experts.

DR. NISSEN: I am trying to make sure, I am trying to decide how much weight we should put on the TDM data that we heard, and the question is obviously if the issue is renal safety, and if we have another study albeit with a different

population, but is it informative about, you know, what the TDM regimen would look like from a renal safety point of view, and I am kind of thinking that it is, but I would like to hear other perspectives.

DR. TEERLINK: I think the point that is being made is that while you can perhaps extrapolate in terms of the renal toxicity, you then lose your ability to interpret how those changes affect your ability to prevent cardiac rejection, and that's the across-organ comparison that, sure, you can look at the safety issue, but then you lose the efficacy comparison, and that is the challenge here, and we all have to kind of be comfortable with how we are going to extrapolate or if we are going to extrapolate that.

LT TRACY: That's true and also it is important to note that the two studies that used concentration control with everolimus with reduced cyclosporine in kidney, the A2306 and A2307 studies, those were uncontrolled studies, so in order for the sponsor to draw some sort of

comparative conclusions, they then submitted data that did across-study comparisons looking at the original kidney studies, the B251 and B201, and used the comparator arm there, the MMF arm.

We have raised several concerns regarding those analyses particularly the concern regarding across-study comparisons whereby the use of across-study comparisons should only be done in situations where there are no other data available or in cases where the designs are so similar and the patient population is so similar, but rarely that's the case.

As you can see here, the donor and recipient baseline characteristics were quite different between studies. The percentage of total living donors in the original B251 kidney study was much greater than among the concentration controlled studies, as well as the percentage of black patients in that study was greater.

I also have data showing there were differences between the studies or among the studies regarding the risk factors for

cardiovascular disease. More obese patients were observed in the B251 study than in the two concentration-controlled studies.

Diabetes was more frequent. I mean the darker gray column illustrates the cases where there were imbalances in baseline characteristics or comorbidities.

So, our conclusion, those analyses were looked at by the agency, but certainly not considered definitive.

DR. CAVAILLE-COLL: I would like to clarify a little bit about the extrapolation from the kidney information into the heart transplantation. I think that there are several points. One of them, when we are looking at the effect of the toxicity of an immunosuppressive regimen on renal function in kidney transplantation, we also have to factor in the contribution of rejection, too.

If you go to a cyclosporine-sparing regimen, and you have an episode of rejection, you have lost a large amount of function. So, I think

the issues there are a little bit different.

The other things that we have numerous examples now where the safety and efficacy of a regimen in one organ has not panned out in another. I mean I think it's notable that for this class of drugs, the mTOR inhibitor Rapamune has a black box warning about the problems in liver transplantation and lung transplantation, and there also have been experiences with other drugs that have been shown to be safe and effective in one organ, but then have been associated with increased toxicities or deaths due to infection.

So, the two issues are looking at renal function in kidney transplantation is more complex because that is the organ of target. The other thing is that there are just too numerous examples that the safety and efficacy of a regimen in one type of organ doesn't necessarily predict it in another.

DR. HIATT: You mentioned feasibility of therapeutic drug monitoring, and I also noted that about half the patients were unsuccessful meeting

the exact proposed criteria for that, and did you play with that percentage, if it were to increase to 75 percent? I think you said 25 percent were successfully monitored, what that would have done to the real toxicity using the models that were proposed?

LT TRACY: I personally did not do any of the modeling. The clinical pharmacologists and the pharmacometricians did all the modeling, and there will be a presentation next regarding that. Perhaps you could ask them that question.

DR. PROSCHAN: You showed the 48-month mortality. In fairness to Novartis, you would really have to have a whopping effect to see a significant difference in mortality. On the other hand, 48-month MACE results, maybe you wouldn't have to see, I mean because that event rate is much higher, and I am wondering if you have that.

I think we saw the rate at earlier times.

LT TRACY: Do I have the 48-month MACE data? No, I do not.

DR. PROSCHAN: We saw 48 months?

LT TRACY: The sponsors, did they present 48 months or 24 months?

DR. PROSCHAN: I thought it was 24 what

they showed.

DR. TEERLINK: You had mentioned that the IVUS data was 1 of 10 secondary analyses and it was No. 6 on the list. Now, obviously, this committee has dealt with secondary endpoints in multiple different ways and things.

Was there any indication to give us guidance in terms of how to weight this as a secondary endpoint at all, or should we just ignore it? From a statistical standpoint, is there any justification to look at it statistically from the trial design?

LT TRACY: That's a tough question, because I do believe that there are trends favoring everolimus in decreasing the intimal thickness.

DR. TEERLINK: But when you do 10 different statistical tests--

LT TRACY: In the most rigorous case, no, because you would have to make several adjustments,

you would have to make several adjustments for the multiple endpoints that were observed, but certainly if there was a secondary finding of survival benefit, then that without question would be not debatable.

But here it is a little bit less clear given that there were several changes throughout the study, there was this disproportionate rate of treatment discontinuation that extremely biases, potentially biases the IVUS results, the issue with the need to switch to a therapeutic drug monitoring regimen due to toxicities, which makes the data, in my opinion, a little more dirty to draw grand conclusions on.

DR. NISSEN: Let me choose to answer that a little bit for you. You don't do IVUS, you don't do IVUS as a casual procedure. I mean this is a very invasive, expensive, intensive, thing to do in a couple hundred patients.

I think that the ranking, saying that it's listed as 6, I don't know what some of the others are, but there are things that you can look at just

by having a case report form. You don't do an IVUS substudy unless you are really pretty serious about looking at the data.

So, I guess I would challenge you a little bit about suggesting that it's exploratory.

The other difficulty that I have with the analysis you made is that I think if you look at the primary endpoint, and you do an imputation, let's say, using the ranks as they showed up there, it is actually pretty robust, it's pretty hard to make it go away.

So, my view of it is that it is somewhat more robust than I think Lieutenant Tracy's analysis. I recognize all the points you made, but, you know, this is something that I live with, which is IVUS, and I have looked at a lot of IVUS data over a lot of years, and I think it is informative. How much weight we want to put on that is a discussion for the committee, but I think that it is not a casual collection of a secondary endpoint.

LT TRACY: I just want to add one more

thing. Given some of the concerns that the agency had with this subgroup analysis, the sponsor has in their new study, the Study 2310, their plan is to perform IVUS in selected sites whereby all patients will undergo IVUS, whereas, this study, it was investigator-driven, so not all patients at one site underwent IVUS.

That adds some concern in interpreting the results, as is the issue, the selection of patients at 12 months rather than at baseline.

DR. HIATT: Okay. Thank you very much.

Let's move on to the next presentation.

Hold on just a minute. It is seven after 1:00, so this is the public hearing time, but I think we can delay that, can't we? If it's all right with everyone, I could delay this announcement until the FDA has completed their presentation, is that okay? It would make more sense.

Safety and Efficacy of Everolimus

DR. HERNANDEZ: Let's try to do this fast, and I am going to make a little change over here.

Instead of saying good morning, I want to say good afternoon.

My name is Arturo Hernandez and I will present the clinical overview of the safety findings in the Study B253.

[Slide.]

The safety population consisted of all randomized subjects who received at least one dose of study medication and had one follow-up visit. In this case, all patients in the intent-to-treat population met this definition and therefore the numbers of individuals in the intent-to-treat population and the safety population are the same.

In other words, the denominator in all safety analyses never changed regardless of the number of discontinued patients over time, therefore, affecting accrued rates, which, of course, you know, this can be the interpretation of these data should be done with a little caution.

Adverse events were reported while the subjects were still on study medication, and within 7 days after the patient was discontinued.

Non-fatal, serious adverse events include subjects who still were on study medication and up to 30 days after discontinuation.

[Slide.]

You know this graph very well. In order to understand the relevance of the safety data, we should keep in mind the degree of drug exposure that was achieved in this study. This slide summarizes the mean cyclosporine blood concentrations achieved at 12 months in Study b253.

These include subjects who remained on the study medication on the safety population. About one-half of these patients in designated clinical sites received induction therapy with ATG or OKT3.

These centers, cyclosporine TDM was used for local practice. The centers that didn't use induction therapy used the TDM regimen for cyclosporine as described in the graph, in the yellow dotted lines.

As you can see, during the first month and the second through the six months, the mean cyclosporine trough concentrations in all treatment

groups lie very near or below the lowest limit of the protocol-defined target concentrations.

[Slide.]

This slide summarizes the number and proportion of subjects who received concomitant administration of additional immunosuppressive agents other than the randomized study medication presumably to treat episodes of acute rejection.

Despite the observed difference in acute rejection, Grade 3A or greater, similar proportion of subjects received methylprednisolone in the RAD 1.5 mg group, and the control azathioprine group.

A similar proportion of subjects received antibody treatment across all treatment groups.

[Slide.]

This slide summarizes the rate of discontinuation from study medication at 12 months. This is the double-blind portion of the study, and at 24 months, the extension phase.

Approximately 30 percent of the subjects discontinued study drug by 12 months in the RAD 1.5 mg arm and the control azathioprine group. High

rates of discontinuation from the study medication were observed in the RAD 3 arm, as you have already heard this before.

Adverse events expressed here as number and percentage of discontinuations were the leading cause of discontinuation from the study medication across all treatment groups, accounting for more than 50 percent in the RAD groups, as you can observe.

At 24-month visit, the open-label phase, the discontinuation rate from the study medications were high in all treatment groups. Approximately 40 percent had discontinued study medication in the 1.5 mg arm and also in the azathioprine group. Again, high rates of discontinuation from the study medication were observed in the RAD 3 arm.

[Slide.]

This slide presents the most important reasons for discontinuation from the study medication. The figures are expressed as numbers and percentage of the total of discontinuations.

Unsatisfactory therapeutic effect was a

notable reason for discontinuation of the study drug in the RAD 1.5 and azathioprine group, while abnormal laboratory values and withdrawn consent were more prominent in the RAD 3 arm. This is just to note that there were different adverse events that led to discontinuation.

[Slide.]

In addition to premature discontinuation, there were also numerous dose reductions, as well. The incidence of dose reductions was higher in the RAD arms compared to the azathioprine group.

The most common reason for dose reductions was adverse event. As you know, the most common adverse events were creatinine increase and renal dysfunction.

Again, the white blood cell count abnormalities were more frequent in the azathioprine group. Platelet abnormalities were also important contributors for dose reductions in the RAD arms.

[Slide.]

In our safety review of Study B253, we

analyzed the morbidities post heart transplantation in the safety population. We looked at the morbidities associated with the use of immunosuppression, namely, infections including pneumonia.

We looked also to morbidities that potentially are associated with antiproliferative effects of mTOR inhibitors, such as wound healing complications, gastrointestinal hemorrhage, bone marrow effects, lymphocele, pericardial and pleural effusions.

We looked at morbidities potentially associated with the concurrent use of mTOR inhibitors and cyclosporine, such as lipid abnormalities, renal impairment, and hemolytic uremic syndrome.

[Slide.]

Infections in general were common in this patient population, where numerically higher rates of infections were observed in the RAD 1.5 and significantly higher in the RAD 3 when compared to the azathioprine group.

Bacterial infections were significantly higher in the RAD arms compared to the azathioprine group. In contrast, viral infections were

significantly higher in the azathioprine group versus RAD arms, in mainly CMV and herpesvirus were the most notable viral infections.

Numerically higher rates of fungal infections were observed in the RAD 3 arms compared to the azathioprine groups. Bacterial, viral, and fungal infections were numerically higher in the RAD 3 groups versus the RAD 1, suggesting a dose-related effect.

[Slide.]

Pneumonias. In this slide, we summarized the occurrence of pneumonias in the safety population, again meaning subjects that remain in the study group up to 24 months.

The events presented here as adverse events, the abbreviation AE, DAE, which means discontinuing adverse events, or adverse events that lead to discontinuation, and non-serious adverse events.

Basically, the sponsor choose to exclude from serious adverse events patients that actually died, and the definition that we use for serious events is that this event has to be fatal. This could cause some impairment, maybe required surgical and medical intervention in order to

prevent fatal or worst outcome.

All types of pneumonia reported as adverse events were 3- to 4-fold more common in the RAD treatment groups compared to the azathioprine group. All types of pneumonia included pneumonia NOS, bacterial pneumonias, and other type of pneumonias.

The pneumonia rated as severe by the investigator, this is a very interesting point. The investigator was rating the adverse events as mild, moderate, or severe, so when he considered that the patient has a pneumonia that was severe, it was reported, and also when they were reported as non-fatal serious adverse events were again 3 to 4 times more common in the RAD treatment groups compared to the azathioprine group.

Pneumonia was the reason for discontinuation from the study medication in 6 patients in the RAD 3 group compared to 1 case in the RAD 1.5 and 2 cases in the azathioprine group.

Finally, pneumonia was the primary cause for death in 3 cases, 2 in the RAD 3.0 mg group, and 1 in the azathioprine group.

[Slide.]

This slide summarizes the wound site

related complications potentially associated with antiproliferative effects of the TOR inhibition. Wound infections reported as an adverse event or non-fatal serious adverse event were more common in the RAD arms as compared to the azathioprine group.

Wound dehiscence or wound complications reported as non-fatal serious adverse events and incisional hernias were also more common in the RAD treatment groups. Lymphocele is also known as a potential complication of the use of TOR inhibition, and was more commonly reported as an adverse event or non-fatal serious adverse event in the RAD treatment groups as compared to the

azathioprine group.

Before we speak about pericardial complications, we note that the pleural effusions reported as non-fatal serious adverse events were also more common in the RAD groups.

[Slide.]

Pericardial adverse events are potential complications of heart transplantation, and part of the spectrum of wound healing complications, which may be increased with the use of antiproliferative agents.

This slide summarizes the occurrence of pericardial complications in the safety population at 12-month analysis. Pericardial effusions reported as adverse events or non-fatal serious adverse events were more common in the RAD treatment arms.

Cardiac tamponade reported as an adverse event or non-fatal serious adverse event, which for me, any cardiac tamponade is a serious adverse event, was more common in the RAD treatment groups.

[Slide.]

Now, we will describe the gastrointestinal hemorrhage that we find in this review. Also, there are multiple potential causes of GI bleeding

post heart transplantation. For clinical and clinical reports of GI bleeding and ulceration, mainly intestinal ulcerations associated with TOR inhibition made us take a very close look at this complication.

Gastrointestinal bleeding may be a potential consequence of the antiproliferative effects of TOR inhibition on healing of mucosal injuries.

Gastrointestinal hemorrhage NOS was 3 times more common in the RAD arm compared to the azathioprine. A dose-related effect was observed in the incidence of GI hemorrhage between the RAD arms. In the RAD 3 arms, 3 patients were discontinued from study medication due to gastrointestinal hemorrhage and 1 patient died from gastric hemorrhage.

[Slide.]

Anemia, leukopenia, thrombocytopenia are

potential manifestations of antiproliferative effects in bone marrow. Anemia reported as an adverse event was common in this patient population and most common in the RAD 3 treatment group including as a reason for drug discontinuation or as non-fatal serious adverse event.

Leukopenia as an adverse event was also common in this patient population and to a greater extent in the azathioprine group.

[Slide.]

This graph shows the mean hemoglobin and mean leukocyte counts over time in the safety population. Again, patients that were discontinued due to anemia or leukopenia were not included in this analysis.

Hemoglobin mean values involved after transplantation in all groups, however, the improvement in the RAD arm is less optimal compared to the azathioprine group, and the differences were statistically significant.

Mean leukocyte counts decreased significantly after drug exposure in the 3 arms.

The mean values in the azathioprine arm were significantly lower compared to the RAD 1.5 arm over time. Also, the values remained within normal limits, 5 to 10. No significant difference in mean value over time was observed between the azathioprine and the RAD 3 group.

[Slide.]

These figures show the mean triglyceride and cholesterol values over time in the safety population. We included here a little bit more measurement points rather than baseline 12 and 24 months in order to have a better sense of the lipid abnormalities over time.

In this graph, on the left, the reference line at 2.3 millimoles per liter represent the upper limit of the normal triglyceride values according to the National Cholesterol Education Program, Adult Treatment Panel 3.

In the graph on the right, the reference line at 5.1 millimoles per liter represents the upper limit of the desirable cholesterol level according to the National Cholesterol Education

Program.

As we recall, the statins excluding lovastatin in the study were used per protocol in all patients including those patients that have normal lipid values, so every patient was included.

When you try to do this intervention, you are looking to something else rather than lipid lowering effect of statins. As we have learned a little bit more about statins, we know that statins have other effects rather than only lowering lipid in blood.

Despite the use and dose optimization of these agents, mean triglycerides and cholesterol rose rapidly and remained well above the desirable upper limits in both RAD groups. I will show you the graph to take a look at the low density lipoproteins, which is also kind of interesting to see.

[Slide.]

Renal function impairment is a well-known hazard of the current use of TOR inhibitors with cyclosporine, and this fact has been documented

with everolimus in two, Phase 3 studies in renal transplantation.

This slide summarizes the mean calculated creatinine clearance over time in the safety populations. Again, this graph did not contain information on patients who stopped study medication beyond 7 days after discontinuation due to renal dysfunction, creatinine increase, and any other discontinuing adverse events.

As we know, the most frequent discontinuing adverse events were renal dysfunction and creatinine increase.

After a transient improvement in renal function, the creatinine clearance dropped reaching its nadir between 6 to 9 months post-transplantation in all groups. The dropping creatinine clearance over time was significantly greater, statistically significantly greater in the RAD arms compared to the azathioprine in all comparison points, and the difference in the creatinine clearance among the RAD arms did not reach statistical significance. Both behaved

pretty much the same regarding whatever doses you used to lower the high dose.

Approximately, after 12 months, cyclosporine dose was minimized in patients with renal dysfunction per amendment 3. The mean creatinine clearance showed no significant improvement in the RAD arms. In contrast, the azathioprine arm showed an important improvement and return to baseline values by 18 months and remained stable at 24 months.

These observations suggest that the nephrotoxic effects on cyclosporine were reversible when the cyclosporine was reduced in the azathioprine arm, however, these changes were irreversible in the RAD-cyclosporine combination regardless the cyclosporine dose reduction.

Furthermore, I just was wondering if just this graph that will maintain the same levels, it is just a reflection of hyperfiltration in kidneys that are heavily damaged.

[Slide.]

This slide focuses more closely in the

calculated creatinine clearance during the first 6 months post-transplantation. As we can see in this graph, as early as one week after transplantation, and I would say as soon as we--as to the drugs--we can observe a meaningful difference in calculated creatinine clearance among the treatment groups.

Heart transplant recipients begin with abnormal renal function as demonstrated by the mean creatinine clearance hovering at 6 to 60 mL/minute. A transient improvement in renal function is observed after successful heart transplantation are suspected.

The recovery is blunted [?] in the RAD treatment groups compared to the azathioprine control. These findings suggest an early nephrotoxic effect on the RAD-cyclosporine combination.

[Slide.]

This slide shows the estimated creatinine clearance change from baseline. So, after the third month post-transplantation, the estimated mean change in creatinine clearance from baseline

was significantly negative in both RAD arms compared to azathioprine arm. The difference between the two RAD arms was not statistically significant, and we are looking at the minus 13 and minus 17 milliliters in creatinine clearance less in the RAD arms.

[Slide.]

This last slide depicts the proportion of patients with serum creatinine greater than or equal to 2.5 mg at 12 months for transplantation in the three arms of Study 253 and the two cohorts from the National Society of Heart Transplantation Registry data.

Basically, this illustrates how much nephrotoxicity is the community willing to tolerate. Bars in red, green, or blue represent the RAD 1.5, 3.0, and AZA respectively. Bars in light blue correspond to the two cohorts of the International Society of Heart Transplantation Registry data in the periods that are depicted over there.

As you can observe, unacceptable toxicity,

nephrotoxicity is observed in the cyclosporine-RAD combinations.

[Slide.]

The impact of full dose cyclosporine plus everolimus on renal function was early and persistent, and may be not be reversible if renal toxicity is sustained for a period of time to allow irreversible changes to take place.

Complications potentially related to the antiproliferative effects of everolimus, such as wound healing problems, pericardial complications and gastrointestinal bleeding were also more common in the everolimus arms.

[Slide.]

Pneumonias were more frequently observed in the everolimus arms.

Dyslipidemias occurred early or worsen after drug exposure and persisted despite the use of statins and attempts to optimize lipid lowering therapy.

[Slide.]

Overall, the potential risks associated

with the use of everolimus-cyclosporine combinations, we felt outweighed the potential benefits.

There is a need to develop a regimen that could minimize these toxicities while providing adequate protection against allograft rejection.

The next talk will address the exploratory approaches that could be used to select the TDM-based combination regimen for future studies.

I just want to take a second if you want to show the next slide, please.

[Slide.]

This slide, what it shows is the levels of low density lipoproteins over time. It has been in several trials and studies in animals and humans that the non-atherogenic level lies closer below to 100.

As a matter of fact, individuals that are maintained over for some reason they have a low density lipoprotein in the range of 100, they live longer and present less teratogenic lesions if some are present.

What we see is that the levels of LDL almost return to desirable levels what we want to be in the azathioprine group, and despite

intensification on the statins, they remain at higher levels in the RAD arms.

It is important to understand that statins is a very big confounding factor because statins has other effects, mainly what we should call the angiogenesis effects of these drugs, and to make this a little bit more complex, these drugs has demonstrated to have dual or different effect regarding low-dose versus high-dose in the effects, the lower doses of these drugs being able to stop this angiogenesis, stop endothelial proliferation, and differentiation of migration, or arrest these effects if higher doses have been obtained.

As a matter of fact, in the reversal trial, it was seen that patients that had intensive treatment, this means higher dose of atorvastatin, 80 mg, were able to remain pretty much the same as the baseline. When the treatment not as intensive at this dose, using lower doses, they pretty much

slow, but still there was some progression of atherogenesis.

So, this is very, very important to take into consideration when we look at this data.

Thank you.

DR. HIATT: Thank you very much.

Some questions?

DR. BURCKART: I had two questions. One was relating to your--if you could put the slide back up there--the 24-month serum creatinines, calculated creatinine clearance.

Could you go through your logic again in saying that reversible versus irreversible?

DR. HERNANDEZ: Yes. This is basically a physiological observation. What we have is we have a creatinine clearance calculation. As a matter of fact, it is done by Cockroft-Gault. It is not optimal, but this is what we have.

What I see here is that after 12 months, there was an intervention in patients that had renal toxicity to decrease of cyclosporine, and what is observed after the 12 months, after the

intervention, is that in the azathioprine arm, the calculated creatinine clearance improved and reached the baseline values.

These tell me that whatever vasospastic or whatever changes are there in the azathioprine group may be a reverse if I quiz this.

DR. BURCKART: I thought we had been told that there was no intervention really until before--

DR. HERNANDEZ: Yes. After the 12 months, there was an intervention by amendment 3 in which patients with nephrotoxicity were targeted to decrease the doses of cyclosporine in all patients that had toxicity.

DR. BURCKART: But, in fact, we were told that amendment actually didn't go into place until patients were on at least 21 months on the protocol.

DR. HERNANDEZ: Yes, there is a difference. I just put 12 months, but at the time that the patients reached the 12 months, the last patient reached the 12 months, probably the first

patient was more than 12 months.

DR. HIATT: It is hard to draw any conclusions what TDM would or would not have done given the timing. I mean the real hypothesis here is that an early TDM regimen of cyclosporine would obviate this, and we can't tell that.

DR. BURCKART: The point here is that if, in fact, there was no intervention in terms of changing cyclosporine, then, it's impossible to make any conclusion about reversible versus irreversible.

DR. HERNANDEZ: What I can say is that I wouldn't be so far because we don't have biopsy levels. We don't have biopsies, so we don't see the tissue, but what I can say is that we have better creatinine clearance in the azathioprine group. As a matter of fact, if we don't do an intervention, the tendency over time is to decrease the cyclosporine levels.

DR. HIATT: Let's be careful not to over-interpret that.

DR. BURCKART: The other question is about

statins. I think it was Dr. Barr this morning that made the point that so many of the heart transplant patients get statins even if they are not on TOR inhibitors.

Do you know the information on this patient population in this study as to a percentage that got statins in the everolimus group versus the azathioprine group?

DR. HERNANDEZ: Approximately 90 percent in each group got statins. What we don't know is what is statins.

DR. BURCKART: You say 90 percent of--

DR. HERNANDEZ: Ninety percent of the patients got statin drugs.

DR. BURCKART: In the azathioprine group also?

DR. HERNANDEZ: In both, in all three. But what we don't know is what amount of statins they got.

DR. NISSEN: People should keep in mind that the primary statin that is used in these patients is pravastatin because of the lack of

cytochrome P450 3A4 inhibitor, and usually, the dose is 40 mg. There doesn't tend to be a lot of adjustment unless the people have extreme hyperlipidemia.

DR. MANNON: In the setting of the context of treating hypertriglyceridemia, atorvastatin would probably be the more potent agent if you are going to use a statin as your primary therapy for hypertriglyceridemia, so I think that is an assumption that we can't make.

DR. NISSEN: No, we can't make the assumption. Just keep in mind that there is a fairly standard regimen that is used in these patients. Probably there is going to be some drop in to more potent statins, but it is hard to know how much.

DR. HIATT: Then, there could be further dose adjustments obviously there, too.

Did you want to make a comment?

DR. KOBASHIGAWA: If I might. Statins are my interest. What we know about statins in transplantation is that there are a lot of side

effects and also statins, when they are used with cyclosporine, blood levels are raised about 20-fold.

When you look at enzyme inhibitor concentration levels, looking at bioassay, which we have done in our unit, it is raised about 8-fold, but we are limited by the side effects of statins and calcineurin inhibitors. They cause myositis and rhabdomyolysis.

So, we really cannot go very high levels like 80 mg of Lipitor or 80 mg of simvastatin. In fact, we are limited to 10 mg of simvastatin. Look at some randomized trials with simvastatin versus pravastatin, and if you go beyond 10 mg of simvastatin, you start to get more myositis.

So, to think that you had more higher doses in the everolimus group, that is not going to happen, because you are limited by side effects.

So, I think, as Dr. Nissen pointed out, there are programmed amounts that we start with, like pravastatin, 20 mg, we might go up to 40 mg, but there is a risk by doing that, certainly not go

up to 80 mg of the drug.

So, again, I think it is more than likely--we don't have the data--but more than likely evenly balanced, because we are all up to the maximum amount that we can tolerate.

DR. NISSEN: I guess that was my point, and the other point that I wanted to make is that again, that was my manuscript that was being referred to regarding the pleiotropic effects, that they really are seen with the 80 mg dose of atorvastatin having a big effect on inflammatory markers, and so on, and it is just not done in transplant patients for the reasons that were just stated.

DR. HIATT: Thank you.

I think we have one final presentation.

Everolimus and Cyclosporine Exposure-Effectiveness and Nephrotoxicity Relationships

DR. GOBBURU: Good afternoon. My name is Joga Gobburu. I work with the Office of Clinical Pharmacology and Biopharmaceutics, the

Pharmacometrics team.

My task here today is to summarize the exposure-response, particularly the exposure effectiveness and exposure nephrotoxicity relationships of everolimus and cyclosporine combination.

This review is based upon the expert opinions of Dr. Lee and Dr. Wang, who are sitting in the audience.

The key issue we are dealing with here is whether the benefit-risk profile of everolimus-cyclosporine combination is acceptable or not.

Now, if we were to only talk about risk and have to answer a question is it acceptable or not, simply analysis of even counts of patients would suffice, but we are asking for more than that - what would be an optimal dosing regimen that would balance the benefit and risk.

For that, we need to at least pretend or know what are the predictors of effectiveness and toxicity.

[Slide.]

So, the clinical pharmacology review found that the effectiveness was higher in patients who

had higher everolimus and cyclosporine concentrations.

The review also notes that the nephrotoxicity is not random, it is not just dose related, but it is indeed exposure related meaning patients who had higher cyclosporine and everolimus combination concentrations had higher probabilities of nephrotoxicity as determined by the changes in creatinine clearance.

The sponsor developed a quantitative relationship between the exposure and effectiveness and exposure nephrotoxicity which was further used to project the likely outcomes of a modified dosing regimen for the combination of these drugs to be tested in future trials.

I will not be going into other toxicities that Dr. Hernandez has already presented the oral risk profile of this combination.

[Slide.]

At the end, hopefully, you will have a chance to appreciate the potential outcomes from simulations of this regimen, and the intention is to target cyclosporines during the first month as were observed in the B253 trial, observed, not planned.

Subsequently, the idea is to taper the cyclosporine concentrations faster than was used in B253 trial. When it comes to the everolimus, the notion is to use therapeutic monitoring so as to achieve concentrations either between 3 and 8 ng/mL or 6 and 12 ng/mL.

I will describe now what we did and what we found.

[Slide.]

The only data we used for the analysis was from the B253 heart transplantation trial. As far as the exposure-response analysis, we used the prespecified composite endpoint as far as the effectiveness is concerned, and the sample size used were 201 patients for the azathioprine arm, 387 patients for the combined everolimus arms.

As far as the nephrotoxicity, we quantitated the relationship between exposure and creatinine clearance from base through time zero, post-transplantation through 6 months, so the whole time course of the change in creatinine clearance. Again, these are the sample sizes that were used for both the azathioprine and everolimus arms.

[Slide.]

One might surmise why do we ever want to

understand the exposure-response relationship. Especially for this combination, it is important to understand the exposure-response relationship for the following reasons:

The first reason is its large variability. My next slide shows the variability in the exposures of everolimus between the two doses.

Drug concentrations are indeed believed to drive the effects, both desired, as well as undesired, and that is the reason why we use TDM at least for cyclosporine, and whether it is meaningful for everolimus is under discussion.

There is interaction, pharmacodynamic

interaction in terms of effectiveness and toxicity with everolimus and cyclosporine. So, looking at the 2-dimensional view of the response might confound the effects of the second drug. So, that is why a more sophisticated analysis is indeed needed.

Also, it is important to understand the time course of creatinine clearance. It cannot be ignored, because we are talking about dosing regimens that change over time, so we need to understand how these changes are correlated with the changes in the creatinine clearance.

A further benefit would be to use these relationships to explore other dosing regimens probably to be tested in the subsequent trials, which might preserve the effectiveness, but minimize the nephrotoxicity.

So, is that possible? That is what we have worked on.

[Slide.]

This slide shows that there is considerable variability in the everolimus

concentrations between 0.75 mg b.i.d. and the 1.5 mg b.i.d.

As you can see, the X axis here is the everolimus concentrations, the Y axis is the number of patients, and the red bars are for the low dose, the yellow bars are for the high dose. They are all intertwined quite tightly between the concentrations, so per se, not seeing a dose-response relationship for a particular toxicity might not mean that there is no drug-related effect. It still could be concentration based.

[Slide.]

Now, this slide, you have probably seen already 10 times. It shows, on the X axis, the time post transplantation, and the Y axis shows the cyclosporine.

I want to draw a slightly different inference from this for your benefit. As you see, the three lines here indicate the cyclosporine concentrations in the three treatment groups, but one interesting observation we found was at least

let's say for the first one month, the mean concentrations lie on the lower limit of the target range, so we can only speculate the reason for that.

We are not sure why 50 percent of the patients had concentrations below the current concentration to start with in the trial.

[Slide.]

So, we used the concentrations measured through the trial. Somebody commented there were about 13 concentration measurements in each patient, and we used the composite endpoint.

So, you have on the X axis, the cyclosporine concentration range. On the Y axis is the probability of failure. It is just to remind you the primary endpoint, the lower the number, the better.

So, you see here, that is the relationship between cyclosporine and the probability of failure, and these four lines indicate for the everolimus at 4 different concentrations, 3, 6, 9, and 12 ng/mL.

As you see, at about 250 ng/mL of cyclosporine, you have about 45 percent or so of even trade for the azathioprine compared to about

32 [?] percent for the 3 ng/mL everolimus, compared to 25 percent for the 12 ng/mL, so pushing the concentrations higher than 12 ng/mL of everolimus is going to add benefit, but as you see, there is an influence of the everolimus concentrations in terms of effectiveness.

[Slide.]

It's a similar story, but now it's for nephrotoxicity. Again, the X axis is the cyclosporine concentrations, the Y axis is the mean creatinine change from baseline at month 6.

So, the solid line here, the yellow line is for the azathioprine arm, and as you see, these are the four lines depicting the relationship at different everolimus concentrations.

There are two key points here. One is you see a wide granule [ph] effect for the cyclosporine per se, but when you are going to the everolimus arms, there is about 5 mL/minute difference between

3 to 12 ng/mL through the cyclosporine range.

So, this supports the notion that faster tapering of cyclosporine could probably contribute to more controlled nephrotoxicity.

[Slide.]

So, what we have done is we now quantitated the relationship between exposure and effectiveness, the time point, and exposure nephrotoxicity. So, now given a new regimen that was presented by the sponsor for the protocol, it would be 1.0. This regimen is close to that, it is not identical.

So, you have the low dose everolimus group here, where the intention is to target patients between 3 and 8 ng/mL, and for the high dose everolimus group, the intention is to target patients between 6 and 12 ng/mL.

The first line is the target concentration, cyclosporine concentration for the first one month, which is 200-350 for both arms. That number is derived from B253 observed concentrations, and then we didn't want to touch

that portion because it is believed that that is very important for the effectiveness.

But later, from month 2 to 6 and beyond, there is a faster tapering of cyclosporine that is proposed here.

DR. HIATT: Go back and to clarify that, there is obviously a different base on the everolimus dose, the concentration. You have got it stratified there.

DR. GOBBURU: Yes.

[Slide.]

So, what we did was we have this proposed taper, faster tapering cyclosporine regimen, and we have a quantitative relationship based on the B253 observed data.

So, if we were to assimilate what happens in the next trial, then, what we found was that for the everolimus 3 to 8 ng/mL group, and 6 to 12 ng/mL group, the effectiveness was pretty comparable to that observed. This is for the B253 observed results.

But when it comes to the nephrotoxicity,

the mean change in creatinine clearance is now about minus 2. It decreased by 2 mL/minute at 6 months--this is again a mean, we are not talking about the patients who are probably at higher risk--compared to about 13 and 19 mL/minute at 6 months in the observed trial.

So, this gives us a reason to believe that these two drugs can be used by giving a more optimal dosing regimen to preserve the effectiveness and decrease the nephrotoxicity, but this probably needs prospective testing to confirm this hypothesis.

[Slide.]

So, in summary, the clinical pharmacology review states that the effectiveness is higher in patients who had higher cyclosporine-everolimus concentrations, and the nephrotoxicity is not random, not just dose-dependent, but is indeed exposure-dependent, and that alternative dosing, potential alternative dosing could preserve the effectiveness and reduce the nephrotoxicity that should be tested in prospective trials.

DR. HIATT: Excellent. Thank you. Very helpful.

Questions? Yes.

DR. ABERNETHY: I am still trying to understand the data that support everolimus concentration monitoring. If you go to your second to the last slide, it is unclear to me from that or anything else we have seen today why you are capping the exposure at 12 ng/mL.

I see nothing but no change in toxicity and increased effectiveness. Now, in converse, data we saw this morning, I can't give you the slide, but I came to my own qualitative conclusion that there was a very poor relationship between toxicity and everolimus concentration.

Can you help me with that?

DR. GOBBURU: Well, we actually hope that there will be discussion about TDM for everolimus at this meeting. All I will try to do is present the data, and then maybe that will help you during your discussions.

DR. HIATT: Maybe someone can list it, but there are several toxicities that were dose related.

DR. GOBBURU: That's right.

DR. HIATT: And I just have to go back and pull those out again. Some seem to be not dose

related.

DR. GOBBURU: Yes. That is one of reasons why people might have thought about capping the concentrations at 12.

DR. HIATT: So, maybe this is a more appropriate time to ask a question that I asked earlier. If you were basing these models on therapeutic drug monitoring, what is the compliance with that, and did you test the compliance? Was that 100 percent compliance with TDM, and what if it's not, because, you know, as you saw here, about half the patients were not successfully monitored at that level.

Can you comment on that?

DR. GOBBURU: It's a very good question. In the simulations I showed you here, we did assume

the same noncompliance rate as that observed in B253, about 50 percent, so we, in fact, said that okay, 3 to 8 is the target range, but people could go, in fact, to 1.5 or 16.

DR. HIATT: If you tighten that up, I mean if for some reason you could have better monitoring than what was observed in this trial, does that change your conclusions at all?

DR. GOBBURU: Let me show you a backup slide I have that might help you.

[Slide.]

This is the variability of everolimus exposure from the sponsor's analysis. As you see here, even in our reviews, the total variability is about 75 percent in everolimus concentrations, but if you split them into within and between subject variability, then, they are pretty even, about 40 percent each.

So, narrowing the window, we may need to consider the variability also in terms of the pragmatic, the practicality of achieving that concentration.

DR. HIATT: Particularly, what you can narrow is between subjects, you would hope.

DR. VENKATARAMANAN: So, when given the

patient population, and given the variability in the everolimus concentration, taking 12, 13 data points, do you feel comfortable in terms of coming up with the predictions with your exposure models, how confident in terms of the ability of the model to predict?

DR. GOBBURU: Let me be very clear in my answer. The difference on the purpose, as you heard from Dr. Tracy, these concerns about the use of exposure-response to make a confirmatory decision is different from that you would need to design a future trial.

So, what I presented is scientific basis for choosing a dosing regimen to be tested in the future trial 2310. So, in terms of that, I personally cannot think of any better way to come up with a good guess.

DR. VENKATARAMANAN: It's a question of the number that you have, you feel comfortable in

using that, you would have liked to have had additional points for a better model prediction?

DR. GOBBURU: Yes, I think that is a reasonable collection of sample points.

DR. PICKERING: I have a question that may need to be answered by the sponsor, but I think we were told that nearly half or 40 percent of patients were on antibody therapy, and those patients used therapeutic drug monitoring for cyclosporine, is that right?

DR. SOMBERG: Yes, half the patients were on antibody therapy, but, in fact, although the protocol did not specify the cyclosporine range for those patients, the cyclosporine use was essentially identical whether patients were treated with antibody or not, and all patients were monitored by cyclosporine TDM in all cases.

DR. PICKERING: I was just wondering if they would have lower levels.

DR. SOMBERG: Would you like me to--

DR. PICKERING: No, I will take your word.

DR. BURCKART: I could just comment about

compliance. Did you mean, when you said 50 percent compliance, you were relating to IVUS?

DR. HIATT: No, to therapeutic drug monitoring. That's the number you used from the study, of the number of patients, once they got into that part of that protocol, followed the TDM protocol, was that correct? You might want to clarify. Both of you need to clarify that.

DR. SOMBERG: All patients followed TDM. I think what you were getting at is the number of patients whose values fell outside of the range. I think that is characteristic of all patients with immunosuppressant drugs. The inter- and intrapatient variability you describe, I think is something you would say is typical of most immunosuppressants.

DR. GOBBURU: Yes.

DR. BURCKART: It is not surprising that your initial values were outside the range whereas, later they weren't, because obviously, we don't have enough information about patients to always start them on the right dose, but, in fact,

aggressive therapeutic drug monitoring is in every transplant center, part of cyclosporine therapy, so basically, people are aggressive about getting them into the range, but you just aren't able in the first, initial post-transplant period to do that.

DR. HIATT: Other points of clarification?

Before we go to the open public hearing, I want to ask Paul Oldam, do you have any questions of the sponsor or the FDA? You have been rather quiet all day and I just thought I would give you a chance.

MR. OLDAM: I have a general question. This morning, Dr. Barr presented a graph, a bar chart showing the relationship of cyclosporine, tacrolimus, and the other three medications, and this clearly shows that azathioprine is declining in usage over a period of time from whatever, 1985 to 2004, and Rapamune is coming up slightly.

Why are we looking at it this way? Is Rapamune a viable alternative to using as azathioprine in this study, because nothing has been presented about that drug?

DR. SOMBERG: If I could ask Dr. Barr to come up, and I will make an initial comment. Rapamycin or sirolimus is not approved in this

indication. I think Dr. Barr will comment, and Dr. Starling may also want to come up and comment on why it is gaining increased use.

DR. BARR: As I mentioned earlier this morning, I think that the problem with the data from the era that we were azathioprine based was such that we were concerned with long-term outcomes significantly in addition to acute rejection. That was one of the reasons that there was an immediate gravitation toward mycophenolate mofetil.

The point that you bring up on that one slide that is from the SRTR, over the past decade, showing that rapamycin is increasing is because of this issue that is perceived that this is antiproliferative and is going to have a beneficial effect on coronary disease knowing that that is still a major reason for death long term.

I think that, you know, frankly, here, you have an example, and this is a pure personal

opinion, where you have got a drug that is of the same class, that is being extensively studied and evaluated in combination with a calcineurin inhibitor, and right now all of us clinically, and Rapamycin is being used increasingly in the United States, are doing it really in a very laissez-faire fashion, where we are doing it in the clinic setting for patients who either have breakthrough rejection or concerns with atherosclerotic progression, and we are giving it with prograf [ph] or cyclosporine without the kind of detailed studies that you have seen here.

But there is a 10 percent, as you pointed out, there is a 10 percent use of that drug right now, and that is just at the time of discharge. It is actually higher if you start looking, and we will have more registry information within the next year, but probably it is going to approach 20 percent within the next year or two by the time a patient is one year out.

So, the use of this class of drugs is being used.

MR. OLDAM: Of the five drugs that are here, which are approved? Cyclosporine is approved.

DR. BARR: Mycophenolate mofetil. Cyclosporine and mycophenolate mofetil are the only two drugs that are approved for cardiac transplantation.

MR. OLDAM: So, Imuran is not.

DR. BARR: No, but that was a time-honored old drug that has been used from historical times literally. Before cyclosporine was used, it was basically azathioprine and steroid protocols. Those slides I showed you from the early days when Shumway was first working on this, that is the only drugs that were available along with other, more potent, basically chemotherapeutic agents.

I hope that answers your question.

MR. OLDAM: It does. Thank you.

DR. HIATT: Thank you, Paul. Did you have any other comments for the FDA or the sponsor?

MR. OLDAM: Well, being the new kid on the block, and being in business all of my life, I am

very impressed with the thoroughness of the data that is being presented.

DR. STARLING: If I could make a comment to respond to your inquiry. My name is Randall Starling. I am a transplant cardiologist at the Cleveland Clinic. We have a large heart transplant program at the Cleveland Clinic. We have done 1,200 heart transplants. We follow about 750 living patients in our clinic.

I was surprised recently to see that approximately 150 patients in our clinic are now on sirolimus, and I think that this tendency, as Dr. Barr just mentioned, is growing in the longer term survivors because of a very limited dataset, less than 100 patients. It was published in Circulation a few years ago from a study at Columbia.

It gave some signal of efficacy in reducing cardiac events and transplant vasculopathy. Just on that basis, it has resulted in a rather quick proliferation of the use of the drug, no pun intended, to attenuate transplant coronary disease.

As Dr. Barr said, the concern that we have is a relative lack of knowledge how to use that drug, how to balance it with calcineurin inhibitors

and what really are effective target levels.

DR. HIATT: Does the committee have any other questions for any of the FDA presentations?

DR. NISSEN: I just had a comment. I thought the FDA presentations, all of them were really superb and very helpful, and I want to thank each of the presenters for a lot of clarity and what your perspective is.

Open Public Hearing

DR. HIATT: At this stage of the meeting, although it has been delayed by an hour, we are going to go to the open public hearing. I am going to just read that.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the

context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor or his product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So, I will just turn and ask is there anyone here from the public who would like to make a comment or a statement?

[No response.]

DR. HIATT: Going once, going twice.

Okay. Thank you very much.

Committee Discussion

DR. HIATT: The next phase is a bit more continued discussion. I think before we go into questions to the committee, I would like to try to summarize some things and then ask for just a bit more comment on these proposed trials.

Forgive me if I have got this wrong, but I think what we know is that this drug, everolimus, does beat azathioprine biopsy rejection as part of a composite endpoint. We also, I think, have been shown data that this is probably both dose and concentration related, so higher dose gives you better efficacy.

We don't know whether that effect on particularly that component of the primary, which is biopsy-proven rejection, will lead to better outcomes, such as complete rejection, hemodynamic compromise, and mortality, but the concepts were raised that that might be a reasonable speculation.

So, we are extrapolating a little bit that the benefits that were seen early might be proven

later.

Similarly, this compound may improve or help prevent vasculopathy, and that data was challenged a bit, but if we believe that, we were also told that we might have to extrapolate a bit into seeing the benefits on late cardiovascular events and mortality that one couldn't see early on in the trial.

We also were shown data that both doses of drug worsen renal function, and, in fact, if you just count the numbers--I don't know if this was presented--but those patients going to hemodialysis, 17 on the low dose, 16 on the high dose, 9 on azathioprine, so there is numerically, a few excess endpoints, if you will.

But we are, number one, told that maybe if you can do therapeutic drug monitoring, you might actually mitigate that, and also, we were told that we need to extrapolate it, that worsening renal function may cause worse outcomes, so much like I think we are extrapolating a bit that biopsy-proven acute rejection may translate to a better long-term

outcome, if you can prevent that, if you can prevent vasculopathy, that may translate to a better outcome.

One also has to speculate or extrapolate that the worsening renal function may translate to more kidney failure and end-stage renal disease.

So, I think we found ourselves speculating a bit on both sides of the risk-benefit equation.

I think the other thing that has also been brought up today that really has impressed me quite a bit, is the feasibility of doing these trials and that the sponsor's willingness to do this is to be applauded, and that this has been a very challenging area to do clinical trials in, and given the limitations, that they have done an excellent job in doing those studies.

So, that is where we are at the moment. We are going to go into some questions in a minute, but I think you will notice, and it became apparent to me as we were preparing for this meeting, that other studies have been reviewed by the FDA and, in fact, are being initiated, and we

have been asked to comment on that, but we haven't been given a lot of information until today about what those studies are.

So, I think rather than bringing up those questions later, if we would like to perhaps go back to the slides that were shown on the risk-benefit presentation, Slide 3 and 4, CR-3 and CR-4, there is a European and a U.S. study. Maybe this would be a good time for us to just look at that a bit more.

If the committee has additional questions or clarifications, maybe backup slides around the design of these studies, their primary and secondary endpoints, how robust that is, and I think to help us answer the questions, it might behoove us to know a bit more about what these studies will or will not tell us.

What I would like to do is address those questions and once we have resolved any further discussion around what is actually going forward, then, maybe we could focus our attention on the questions that have been put forward to us.

Does that seem reasonable? Okay.

If the committee has questions about these, we will have a bit more discussion about

this particular trial and then when we are done with that, the proposed U.S. study, so I would like to entertain questions now on that.

DR. PICKERING: Presumably, the sample size, which is I guess not very big, was predicated on the primary outcome, and my question is how confident are you that you would see any difference in the secondary outcomes, or are you expecting equivalence again?

DR. SOMBERG: This particular study was designed for the secondary endpoint to show non-inferiority with the primary endpoint being renal function. This is obviously a much smaller study than the one starting this month in the U.S. This is exclusively a non-U.S. study.

DR. TEERLINK: Then, maybe I misunderstood, but I thought it was said that the study was powered for a non-inferiority for the primary being a change in creatinine clearance, or

did I misunderstand?

DR. SOMBERG: With equivalence being not different than 7 mL per minute.

DR. TEERLINK: Right. So, the power of the study, it is not powered to actually look at non-inferiority between the two regimens in terms of rejection.

DR. SOMBERG: But we also look to see the degree of power would have to not show a difference there. I don't have that number on the top of my mind.

DR. PICKERING: That was the question. What was the power to show?

DR. SOMBERG: The power to show non-inferiority in the 2411 study for the composite endpoint.

DR. LI: The nonequivalence margin for the composite endpoint is the 10 percent. We have about 80 percent power to show. The Certican arm is non-inferior to MMF arm using the 10 percent as the nonequivalence margin.

DR. HIATT: Could you just give us your

name, too, please?

DR. LI: My name is Yuli Li.

DR. PROSCHAN: Is that sample size per arm or total?

DR. SOMBERG: Total.

DR. PROSCHAN: That analysis sounds not plausible with a total of 176 patients, 80 percent power for a 10 percent--

DR. TEERLINK: Especially since the second study, which is 630 patients, was supposedly powered for the same endpoint.

DR. SOMBERG: We will up the statistical statement from that protocol.

DR. NISSEN: Actually, I do understand this, because what should we assume the one-year survival rate to be, John, survival and Grade 3 rejection?

DR. TEERLINK: Whatever they have from their old study.

DR. NISSEN: What I am suggesting is plus or minus 10 percent is actually quite a wide margin for a one-year follow-up.

DR. PROSCHAN: Right. I mean if you are talking about a difference of 0.10, not a relative 10 percent.

DR. NISSEN: That is exactly right, and that is what they meant, and I understood that very clearly. So, the confidence margins around non-inferiority for efficacy are wide. They are much narrower for safety.

DR. HIATT: I think actually the reason to discuss this study, I don't think is so much on the secondary for efficacy, because I think we know a lot about that. I think it is what can we learn about the safety.

This was brought up earlier, but the cyclosporine dose--this is regimen comparator, not dose comparator--what are we going to learn about I guess cyclosporine levels and their interaction in terms of short- and long-term renal function here?

DR. GALLO: Excuse me, can I just clarify one point? I am Paul Gallo from Novartis Biostatistics

I think the question about the power is

because the study is powered for the 10 percent margin, but not under an assumption of equivalence, but under assumption of actually some advantage, and I think that is why we have the power for this sample size.

We have done that actually quite frequently where we feel we have a little bit of an advantage, not enough that it's feasible to run a superiority trial, so, for example, we might say with a non-inferiority margin of 10 percent, if we are truly 5 percent better, we size trials on that basis. I don't know all the numbers, but something like that is what is going on here.

What we are conditioning on is actually a slight advantage.

DR. PROSCHAN: But when you say 10 percent non-inferiority margin, again, you are talking about a difference between the two arms of 0.10, not a 10 percent relative benefit.

DR. GALLO: Right.

DR. PICKERING: Could I ask one more thing? Do you have any sort of European registry

of how frequent the incidence of renal failure is going to be, and is everybody using reduced dose of cyclosporine in the European--

DR. SOMBERG: They are. Actually, Professor Lehmkuhl has the largest experience, if I could allow him to address that. Specific to a registry, we have a small registry that is just underway, so we have no data from that, but the largest experience, which has been presented publicly this spring, comes from Professor Lehmkuhl.

DR. LEHMKUHL: My name is Lehmkuhl from the German Heart Center in Berlin. We did about 1,500 transplants so far. We are taking care of 900 maintenance patients. Certican has been approved by the German Authorities in March 2004, and since then, we have introduced it to our routine protocol.

So far we have treated 35 de novo patients, but it was our philosophy to say that we have to do drug monitoring an to lower, aggressively lower cyclosporine. I published these

data, and there is some more data coming up in December in Transplant Proceedings.

Patients are doing well with this regimen of actually lowering the cyclosporine very aggressively. We have another 140 patients, maintenance patients set on everolimus for the same question, can we do a cyclosporine reduction protocol in these patients to save renal function.

[Slide.]

This is a slide that has been prepared for me to show you we are far more down with our cyclosporine mean doses compared to where the patients were in the B253 study, and actually--is there a slide on the kidney function, as well? This is just the difference between kidney function.

It's clinical practice, I have to say, and what we see is during the first 4 to 8 weeks, renal function deteriorates, but then by months 3 to 6, it improves, and is hear to pre-transplant kidney function, but this only happens when the cyclosporine is reduced aggressively.

This idea is looked at in what we call the non-U.S. trial 2411. It is not a European trial because Brazil is also on-board, and we hope that

we can present some data in I think it's the second quarter of 2007.

We are also doing a study in Germany on maintenance patients where we have gone one step ahead, and we are also lowering the cyclosporine doses in the MMF group, so that the idea is, in general, to preserve renal function by lowering cyclosporine, and we can do it safely.

We also looked at our patients, these de novo patients in the clinical setting with regard to rejection, and we have the advantage in Germany that we place an Emik [ph] system. This is an ECG system where we have telemetric analysis of rejection data every day from the patient, and we are not just relying on biopsy, and we see very low rate of rejection in our patients.

So, we feel very comfortable with using Certican in combination with a very low level of cyclosporine, and see, from a clinical point of

view, no more episodes of rejection.

DR. HIATT: It looks like in both studies, cyclosporine is going to be dose adjusted in the MMF arms, or was not going to be, but you suggested that that might be a reasonable thought.

DR. LEHMKUHL: Sorry, your question again?

DR. HIATT: The question is why not do dose adjustment of cyclosporine in the MMF arm in the European study, and we will come back to the U.S. study.

DR. LEHMKUHL: Yes. Instead of clinical practice to keep up cyclosporine, and there is no data to support this, to lower it in the second step, this would address two questions in one study, so the next step would be actually to look at a lowered cyclosporine in the MMF group compared with a lowered cyclosporine in the everolimus group, that would be the next step, because otherwise, in the one study you are addressing two questions.

DR. HIATT: Sure, I agree. I think it is just the questions about bias seen against the MMF

arm in terms of renal toxicity with the current design.

DR. LEHMKUHL: That is the clinical standard so far.

DR. BURCKART: What are you doing with the statins in the European study?

DR. LEHMKUHL: We are being very aggressive. Everyone is getting a statin. We start the statin early, on the fourth day, and we are using fluvastatin, because we feel that fluvastatin has hardly any interactions compared to other statins with cyclosporine.

We monitor our patients for myositis, for rhabdomyolysis, and CK values. We have a protocol where when we look at the CK values, it may jump up to 5-fold until we react. If it's between 5- and 10-fold, the upper limits, then, we consider withdrawing the drugs responsible for myositis or the rhabdomyolysis, and if it's over 10-fold, then, we forward our patients to the noritis [?] and we do a muscle biopsy.

DR. BURCKART: But you are using it in

both arms, is that right, in the MMF?

DR. LEHMKUHL: Everyone is getting it.

DR. KASKEL: Is it fair to say that your study is the most aggressive decrease in cyclosporine dosing to date?

DR. LEHMKUHL: Yes.

DR. KASKEL: And the rationale for that?

DR. LEHMKUHL: Well, the rationale is when we look at the study results from the B253 at our center, and we discussed it, whether to use everolimus or not, we saw so much benefits or we believed to see so much benefits on the coronary arterial patee [?], that we felt we want to use this benefit, but not encounter the problems, and the study had, at the time it was designed without tissue, drug monitoring, and without lowering the cyclosporine.

DR. KASKEL: There is a historical paper by Brian Meyers from Stanford over 15 years ago, looking at heart transplant patients, and he showed very clearly in an algorithm that the window of opportunity to prevent nephrotoxicity is within 3

to 6 months, so your rapid decrease in cyclosporine has a very good basis.

DR. LEHMKUHL: Actually, it's not a controlled clinical trial, it's clinical and medicine we are doing, and this is something I always look at very critically when we look at studies, because, of course, evidence-based medicine is very important to conduct, and we need evidence, but mostly if we look at the evidence that is being provided by studies, we often see that from the exclusion criteria it is not the real clinical setting we are actually living in every day. It usually accounts for 5 to 10 percent of patients that you actually encounter as a doctor than in clinical reality.

The point I wanted to make was there is a subset of patients where we looked at how far we could go down, and there is 18 patients in whom cyclosporine was less than 200 during the first month, and less than 175 at 1-3, which is the most aggressive lowering of cyclosporine, and we saw that renal function improved even more markedly

compared to the whole group without losing efficacy.

So, the question that needs to be answered and addressed is really how far down can we actually go.

DR. SOMBERG: Dr. Hiatt, I think Dr. Starling has a comment to make in terms of the MMF-cyclosporine combination.

DR. STARLING: Yes, to address your question, Dr. Hiatt, I just wanted to mention that although MMF therapeutic drug monitoring is not a universal standard in cardiac transplant centers, it is adhered to by many centers including our own.

The literature that is out there, which is most extensive in kidney transplantation, has shown pharmacokinetic interactions between a variety of immunosuppressive agents, the mTOR inhibitors, and specifically both of the calcineurin inhibitors that are commonly used, cyclosporine and tacrolimus, as far as achieving what are perceived to be adequate trough levels of mycophenolic acid mofetil, so there would be some reluctance in

designing a clinical trial to be too aggressive in reducing calcineurin inhibitors without simultaneous therapeutic monitoring of the MMF.

DR. DeMETS: Could I ask one more question? The paradigm that is often used in non-inferiority trials, at least in some circles, is you estimate the relative risk of your new therapy relative to the standard, but that is the first part of the question.

The second part of the question is what is the relative risk of your standard to placebo, because you would like to get some idea are you beating placebo or not, so the question is are you confident or are there data--I don't know the field that well--but are there data that would help you estimate the effects of either standard you are using, or the azathioprine, for that matter, relative to placebo, do we know that?

DR. SOMBERG: This is an area in which the placebo-controlled trials have not existed, and the history was azathioprine plus steroids initially, and it was really, I believe heart transplantation

was only performed at Stanford and Richmond, Virginia, until cyclosporine came along, so then it was cyclosporine and azathioprine and steroids, and then after that, other drugs, such as mycophenolic acid or everolimus have been compared to azathioprine, so we don't have that placebo standard.

DR. VENKATARAMANAN: The dropout rate in the 3 mg everolimus dose has been discussed as one of the confounding factors. In the new proposed 2411 study, the MMF dosing is 3 grams per day, and there is already data shown that with the 3 mg MMF dose, you have a much higher dropout than even the everolimus 3 mg, meaning that you are likely to have a lot more trouble in the MMF arm in this new design that is potentially going to confound the overall interpretation of the study design.

DR. SOMBERG: I don't think it will. Three grams per day is the labeled indication for MMF in heart transplantation. When I talked about the higher dropout rates in the MMF study, they were similar to azathioprine.

I just was making the point that the rates in 253 were not unusual, they were quite consistent with what we see, but just as 1.5 had a similar

dropout rate to AZA, 3 grams of MMF had a similar rate to AZA, and that is the way it is labeled.

DR. EISEN: I think that is an important point, that with the 3 mg dose of MMF, there was there was that high dropout rate, but yet in clinical practice, especially with TDM, that was increasingly being used to manage these patients, you don't see the dropout rate.

So, what you see in the clinical trial, you may not see in real practice, and it may well be with real practice with everolimus, you may not see that.

DR. VENKATARAMANAN: Related to that, there are several concentration controlled studies with MMF also. Was that not considered as an option rather than the 3 gram fixed dose of MMF?

DR. SOMBERG: There were discussions about that, but that practice obviously is used in some centers, but not broadly, and it was felt most

appropriate to study it versus the way that MMF is used according to label.

DR. HIATT: Okay. Obviously, drug monitoring may change compliance, it may improve it.

I think, if we could, just go the next slide, which is CR-4, and I think this is probably a little bit more important, because this is the study that has been discussed with the FDA. It starts this month.

Originally, we were asked to dream up a design, but I guess we won't have to do that. That's nice. But maybe it would be helpful if we understood this a little bit more.

I think in the context of answering the questions, does this study design really address the deficiencies that we have seen today, that we would like to have covered, so I want to open it up again to the committee.

MR. OLDAM: Is this a U.S. study?

DR. HIATT: Yes.

DR. SOMBERG: It is a global study, but of

the 630 patients, 350 will be in the U.S. If it was exclusively a U.S. study, it would require 20 or 25 percent of all U.S. heart transplant patients, but 350 of the 630 patients will come from within the U.S.

DR. HIATT: The first question would be on the primary. So, now it's a non-inferiority comparison, not a superiority comparison.

DR. SOMBERG: Correct.

DR. HIATT: I don't have a problem with that, but does anybody on the committee have any questions about that particular aspect of the study?

DR. NISSEN: I just would say that given the size of the study, almost no matter how you power it, this is about as large a study as you could ever ask for in a transplant population, so we are going to get as much information statistically as we are going to get any other way.

So, then the only question to ask is, is it the right arms, and I think, looking at this, it does look like the right arms, but any more

statistical power would be really unattainable, I think.

DR. HIATT: Yes, and I am not asking for that. In fact, I think that is the right thing to do. I guess when it comes to the secondary renal function endpoint, hopefully, we will learn enough about that to show that the safety can be improved. That, to me, is probably one of the key goals of the study, and I would be more interested in discussion on that.

DR. MANNON: Was there a choice about, you know, in the European study, I guess it is 6 months, so is there a rationale for waiting for 12 months? I mean you will have a DSMB, of course.

DR. SOMBERG: No, there absolutely is a rationale, and in discussions with the agency, it is felt that 6-month follow-up after you have reached your final cyclosporine target is appropriate. So, there is where the second 6-month period, the full 12 months comes in.

DR. MANNON: And functionally measured by serum creatinine, I am assuming, or are there

additional markers of function?

DR. SOMBERG: No, that is how it is being mentioned. I mean some interesting points have been made today about cystatin C and alternatives, which we will consider, but as planned right now, it is creatinine and creatinine clearance.

DR. KASKEL: Along those lines, I have to mention this. Currently, in an NIH study looking at chronic kidney disease in a pediatric population, using Iohexol measurements, done over 5 years at 3 separate time points, to get a grasp on how we measure kidney function, and comparing that to creatinine clearances and cystatin C, so I would encourage you to look into possibly, at least for the subcohort, use of these methods, although they are tedious.

DR. SOMBERG: Thank you.

DR. HIATT: If we are speculating that the IVUS endpoints will play out later, tell us again, your follow-up ends at 12 months?

DR. SOMBERG: the basic study is a 2-year study, and it will be extended to provide, not just

for selected patients, but to try to provide as complete a follow-up out to 5 years in as many patients as we can.

DR. NISSEN: I wanted to comment on the IVUS endpoints. I know that traditionally, this intimal thickness measure has been used in transplant studies, but it is really not the most robust IVUS measure.

There are volumetric measures that are actually quite a bit more powerful, and I would go back and look at the 253 study, and I would pick the IVUS parameter which has the greatest amount of statistical power, because that is what we have done in the atherosclerosis trials.

What you really care about is not the one spot that is the thickest in the coronary. What you care about is the total volume of neointimal proliferation occurring on any given regimen.

So, I would argue that if you are using the old endpoint, you may not be using the right endpoint.

DR. SOMBERG: I think that is very fair,

and Dr. Kobashigawa may want to comment. I think as somebody who has tremendous experience with MMF in this setting, part of what I know has impressed him is the fact that this finding was consistent across intimal volume, intimal area, cross-sectional stenosis.

DR. NISSEN: Oh, I recognize it is consistent, but I want you to use the most sensitive endpoint, so you get the most information.

DR. KOBASHIGAWA: Dr. Nissen, I agree. When you look at burden, you are looking at volumetric, and that is actually listed as one of the endpoints. What we do know, though, is when we use maximum intimal thickness, we do have endpoints in terms of outcomes.

We don't have that on volumetrics. We actually do have that when we look at the validation study, we looked at intimal area, we looked at cross-sectional percent stenosis, they do predict poor outcome when we look at certain thresholds.

So, we do have many points, but because the older data did not have the automatic pullback, we don't really have the volumetric data, but

again, I do agree in principle that that is the way to look.

DR. NISSEN: You don't want to get locked into an archaic method of analysis, because that is how people started doing it, you know, 15 years ago. If you really want to be able to make the case when this study is done, that everolimus in this regimen is an effective regimen, then, you really do want to look at the most sensitive endpoint.

I am not sure how many patients you are going to have IVUS in but if you are at any level of statistical power, the more information you can get, the better.

DR. KOBASHIGAWA: I agree.

DR. HIATT: Are there other questions or comments?

DR. SOMBERG: There may be just a few things I want to comment just to make sure

everybody knows the types of things we are trying to answer, because in many ways, this is not just being done to confirm the results that we have shown today.

We think, for a variety of reasons, we do show a compelling benefit-risk and that the clinicians feel quite comfortable they can move forward, but it extends this in a few ways.

One, we are looking at two different concentrations. As I mentioned, in the renal study, we saw that when we use less cyclosporine, patients did have a better safety profile, so both the 3 to 8, which we are recommending, and somewhat overlapping, but higher exposure, 6 to 12 is being studied, and also we are taking the opportunity, consistent with the FDA's modeling, to go down a bit lower on cyclosporine, to try to even further enhance the renal picture.

The other thing I want to point out is again, as has been mentioned several times, it is hard to do these studies, it takes a long time. These data won't become available until early 2009,

so a submission and review, if successful, would lead to a drug being available at the end of 2009 or maybe early 2010.

One of the clinicians may want to comment in terms of that timing versus some of their patient needs.

DR. ABERNETHY: If I could just ask a question, I think to anyone, but the higher everolimus trough concentrations, I believe I understand why they are there, but I am trying to think of how this study can go wrong, because you don't want to invest what you are going to have to invest and then take a risk of that.

So, I guess I am convinced that there are concentration-related everolimus toxicities, perhaps thrombocytopenia, I guess. If that is the case, then, kind of how does it proceed as early in the trial that arm has an unacceptable toxicity?

DR. SOMBERG: There is a Data Safety Monitoring Board, and I guess the decisions become whether, as has happened with tacrolimus and its registration or other programs, the concentrations

need to be lowered or whether it becomes clear that that is not an acceptable arm, I guess those become two potential options in terms of how that trial might need to be altered if things don't go well.

DR. ABERNETHY: I am just having this concern that you are kind of in the unknown there, and here, it seems like we are really trying to learn as best we can the dosing of everolimus. I guess what I am sort of saying is you are changing two things at once here. You are doing a more rapid decrease of cyclosporine, and you are upping everolimus.

DR. SOMBERG: I think you are absolutely right, and I think one of the problems here is the limited number of opportunities we have to answer critical questions. In the briefing book, one thing that I think both supports the likelihood that the IVUS effect is real, and is potentially very meaningful, is higher exposure to everolimus seemed to be associated with even lower incidence of vasculopathy.

The study Scientific Committee that helped

us design this study, several of which are here today, felt that was an important reason to have the 6 to 12 mm group, but anytime you have--there is a variety of issues that can come up, if there is really truly adequate separation, and do the safety issues come into play, and I will certainly spend more time considering that. I thank you for that comment.

DR. TEERLINK: Will this study be able to be stopped early for efficacy? If so, I would strongly discourage you from doing that.

DR. SOMBERG: There is certainly no plan that is not the plan we have.

DR. HIATT: Actually, that is a great comment. If we really I think are struggling with toxicity issues, and you have early stopping rules, you will miss that. So, I think I would second that.

DR. SOMBERG: No, there is no plan in the DSMB charter to do that.

DR. PROSCHAN: I was wondering how you determined what margin is important, I mean what

margin is really not inferior. I mean how did you make that determination?

DR. SOMBERG: In terms of the sample size calculation?

DR. PROSCHAN: Right.

DR. SOMBERG: It is an interesting question and one that I think needs to take into consideration how often an event occurs, as well as almost in sort of a utility analysis, talking to a large number of clinicians in terms of what would be clinically, meaningfully different.

Obviously, a 10 percent margin for an antibiotic with a 99 percent cure rate would certainly not be acceptable. Here, we have 10 percent has been a tradition in transplant in a variety of studies, and actually, I may have misspoken earlier.

Actually, for efficacy in this study, it is 13 percent, which is related to the fact that that is sort of the same kind of relative risk in heart transplantation given its higher risk of rejection as compared to renal. In a lot of

discussions with clinicians in terms of what difference would bother you, what difference would be clinically concerning or meaningful.

So, for rejection, it was in that 13 percent range, and when we talk about renal function, it tends to be more in the range of about 10 mL per minute.

DR. EISEN: I guess I just want to make a comment again as a clinician. We saw many different adverse events that occurred in the setting of this trial, and I guess the way that I would phrase it is kind of welcome to transplantation, that this is something whenever you go into transplant clinic and see patients, you see these sort of things all the time, and they really are manageable. If they weren't manageable, you wouldn't have the survivals that we have, and this is with the approved medications that we have and with the off-label medications that we are increasingly using.

But the reason why we are using medications off label, is because the medications

that are approved really don't provide us with the benefits in terms of reducing rejection or reducing cardiac allograft vasculopathy.

We are not sure that the off-label drugs do, but we really have no choice. So, I think that we have things that can favorably affect the biggest problems we have, which are cardiac allograft vasculopathy and rejection, I think we are willing to accept some of the adverse events we have seen, because we see them anyway. This is just part of what we do on a day-by-day basis.

DR. HOSENPUD: One other comment. In responding to Dr. Teerlink, I think that the issue with regards to stopping a study too early is a critical one, but at the same juncture, that is why we have the 30 percent dropout rate.

We are not going to let a patient do badly. As Dr. Nissen said, these patients are precious to us, and so if a patient starts having rejection over and over again, and we have a patient in a blinded trial, that patient is probably going to be pulled, and that patient is

going to drop out. If you look at study, all 4 of the randomized trials in heart transplantation, they all have a 30 percent dropout rate for exactly that reason.

DR. DeMETS: One of the things I would hope you would address in both of the new studies is this issue we just discussed, that off treatment doesn't mean off study.

DR. HOSENPUD: Agree.

DR. HIATT: I think we are actually approaching the questions to the committee, and in order to do that, we need to get little setups. We will take a five-minute break or so and we will get to the questions.

[Break.]

Questions to the Committee

DR. HIATT: This part of the meeting will be basically the committee discussing the questions, and I think that if we have any questions for clarification either from the FDA or from the sponsor, we will ask you, so please be prepared for that. Otherwise, most of the

conversation will be within the committee itself.

If we could post these questions, I think we will just go ahead and get started.

This is the first question. This is a rather straightforward question.

Novartis has presented the results and extensively discussed the use of a "fixed-dose" everolimus regime with "full-dose" cyclosporine in B253. Both FDA and Novartis agree that this exact fixed-dose regime should not be used for the prophylaxis of organ rejection in cardiac transplantation.

Do committee members agree with this conclusion?

Paul, I am going to start with you.

MR. OLDAM: From what I have seen, I agree, yes. I think we have to be careful, if we went forward this way, how it is all administered, though, in view of the risks involved with toxicity and whatever.

DR. HIATT: So, your vote is yes, you agree.

MR. OLDAM: Yes.

DR. PROSCHAN: Yes.

DR. MANNON: Yes.

DR. HIATT: Yes.

DR. BURCKART: Yes.

DR. TEERLINK: Yes.

DR. ABERNETHY: Yes.

DR. VENKATARAMANAN: Yes.

DR. CUNNINGHAM: Yes.

DR. NISSEN: Si.

DR. PICKERING: Yes.

DR. KASKEL: Yes.

DR. DeMETS: Yes.

DR. HIATT: That was easy. On a roll.

This is a bit of a tougher question.

Novartis has proposed an alternative TDM-based regime for the use of everolimus in combination with cyclosporine. The proposed regimen has not been prospectively tested in a cardiac transplantation study.

In the absence of a prospective study of this regime, do committee members believe there is

sufficient information available to conclude that the regimen as proposed by Novartis has been demonstrated to be safe and effective for use in heart transplantation?

Now, you see there are several components to this question that come later, but I think that what I would like to do is first get a vote and some clarification and comments on the first part of this question and then we will turn to the other components.

Before we do that, I would like to ask Dr. Albrecht if you could please clarify some of the concentration discrepancies that you have come up with.

DR. ALBRECHT: I will. What I actually noticed during the presentations, and I wanted to bring this to your attention so that as you discuss this and vote on this, you can give us some direction and guidance as to the following.

I don't know if we will be able to post all these slides, but let me just start with the following.

Dr. Hunsicker, in his presentation slide CN-26, said that the first month recommended concentration for cyclosporine is 250 to 400

nanograms per milliliter. Then, however, when we heard about the actual exposures during 253, in other words, the proposal was that the first month exposure would be what it was in 253, we heard from Dr. Gobburu, in his Slide No. 10, that the actual exposure was 200 to 350 nanograms per mL.

We then, during the discussion of the European or Study 2411, as well as 2310, heard that the first month range was proposed to be between 200 and 350 nanograms per mL, and in Dr Hernandez's Slide No. 18, you saw that during the first month, there were some differences already seen in the creatinine.

So, what I just wanted to ask the committee is when you talk about the TDM, and depending on your recommendations, can you also tell us what you would recommend in that first month, whether the 250 to 400, or whether, in fact, the 200 to 350 range would be targeted.

DR. HIATT: Do we need to have some clarification on that? Any clarification, we will just invite that now.

DR. SOMBERG: The proposal we submitted was 250 to 400 based on what was recommended in the 253 protocol. In fact, the sponsor would not

object if the committee's recommendation is 200 to 350, which is more reflective of that, that was actually achieved.

DR. HIATT: Okay. Thank you.

Before we go to (a), (b), and (c) of this question, we will start on the other side of the room, David, if you could give us your vote on this question and any commentary you would like to make.

DR. DeMETS: I think my remarks would be that at this point I am not convinced. If you asked me would I vote, I would probably vote no, that it's absolute, because I think the modeling that this is based on has a lot of caveats to it, and we haven't really, you know, the data we have suggests that it is effective and there are safety problems. We don't have any data in this range,

and the rationale it is based on is--I mean I can't think of anything better to do than what was done, I would commend all those who worked on this.

But if you asked me am I convinced that it is safe and effective, the answer is I don't know that, so I would vote no. I guess I view that the answer is in the two studies that are proposed, but on the other hand, the problem that I can't resolve right at this moment is that is five years down the road, and what do we do in between.

But if you ask me am I convinced, the answer is no.

DR. HIATT: Okay. Let's keep going around the room. Fred.

DR. KASKEL: I would agree. My answer would be no at this point, insufficient information, and we will talk about that more.

DR. PICKERING: I guess I would give a very qualified yes. Intellectually, I am not really convinced. There is a lot of extrapolations here, but they seem to be reasonable, and if there was not going to be a study that will give us the

answer, I would definitely have said no, but it looks as though there is going to be a study, and I think that is terrific news.

I would be concerned that between now and 2009, or whenever it is, if we say no, everolimus is not available for off-label usage in this country, unlike a lot of the other agents that are currently being used on the basis of even less data than is available for this drug, so I guess I would vote yes.

DR. NISSEN: I am going to explain what my thinking is here. First of all, I tend to view this as an orphan disease. I mean I think we have had other drugs like this here.

I recall a discussion we had around bosentan for pulmonary hypertension, and a drug that had a lot of toxicity, but was used to treat a disease which there are limited numbers of people that have it, the prognosis for which is very bad, and where an advance in therapy has the potential to do a lot of good.

I am convinced here that there is a

potential for everolimus-based therapy to improve outcomes for patients with transplant disease. Why am I convinced? Because I understand that late survival in transplantation is tightly linked to the development of vasculopathy, and that while these studies were too short to have any chance to show us how that would translate to a survival advantage, there is enough evidence from the studies that have come from two separate groups to suggest that IVUS-measured transplant vasculopathy is closely correlated with morbidity and mortality, including mortality, including the hard endpoint of mortality.

So, I am inclined to lower the bar for this drug in a way that I wouldn't for many drugs, and there are several other reasons why I am inclined to lower the bar.

First of all, this drug is not going to be used by family practitioners. People who treat heart transplant patients are highly sophisticated. They understand immunology, very limited population, highly specialized centers where

clinical judgment has to be applied in choosing regimens.

You heard from Dr. Starling, who heads the world's greatest cardiac transplant center, and he said that 150 of their patients are on Rapamycin, are on sirolimus on the basis of what clinical trials.

So, here you have some very sophisticated people using an agent in this class essentially off label, and there has not really been particularly robust findings, but there is enough of a belief that they do that.

We have a sponsor that has done what would seem to be an almost impossible study. You know, if you had asked 10 year ago could you study 600 patients with cardiac transplantation out of the couple thousand that get treated every year, it is very challenging.

So, I have to give them points for taking on an extremely difficult challenging problem.

I do not want to set an unduly high burden for advancing the field when you are dealing with

an orphan disease and one that we know leads to the demise of patients over a period of time with a very high mortality and morbidity rate.

So, given that, I am really having a difficult time answering the question, because it may be that waiting until 2010 to have this therapy will harm more patients than might be harmed if we approve this drug to be used without perfect information.

We don't have perfect information, I will be the first to tell you that, about how to dose it. But I suspect that in the clinical setting, there will be additional work done.

So, for all the reasons I stated, because of the orphan disease, because of the fact that it is a rapidly evolving science, and because of the fact that drugs in this class are already being used off label, I am going to vote yes.

DR. CUNNINGHAM: I agree with everything you just said, Steve, but I am going to vote no, because the question asks me if I believe that the drug has been demonstrated to be safe and

effective, and it hasn't been demonstrated to be safe and effective, however, I do really wish to--and I am speaking as a representative of the people, consumers, in general, who do expect that we will have the knowledge that drugs will be safe when they are taken.

So, speaking from that perspective, I think we don't know for sure although I really do want to commend the sponsor. I am really impressed with what they have to offer, I am impressed with the fact that they have already got the studies lined up and ready to do.

I think that there is hope that some people in the country will have access to this drug even though it may not be approved, or it may or may not, but there will be this study going on, and it's starting.

I think that is terrific. I think there is great hope in the prevention of the vascular problems. So, I really look forward to the approval of this drug in the future if it is shown to be safe.

DR. VENKATARAMANAN: This is a difficult patient population to study, and the sponsor has done a lot of work in terms of the clinical

pharmacology. Dropout rates that are seen are typical of this patient population, and the drug has shown effectiveness both in terms of allograft vasculopathy and the rejection.

If it is a me-too drug, I would definitely ask for additional safety data. Given the need for such a drug, and what is currently used, without clinical data, a non-approved drug, I have to say a qualified yes.

The qualification comes with the fact that there has to be definite follow-up studies as planned, and also more aggressive follow-up on the renal and the lipid profiles, so that we better understand the mechanisms of what is going on.

DR. ABERNETHY: I would have to say that my thinking is very consistent with what I am hearing all around the table. I think that linked to the Phase 4 study that has been outlined, that I can vote an uneasy yes.

DR. TEERLINK: I concur with many of the underlying assumptions that have been said and still probably vote the other way, not surprisingly.

First of all, is this an orphan disease? Yes, it is in some regards, but we do have

mycophenolate, which was approved, and unlike the PAH symptom where you had only an IV available drug, so now I am not sure we are in the same kind of orphan arena. We actually have agents that are working and have gone through an approval process, as well.

Normally, and also just because physicians are using a drug in a similar class with no data doesn't necessarily suggest that we should be using it. I would remind folks here that there was an acute heart failure drug that was recently approved because people were using noranone and dobutamine, which were hurting people and things, and we needed to reach for that.

So, I think until we see a little bit more, it is important. So, what do we have here

with this trial? Well, normally, we ask for two trials, and obviously, we are not doing that in this case.

Normally, we ask for hard endpoints of clinical events, and don't accept surrogates. The only surrogates that have been accepted traditionally are LDLs or millimeters of mercury, and that is based on hundreds of thousands of patients, not small groups of 50 patients followed for some period of time, 100 patients followed for some period of time.

In general, the other surrogates are felt to be not acceptable because they rarely reflect the composite and comprehensive effect of the drug. They look at a very small segmental aspect of the drug and try to interpret an impute a general clinical benefit from that.

I think there have been a number of exercises that have been dangerous in that regard.

Also, composite endpoints are generally evaluated on the basis of the validity of the data collection and on the relevance of the clinical

events. Clearly, there were some relevant clinical events that were evaluated by the composite, such as death, graft loss, and those items, none of which were at all different.

So, then, I am left with it be changing solely on the basis of the rejection, and they present some very nice slides saying that this should cause a decrease in MACE, and I was ready to believe that, and the time course of that decrease in MACE was within the time course of this trial data. Yet, I didn't see anything different.

So, when I have a patient in front of me asking me why are you using this drug as opposed to one that has been like mycophenolate, that has been approved and things like that, what benefit am I am going to get out of this?

Can I say you are going to live longer? No. Can I say you are going to feel better? I don't see any--you know, there are no symptom things, there is nothing that suggests that. In fact, there is an increase in infections.

Can you reduce side effects? I don't see

any side effects being reduced by this consistently enough across the board to provide a benefit to the patient.

There is this proposal that there is a long-term benefit by reducing coronary vasculopathy. I think that is very important, but as of yet, I don't see any data from this trial, from this experience, from the global aspect of the patient to show that that has an effect.

So, because of those reasons, I think it is an extremely positive hypothesis-generating trial and I look forward to seeing what the next trials show. So, I vote no.

DR. HIATT: Dr. Burckart, you can comment, but you can't vote.

DR. BURCKART: Thank you. I appreciate the opportunity to comment.

DR. HIATT: Sorry, Dr. Burckart, you can vote.

DR. BURCKART: I first want to compliment the Division of Clinical Pharmacology of the FDA on the excellent job that they have done. They really

have been very thorough I think in going through the information and certainly pointing out all of the problems that go along with a very complex patient population and trying to do a very highly controlled study.

At the same time, when you work around transplanters and work around transplant patients, I think you do get, and I would echo Dr. Nissen's comments, and say that you realize what some of the difficulties are with this patient population, and trying to move ahead from where we are now, particularly in the area of the vasculitis or chronic rejection and other transplant of organs.

The IVUS studies weren't perfect, but, in fact, I think they do show promise that we may be able to do something about the inexorable decline in patients over time that was pointed out so clearly by Dr. Barr this morning.

When you are around transplanters, and you have been around therapeutic drug monitoring now, Venkat and I worked I guess in 1982 when cyclosporine first became available in Pittsburgh,

but therapeutic drug monitoring was initiated at that time, and is really a complete part of any transplant program now, whether it be for cyclosporine or tacrolimus, and maybe for mycophenolic acid, so I see no problem in integrating therapeutic drug monitoring for this agent in a transplant population, and have complete confidence that it would be adhered to very strictly by people, particularly when they are using it in a patient population like the heart transplant patients, and knowing the people that we have to manage those patients long term.

So, I would definitely vote yes.

DR. HIATT: Thank you. I think my comments are, as you get around the room, things start to echo each other I think a little bit, but clearly appreciate the challenging nature of the patient population.

I think I agree that in the back of my mind they have been an orphan disease status to some degree. I also was impressed with how background therapies have changed, I think the

statin effects have probably raised the bar for everybody and improved outcomes somewhat.

It is also clear that there are alternative therapeutic regimes here, so I don't think that we are denying patients, you know, just one course of action.

When you go to this question, my first comment is I think the effectiveness, in my mind, is pretty convincing, so I don't feel that more studies need to be done. I think we will learn more as you monitor levels in terms of efficacy and outcomes, and maybe you can optimize that and maybe the low dose regime by a dose adjusting will start looking like the 3 mg regime did.

So, I am not convinced that we need more data for efficacy, but I do believe that the safety concerns have not been addressed, and I think that therapeutic drug monitoring, whether that can correct that or not, I think is speculative, and I think drug safety is a big problem in cardiovascular medicine and in all branches of medicine.

So, because of the unresolved safety concerns, not efficacy concerns, I am going to vote no.

DR. MANNON: My comments will mirror the rest of the table. My vote is no. The reason is I think that the question really links again the issues of safety and efficacy, and I agree that to me, this does appear to be an efficacious regimen, but the issues of safety remain in question, and I am not talking about the issues of hyperlipidemia and leukopenia and thrombocytopenia, because as a transplanter, I accept those, and I think my patients accept those because of the better quality of life.

In the case of transplant in hearts, there is no backup therapy like dialysis. So, I am basing this solely probably on the renal failure outcome, and I think that the impact of renal failure in this country in transplant has been underestimated until Ojo's paper came out, and I don't what the impact, whether there will be significant and substantial reversibility.

We don't have sufficient data from this data to let us know whether there will be ongoing improvement. I think the follow-up studies will really help to answer that, as well. So, again, my vote is no.

DR. PROSCHAN: I also vote no. I am

concerned about the safety, but moreover, I don't think the IVUS results are very convincing at all, and I think that Novartis has done a good job to try and battle the problems that you have, but I think anytime you have 67 percent missing data, you know, Harry Potter couldn't do magic and convince me no matter what you do.

I think when you have that much missing data, and when there is a lot of evidence that suggests that it is not missing in a random way, so I am not convinced about long-term benefit because I am not at all convinced about the IVUS results, and I am worried about safety, so I would vote no.

MR. OLDAM: This appears to be a very, very effective drug, but being a victim of kidney failure myself, I am concerned about the risk, and

I would vote a qualified no. I would like to see this all tested and finally approved with the risk eliminated or at least reduced.

DR. HIATT: It is a rather split decision. It is about 8 to 5, 8 No, 5 Yes.

I guess before we go to this, does anyone want to make any comments about what Dr. Albrecht raised, the yes's about what levels you would want to achieve? Do you want to hear that or not?

DR. ALBRECHT: Yes, we would like to hear that.

DR. HIATT: I can't answer that question, but I think those who voted yes might make a comment.

DR. ALBRECHT: Could you perhaps link that to Question (a) also, or caveat (a)?

DR. HIATT: Sure. These are more discussion points really.

DR. NISSEN: Perhaps what we ought to do is just discuss whether we think there is any advice we can give to the sponsor and to the agency about these trials that are going to go forward.

DR. SOMBERG: Recognizing some of the comments made in the voting had to do with concern about renal function, and with Question (c) that

was posed, we did an analysis that looked at the outcomes in patients with the worst renal function at baseline compared to those, and I was wondering if that might be valuable to show to the committee in terms of whether or not there would be a relevant subgroup that may affect people's thinking.

DR. HIATT: I will put that to the committee. Does anybody want to hear more? Yes, okay.

DR. SOMBERG: This is an analysis that was done in response to seeing what the questions were, and we looked at patients based on their baseline creatinine clearance, and they were divided into quartiles.

[Slide.]

The lowest quartile--again, this is in baseline renal function as shown in purple at the bottom with the other three quartiles above

that--and what this looks at is the risk of developing severe renal dysfunction or a creatinine clearance less than 29 at 12 months based on the renal function that you have coming into the trial.

What one can see is the risk of developing the severe renal dysfunction is much, much greater, almost 75 percent in those who had creatinine clearances less than 50, that is what the bottom quartile translated into, as compared to those who had creatinine clearances greater than 50, so quite a big difference in renal outcome based on your baseline creatinine clearance.

Obviously, the flip side to this question is what about efficacy, is efficacy really different if you separate out those groups, and the answer is it is not. If one looks at the primary efficacy endpoint here, it was not different between the groups based on their renal function.

So, I offer that to the committee.

DR. TEERLINK: Is this only in the everolimus-treated patients? Maybe I am missing it. Are these only everolimus-treated patients, or

is this all?

DR. SOMBERG: Correct, no, everolimus-treated patients. But on the first one--I am sorry.

DR. TEERLINK: The first one? Can you go back to the first one?

DR. SOMBERG: I am sorry.

DR. TEERLINK: So, which group of patients was divided into four?

DR. SOMBERG: I will ask Kevin, who did this analysis, to explain it. We also have the data based on patients that were solely in the everolimus group. I think I put up the wrong slide.

DR. MANGE: Again, it's Dr. Kevin Mange from Novartis.

[Slide.]

This isn't everybody. This is all the study subjects, so this is their baseline creatinine clearance.

DR. HIATT: What it doesn't help obviously is that therapeutic drug monitoring would take

people in the lowest quartile regardless of their treatment, and it would somehow modify that bad outcome.

DR. NISSEN: But what he is suggesting, Bill, is that it would be possible, if we had voted yes, to say that the drug should not be used in patients with a creatinine clearance below 50.

DR. TEERLINK: Actually, I am not sure we even know that from this, if it's just as effective in the primary endpoint. These may be patients who will develop renal failure no matter what you do.

DR. NISSEN: But the safety/efficacy balance is potentially affected if there is a group that is particularly vulnerable to the effects of the drug, that can be informative in terms of a label to clinicians, and they are arguing here, whether you agree with it or not, they are arguing that the upper three quartiles do pretty well at maintaining kidney function compared to the lowest quartile, and that they are suggesting a strategy, if we wanted to go forward with this agent, that would initially approve it, but not for people

whose creatinine clearances were below 50 at baseline.

Now, my guess is that physicians who practice this transplant medicine would probably almost automatically do that, but one never knows.

DR. PICKERING: Did you have patients in the azathioprine group with that degree of impaired renal function at the start of the study, and if so, what happened to them?

DR. SOMBERG: First of all, for the point of this analysis, yes, patients who had a creatinine clearance less than 29 at the beginning, so they had essentially already achieved the endpoint, were not included in the analysis.

This slide that is up currently--I am sorry, the initial one I didn't realize was all patients--this slide breaks it out into, it is just for the 1.5 mg group where again you see the patients with the best renal function continue to do quite well.

Those in the bottom quartile at the outset do quite poorly.

Similarly, for azathioprine, on this next slide, which I think is your question.

[Slide.]

The azathioprine patients also do poorly if they have bad renal function going into that.

DR. HIATT: Of course, you could flip it and say why do TDM if you have good renal function at baseline. You could use the same argument to do that.

DR. PROSCHAN: The second slide that you showed, could you go back to that one? Not this one, not the one you just showed. Yes, this one. So, this P value here is a global comparing all four quartiles?

DR. MANGE: Yes.

DR. TEERLINK: This is azathioprine plus everolimus.

DR. HIATT: Now, we are back to the questions to the committee. I think we will just try to take these (a), (b), and (c). Maybe, Paul, we will go back and start with you, and if you feel comfortable answering those, but from what you have

heard today, you voted no, you might just kind of go through those if you can. These are just discussion points.

MR. OLDAM: With my limited technical knowledge, that is a very difficult question for me to respond to.

DR. HIATT: That's fine. Why don't we keep going.

DR. PROSCHAN: Well, with my expertise in statistics, that is also difficult for me. What I would say is, you know, the evidence presented suggests that TDM might be very effective, but I would want to see a clinical trial to show that.

Some of the simulations that have been done are suggestive. I am talking about just (a) here. I think there has been evidence to show that this might be a promising avenue, but I would want to see a clinical trial.

DR. HIATT: I think while you are at it, why don't you just comment on (b) and (c) if you can.

DR. PROSCHAN: The answer is no to (b). I

voted no to the first question, and I would say it has not been shown safe and effective for all cardiac transplant recipients.

Again, I think there is no question that they have shown that there is benefit on acute rejection. I still have doubts about the longer term effects, because I definitely have doubts about the IVUS results, and I also have a lot of safety concerns.

Now, certain subgroups, I don't know. To me, I can't really say right now. I don't know if there is really enough information to say that. I doubt that I would say okay, in this subgroup, it's okay to do it, and this other subgroup, it's not. I don't think I have enough information to know.

DR. MANNON: Since I voted no, I think I can't answer (a), what information supports it, and I think no again for (b). As far as subgroups, I mean they just showed us some interesting information regarding GFR.

I mean I think the thing is you are sort of limited in this population, if you have got

Stage 4 CKD, to come in with a GFR below 29, almost everybody is going to be on cyclosporine anyway. So, is this going to propel and make things worse potentially, so I might be willing to consider restricting very severe Stage 4 kidney disease, if you are dialysis-dependent already, it probably is irrelevant.

Where Stage 3 is going to be, I think is the population that we saw a big effect on. As far as things like hyperlipidemia and anemia patients coming in, I mean those patients might be that way from their baseline disease, I don't think that that should be a limitation.

Thrombocytopenia may be more difficult to deal with, but presumably, it is drug related, and not an immune-mediated thrombocytopenia, so I don't know if I have to get that specific.

People with GI bleeding, I think we saw an increased risk of GI bleed in the study groups with everolimus, so that needs to be accounted for. I couldn't really see any other risk for pericardial effusion other than being on the study drug

necessarily.

DR. HIATT: I will follow up on that, too. I think the TDM regimen looks very promising, but its imputed safety effects haven't been shown, and need to be shown, and that was my major concern.

The subgroup question, I don't think we can answer that. Blacks metabolize it differently, and there would be some dose adjustments there. There weren't a lot of women studied, and there may be some limitations there.

On the other hand, back to the kind of orphan disease discussion, you take what you get, that's who these people are. I don't think I would go into a subgroup approach. I don't think the numbers will be there to support that.

So, nothing jumps out at me that would say that once you have established what the TDM is, that this shouldn't be something that all patients get, and because of the expertise and nature of the physicians taking care of these patients, I would leave it up to them to deal with any kind of heterogeneity across responsiveness. I don't think

we should try to go there.

DR. BURCKART: I thought the information that it established the lower end, the 3 nanogram per mL was pretty good in terms of biopsy-proven acute rejection, and then on the upper end, you have to choose some toxicity, and in this case, they chose thrombocytopenia, so I thought that was reasonable.

That is probably as good as any therapeutic range gets, realizing that a therapeutic range is an estimate of when most patients are going to do well.

In terms of the safety related to therapeutic drug monitoring, since there wasn't a relationship between renal impairment and drug concentrations, then, I am not sure what you are looking for there. Additional study is not going to make that happen when it is not there already.

I think it has shown effectiveness certainly in the ranges that have been studied, and I applaud the company in adjusting the range in their proposed study, because, in fact, if you are

going to be adjusting cyclosporine, with any of these immunosuppressor regimens, it is not one drug or another, but basically, a composite that perhaps, I mean maybe the therapeutic drug monitoring should, in fact, be more of the type of thing being done by XDX, where you are monitoring peripheral blood and monitoring lots of different things by using genomics.

In terms of special patient populations, the company has already looked at patients with hepatic disease in which dosing would have to be altered. In terms of African-Americans, I think that maybe needs to be included under Question 3 when we talk about changes or things that ought to be done in a study, such as pharmacogenetics, you know, things that are obviously different between African-Americans and Caucasians.

DR. TEERLINK: Briefly, I think you have a great amount of data to help guide you in terms of the TDM program, and for me, I am actually looking at this as a combination of a strategy treatment, so you use your information that you have to adjust

to your CSA doses, as well as to follow the everolimus doses.

Otherwise, you know, the reason actually I think this is important is to show that this new strategy is, in fact, safe and effective, and that you don't lose efficacy by some of the changes that you are doing, and that you do, in fact, benefit safety, and then the same comments in terms of subgroup analysis.

DR. ABERNETHY: With regard to the TDM question, I think that this proposed or this study that is about ready to get up and going should give a lot of information with the higher targeted range that is going to be included in that. At that point, one will simply have to see the data.

I guess my gut feeling is that TDM had already left the station, it is going to happen with this drug whether it makes any sense based on data or not, but one will have the opportunity to look at a much wider concentration range and come to some conclusion about whether that is the right way to go.

With regard to all patients versus subgroups, I feel like we simply haven't seen enough data. To flash a few renal slides in front

and try to make some evaluation, I don't feel comfortable at all in doing that.

I would assume the sponsor and the FDA would look at that data really carefully and just see if there is enough there to make specific thoughts or recommendations, and would certainly trust them to do that.

With regard to certain subgroups, there have been some mentioned. I really haven't seen enough data in any particular group to make a recommendation other than I think one would treat all groups and then look carefully at this next 600 and some patients, and then perhaps begin to develop the database to say whether that is appropriate or not.

DR. VENKATARAMANAN: There is large variability in the pharmacokinetics which is obvious from significant overlap in terms of trough levels both at the 1.5 and the 3.0 mg dosing, so

fixed dosing is not appropriate, so levels would minimize any potential pharmacokinetic variability from one person to the other.

The document that is presented has some information suggesting that at least 3 nanogram per mL is necessary for efficacy, and 3 to 8 nanograms seems reasonable given that we don't have any specific measure other than perhaps some of the side effects for the upper limit.

So, concentration-controlled trial of this nature would definitely be much better than a fixed dosing regimen.

In terms of effectiveness, I don't think that I have any concerns with effectiveness. In terms of safety, as I mentioned early on, perhaps additional intensive monitoring of lipid profiles and aggressive creatinine clearance measurement needs to be done to minimize potential problems in the patient population.

I don't have any specific comments other than what has already been made with reference to the subgroup.

DR. NISSEN: I actually saw a lot of sources of evidence that would help me feel comfortable with the TDM regimen, and by the way, I

interpret this the say way that John does, that I am talking about the rapid downward titration of cyclosporine along with the monitoring, therapeutic drug monitoring for everolimus.

First of all, and I recognize some of the limitations, but the kidney transplant studies I think provide some pretty reasonable evidence that when you rapid taper cyclosporine in the presence of relatively full doses of everolimus, you tend to preserve renal function. So, that helps me some.

The analysis post hoc, although it is post hoc, from everolimus, showing the relationship between cyclosporine exposure and loss of renal function, which is strong, and the lack of relationship for everolimus, helps me there, as well, so again I am comfortable that that makes some sense.

Finally, well, there is also the data with regard to everolimus trough levels and the rates of

Grade 3A or greater rejection, which seemed to indicate that when you get to about 3 or 4 nanograms per mL, you know, you are on a plateau for then on out, suggests to me that that is a safe minimal level. That was part of the reason why I voted yes is because I looked at those data and I said, gosh, that actually make a pretty good amount of sense.

Finally, the experience of the German Heart Center we heard about, where this regimen is actually being applied, and has been reported upon to produce very reasonable rates of efficacy and safety.

So, I took that all together and said it really does support the notion that a minimum level of around 3.0 is needed for efficacy, and that rapid tapering of cyclosporine is strongly associated with preservation of renal function.

So, that makes me thing that the current study design is the correct study design.

DR. PICKERING: I don't have a whole lot to add. I think I was not fully persuaded by the

retrospective analysis, but again the European data seems to be very consistent with that, and the renal studies.

One other point, it has been said that there are a lot of other regimens available, and I think in one of the reviews it said they identified 40 different regimens, but obviously, nobody knows how effective they are. I think as far as I can tell, this is the only one that there is any suggestion that the vasculopathy is affected, and obviously, the other regimens are pretty good at getting people over the first few years, but this is the only one that has a prospect that we know of for the long-term benefit.

DR. KASKEL: Just to review some of the things that have already been said, obviously, any regimen to look at diminishing the incidence of chronic vasculopathy, allograft vasculopathy, whether it is in the heart or the kidney, needs to be supported.

I am encouraged by some of the strictness of the German study that suggests that the rapid

taper of the calcineurin inhibitor may be efficacious.

I think that the current design is encouraging, and I would encourage also to be added to that, some subcohort of studies getting a better measurement of renal function at critical time points in this study, because I think that the limitation of renal function measurements now are not accurate enough for us to make a conclusion.

But based on all this, I am having a change of heart, and that is not a pun, so I am wondering if I could change my vote to a yes.

DR. HIATT: It is really split now.

DR. NISSEN: I am not going to twist anybody's arm, but this is very, very difficult. It is difficult because there are competing issues here. I mean I think that I will bet you anything that some of those yes votes could flip over to no pretty easily, and some of the no votes could flip over to yes.

Perhaps for the agency, what you are seeing here is that we are kind of on the fence

here about this. You know, it is interesting to find myself on the yes side. There probably been no more zealous guardian on the drug safety side, but I want to make sure everybody understands why this is a different situation.

This is a very, very vulnerable, very orphan disease kind of population, and it is not the first time I have lowered the bar a lot for something where I thought that the patients were in great need, and where I thought--we don't reach the level of statistical evidence that we ordinarily would want, you know, David.

I am very rigorous about that, but in some circumstances, you don't want to be a slave to the P values, you want to try to exercise clinical judgment, and just to explain this vote, you know, I think based upon the German Heart experience, based upon the kidney transplant data, based on the post-hoc analysis of 253, that I think the TDM regimen is very likely to work, and I think it might be useful to have it before 2010.

DR. DeMETS: I don't think I am changing

my vote, but I do want to say that I think this program, and this study in particular, I mean it's fantastic that it has been conducted in the way it has been conducted with all the caveats.

I came in the room not sure I was convinced about the efficacy of the primary endpoint, because I was worried about the ascertainment of that biopsy-proven rejection, but the discussion has convinced me that that was probably pretty complete. So, I accept the effectiveness on the primary endpoint although I do share John's concerns that the factors on the biopsy rejection rate, and yet you don't see it translated yet, it is a surrogate of some sense, but nevertheless, I will accept it.

The IVUS data, I think has a lot of problems, and, you know, there is no analysis that can rescue a flawed design, and that endpoint is just flawed, and I think it will be fixed as best one can in the new studies, so I am encouraged by that.

The question about the TDM, we just don't

know, and to get there, you have to do a lot of extrapolations. I don't have the same clinical instincts that some of you do, so I will stick to my statistical evidence, if you don't mind, and based on that, I think that it is very encouraging, very promising, but I think if we really want to find out, we need to do the studies.

DR. HIATT: We have two more discussion points, and one is if you voted yes, and the other is if you voted no, and if you switched your vote, keep track.

DR. NISSEN: It isn't over until the fat lady sings, and you never know, somebody else may change their vote.

DR. HIATT: You are persuasive.

So, why don't we go maybe go around one more time and take these together. Just to keep reversing the order, David, do you want to start with 3, or actually with 4.

DR. DeMETS: Well, I think that we have sort of commented all throughout the day and the afternoon especially about the kinds of issues we

had with the current study relative to the ascertainment and follow-up, and I think those issues appear to be addressed in the new studies, so I think that I don't have anything new to add that would be done.

I think the completeness of the follow-ups, worrying about the ascertainment bias, and perhaps some more sensitive measures of the IVUS, and renal function, but I think that many of those are being addressed.

I do wonder what the implications of a different control arm is in all of this. I mean we are switching controls on these two studies, but it seems like the right thing to do, because that is what is being done, so I think that is the right thing to do, as well.

I did want to come back to one final point, though, and that is this issue of the imputation in a non-inferiority trial, and that is a discussion that the sponsor needs to have with the agency. It is something that I don't strongly believe in, as some do, but nevertheless, it is a

point that should be sorted out.

DR. HIATT: Fred, I think you voted yes, so I am getting you the right question here.

DR. KASKEL: I will just make a plea for measurement of renal function. We are being asked by the NIH to take patients age 2 through 18, put two IV's in them at three time points over five years, infuse Iohexol into one IV, take the IV out of a screaming 2-year-old, and then sample from the IV at three time points over the course of two hours for Iohexol determinations.

So, if we can do it in an infant, I think in a patient who is compromised with a transplant, heart transplant, on these drugs, we can bring a small cohort into a clinic and measure exactly kidney function. That would be my plea.

DR. PICKERING: Well, one of the reasons I voted yes was because of the proposed study that is about to start, and it seems to me that will have a very good chance of giving a good answer to the proposed TDM schedule.

Also, even though it's designed as a

non-inferiority study, there is a prospect that it might show a positive IVUS outcome since mycophenolate, I believe, was not shown to have any effect on vasculopathy.

DR. NISSEN: You know, there is a compromise here that might make some sense, and that is, the 176-patient European study might give enough information on renal safety to close that gap, and I would think about letting that represent a potential route to approval with a commitment to continue the ongoing U.S. trial to completion in a reasonable period of time.

I have to go back and look at the power in the European study, that 176-patient study, but I think it is powered for a plus or minus 7 mL of renal function, and if the agency thought that was narrow enough as a non-inferiority margin to say that the regimen, as modified, is not going to have the renal safety problems that were seen in RAD 253, you might be able to move forward on this more quickly than you would have if you had to wait for the U.S. study.

I would like to see both done, but I am not sure I want to see both done as Phase 3. Maybe one of them can be done more as a Phase 3B/Phase 4

study. Something to think about.

DR. VENKATARAMANAN: I think the European renal study will definitely add safety data plus the proposed heart transplant study must be continued, and I echo a previous statement that more aggressive renal function measurement using [?] or at least Iohexol must be done, and definite use of statin in all the patients, and addressing monitoring of lipid levels in the patients.

DR. ABERNETHY: It seems to me like that the proposed study and the European study currently underway should provide the pertinent additional information, and I have to say, you know, I refuse to campaign for votes, however, I think that the real uneasiness is whether these things should be done in Phase 3 or Phase 4. With me feeling, as I said, uneasily, that I think they should be done in Phase 4.

I have to balance that with kind of this

mix of what I read in the newspaper versus what I am told, and that is, what kind of leverage does the regulatory agency have to really insist that a Phase 4 study get done. In some circles, I am told that they have a lot of leverage, and other circles I am told that they really don't.

So, I guess that my uneasy yes is based in the belief that they have a lot of leverage.

DR. HIATT: I think that is truly an issue, but I think the fact is we have got two studies there, are planned and started, so I am not worried that that is going to not be done.

DR. TEERLINK: At the risk of actually agreeing with my esteemed colleague, Dr. Nissen, I actually agree that I think this program deserves revisitation after the completion of the European study data with a very close eye, though, towards the efficacy and in terms of transplant rejection, and the other adverse effects in terms of infections and these other things that were increased, and they may have been increased by chance, but as I said before, I would really like

to be able to go to the patient and actually tell them that there is some potential real benefit on a clinical outcome or a reduction in side effects before it were approved.

So, I actually would concur with revisiting it after the European study and then considering it for approval with the caveat that the other now Phase 4 study, or both would be Phase 4, but now the second study, the Phase 4 study would be completed, as well.

DR. BURCKART: Both studies will provide data I think from a modeling standpoint. We heard about models, and the studies will obviously give us a chance to go back and see if those models were accurate, and any changes that should be made based upon those models.

Recommendations regarding labeling, perhaps these studies will allow us to make specific recommendations about drug therapy monitoring, and not only the concentration range, since a couple of concentration ranges are going to be studied in the American study, but timing of

initial testing and retesting for therapeutic drug monitoring and changes in dosage, also pharmacogenetics, which I know the FDA is also interested in, and I think has some real practical applications for transplant patients.

DR. HIATT: These questions I think are actually interesting and kind of intentional. I mean Question 2 says do we have enough information to understand a regimen that hasn't been tested, I think the answer is no, but I think 3 and 4 are sort of your bailout, and I think, Steve, that is kind of where I was going to head with this, too.

What is left, and I think I tried to say earlier I don't think efficacy is too ambiguous for me although we talked a lot about whether the endpoints were surrogate or not, that is not an issue, I think it is safety.

If you could answer a safety question, and if you could do that in the European study, you could do that quickly, and we could understand, I would think that if early on, renal function could be preserved, I would be willing to concede that,

and not look for necessarily a late term sort of renal function data.

So, if that could be answered early on, this is approvable, I think. So, I really do think that where we are at here is not a solid yes or no. I think where we are at is how can you move quickly to resolve these issues.

DR. SOMBERG: Could I ask a point of clarification?

DR. HIATT: Yes.

DR. SOMBERG: What time points would you be willing to look at, 6-month time frame versus 12-month, because clearly, we are still talking about late 2007 and probably drug availability in 2008 with the 6-month approval, so it might be helpful to both us and the agency to know what time point you would be interested in, in terms of the data.

DR. HIATT: It would be really nice to see 24-month renal endpoint and count the number of people going in with dialysis or need a transplant, but I wouldn't ask for that here. I think that the

efficacy data, in my mind, is still relatively compelling, and what is missing is really knowledge that you can, in fact, affect the renal outcome by changing the way you dose the regime.

If you can show that in a relatively short term, 6 months, I personally would switch my vote. That is what is missing.

DR. MANNON: I concur with the others who voted no, that I think the European data will be very helpful insofar as renal function. I can't answer, I am not sure that knowing the number of patients that go on dialysis, since they were so small in the original study, with this small sample size will really be effective, but if you have a sensitive measure of GFR or creatinine clearance, you might be able to pick up a difference, and I bet it was powered based on serum creatinine estimated GFR, so you need to take that into account.

Someone had mentioned genotyping, and so forth, for PTP, in CYP 3A4, and that is all exciting, but it is going to have to be a component

of the study. I don't know if it would really change my mind, it would just add additional data insofar as getting more information out of these individuals and whether there is going to be MPA levels requested, not required. It might be sort of nice to sort of look at those kinetics as well.

DR. PROSCHAN: I definitely do not want to switch my vote, but I also think that the European study, it is certainly good to look at that data, but I have doubts that that is going to answer all the safety questions with that sample size.

Some of these safety questions, you know, we talked about the nephrotoxicity, but there is pneumonia, there are other things. It is hard for me to see how that would be, in itself, enough for me. I would want to see the big study that is coming.

DR. NISSEN: I just want to make one more comment about that. You will get a little more out of the European study if you do what Dr. Kaskel suggests and use more precise measures of renal function. I think what he is suggesting is yes, it

is only 176 patients for renal function, but if the precision with which you measure renal function is improved, you may get more clarity.

Now, it won't answer all your questions, Michael, about the other safety issues, but if the agency's concerns, what I heard were focused on the unacceptable renal toxicity seen in the 253 study, that could be addressed with a more precise endpoint in the 176-patient European study.

I would add that even that trial could be amended to increase the sample size a bit beyond 176 if that would constitute an approvable study that would get you over the goal line, that might be a very good way to shorten the time frame that this drug could be made available.

DR. HIATT: Let me also clarify. I think what we are discussing here is what needs to be done in Phase 3 for approval, what needs to be done in Phase 4 to answer all these questions about maybe low frequency events, and so just again to continue to clarify that precise measure, renal function, done early would probably take you over

that threshold, and then all the other questions could be answered out to 2009, because it would be done in Phase 4.

DR. SOMBERG: We can look into trying to amend that trial. In fact, 120 patients have already been enrolled in the European trial, so the ability to get precise early measurements of renal function is limited.

I guess another opportunity to gain the information is in a registry fashion, and this is a field in which it exists, and we have actually talked to existing registries. Would that offer a reasonable alternative to try to provide that kind of safety information faster than one might get it from these trials that again take a few more years?

DR. HIATT: I think no, I really do. I think you need to have a controlled safety data, I think it's just too difficult.

DR. NISSEN: I would actually also agree now, I am increasingly skeptical about observational results in general, unless you see an enormous large effect in these observational

studies, they just don't inform you. I wish I could say otherwise, but I don't believe it.

DR. HIATT: I want to go to Paul now for the last comment, and then we will maybe do some closing remarks.

MR. OLDAM: I certainly would hope the two studies answer the questions that have been raised throughout the course of the afternoon today. I would raise a little bit of concern about whether additional studies would be necessary. Again, as a layman, it seems to me we would get a lot smarter, quicker, in the whole field of transplantation, and what we learn from those two studies may raise some additional questions that have to be answered. I hope they don't.

DR. HIATT: In a way, I think things have hopefully become significantly clearer for you in terms of my sense is everyone here is enthusiastic to see this become approvable, and hopefully clarify what issues remain to be answered, and maybe that could be answered in a quick time, and that would really help resolve what is in Phase 3

and what is in Phase 4.

I want to thank everybody. It has been a productive day. The presentations all around have been fantastic and informative, and I think we can adjourn the meeting.

[Whereupon, at 4:00 p.m., the proceedings were adjourned.]

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