rejection in Black recipients. These data came close to but did not reach nominal statistical significance.

Black patients on 5 mg Rapamune™ had a similar rate of efficacy failure as non-Black patients on 5 mg of Rapamune™, but this is in contrast with the rate of efficacy failure that was higher in Black recipients than in non-Black recipients, given the 2 mg dose.

On this basis we have suggested that this higher dose should be used for Black recipients to achieve the benefit of lower rates of acute rejection. As you consider this suggestion it's important to consider the safety data available for Black patients.

The most important safety results are good patient and graft survival for Black recipients. At the 5 mg dose there was no significant increase in the incidence of serious infections for Black patients on 5 versus 2 mg. Moreover, there were no cases of lymphoma or PTLD in Black recipients on either dose of Rapamune™. There was one case in the Black patient in the azathioprine group.

Finally, discontinuations for any reason

were lowest in the 5 mg group in the Black patients when compared with the other treatment groups.

The data for patient and graft survival from the US study only are shown here. This is the study that was stratified by ethnic origin. Although the numbers in each group are small, there appear to be no real numerical differences in patient survival which was very high in graft survival, which was very good for the 2 and 5 mg group.

It appears on the basis of this evidence that there is a benefit of the 5 mg dose to lower acute rejection in this particular group of patients, and there's no significant cost with regard to patient or graft survival.

Our conclusions from the safety analyses are as follows. Rapamune™ is safe and well-tolerated. It provides excellent patient and graft survival. The incidence of infection and malignancy are comparable to controls with the exception of a higher incidence of mucosal herpes simplex in the Rapamune™ 5 mg group, and a higher rate of PTLD in the Rapamune™ 5 mg group from one study. This

increase is not statistically significant.

Creatinine levels were elevated in patients treated with Rapamune™ in combination with standard dose cyclosporine by comparison with the control groups. This is somewhat different for the 5 versus the 2 mg group. I want to point out again, these results stand in contrast to the effect of Rapamune™ administered without cyclosporine and the effect on glomerular function may be attributable to cyclosporine or perhaps some interaction between cyclosporine and Rapamune™, rather than a direct effect of Rapamune™ itself.

Finally, Rapamune™-treated patients are likely to develop dose-related reversible increases in cholesterol and triglycerides that can be managed with standard medical therapy, and with appropriate management will improve over time after transplantation.

Although Rapamune™ has modest effects on blood cells, no patient developed severe leukopenia. Discontinuations for severe anemia were low. Reductions in platelet counts were generally mild,

dose-related, and reversible. There was no indication of progressive marrow dysfunction from Rapamune™ in these patients.

The combined safety and efficacy data from these studies support Rapamune™ for prophylaxis of acute rejection in renal transplant recipients. Rapamune™ 2 mg is the optimal dose for most patients in combination with cyclosporine and steroids. It effectively reduces acute rejection; the incidence of serious side effects is comparable to control therapy; has the lowest rate of discontinuation of therapy.

The higher dose of 5 mg is safe and effective but the side effects and laboratory abnormalities are more pronounced. Thus, for use in combination with cyclosporine this is likely to be the upper limit of the dose range. The data suggests that a benefit of the 5 mg dose is observed in Black patients.

It is notable that despite the two-and-a-half-fold increase in dose no new, unexpected adverse events were observed; rather, the adverse events characteristic of Rapamune™ are more pronounced.

The benefit of Rapamune™ should be achievable by all transplant teams currently using cyclosporine-based treatment regimens. Indeed, one advantage of this program to use Rapamune™ with cyclosporine is that it should allow transplant teams to incorporate Rapamune™ at relatively low doses easily into their current cyclosporine regimens.

Based on the data from the Phase III studies and the pharmacokinetic behavior we propose the following recommendations for Rapamune™ for recipients of cadaveric and living donor organs. Rapamune™ 2 mg for the majority of patients, Rapamune™ 5 mg for high-risk patients. Black patients were considered to be high-risk in the analyses we've done in Phase III.

Other high-risk patients may benefit from a higher dose but we don't have data yet in that regard. If cyclosporine target concentrations are maintained at the standard levels used for other double or triple therapy at the transplant center, therapeutic drug level monitoring is not required to achieve the efficacy results observed in these

clinical trials or to avoid serious adverse events.

For patients on the 5 mg dose, the side effects are more likely to occur. When confronted with triglycerides not responsive to treatment or clinically significant reductions in platelets, the Rapamune™ dose should be reduced. Improvement in the clinical parameters should be monitored.

This is what was done in the blinded studies and it should be appropriate management when the physicians know the actual therapy and the actual dose.

Finally, we've shown you the data to support the efficacy and safety of Rapamune™ for this first indication; that is, prophylaxis of rejection in renal transplant recipients. Of course, we all know that is the conclusion and we're here today to discuss this conclusion.

I want to thank you for your attention. My colleagues and I will do our best to answer any questions you have at this time.

CHAIRMAN MASUR: Great. Thanks very much. I'm sure there are questions. Why don't we take

questions. We can start over on the left and see who would want to pose any questions. Does anybody want to --

DR. SHAPIRO: What survival data do you have?

DR. CAMARDO: The trial is just being -- the manuscript is just being written. I think the data have been presented but not published yet. Do you want to know something specific?

DR. SHAPIRO: Do you have anything in terms of outcomes on patient and graft survival?

DR. CAMARDO: Patient and graft survival was equivalent in the groups at the end of one year. The efficacy results are a little more complicated. When we looked at the rejection rates read by the local pathologist they were in the mid-20s for cyclosporine and the high-30s for Rapamune™. All of those were sent to a blinded pathologist. The rates all came back in the high-20s and so we're in the process of working that out. But there was no significant difference between patient and graft survival at one year in that study. It was a small

number -- 178 patients. It should be available soon. Is that sufficient or do you want to see data?

DR. SHAPIRO: I have a follow up. What about withdrawals?

DR. CAMARDO: Yes, there were a couple of cases of, I think of leukopenia and pharmacytopenia that caused withdrawal. It was a little less well tolerated in that respect but I believe that was the only major complication that was observed that could be attributed to the interaction.

CHAIRMAN MASUR: Suthan.

DR. SUTHANTHIRAN: The creatinine levels in patients who were treated with sirolimus alone as compared to combination therapy, in a similar fashion did you have a chance -- you probably looked at the lipid levels also in patients who were treated with sero limits alone, cholesterol and triglycides. Were there abnormalities in patients who were treated with monotherapy with sero limits as compared to patients who were treated a combination?

DR. CAMARDO: Well, the lipids are elevated in patients treated with sirolimus alone. It

does appear that when you remove the other complicating factor, which is cyclosporine, it's a little bit easier to manage the cholesterol. And if you -- and you can also manage the triglyceride elevation as well for sirolimus.

But in fact, it's very clearly dose-related. When we looked at this in the sirolimus patients it's clearly worse at the higher doses. When we looked at it in the renal transplant patients, as the dose was reduced from month-1 to month-3 the triglyceride levels in particular continued to fall and became easier to manage.

The means do not go back to normal in any of the patients but they come much closer when you remove some of the other exacerbating effects with sirolimus alone. So I mean, I guess my conclusion is, and the data support it, that it would be somewhat easier to manage the lipid effects of sirolimus if there weren't complicating factors.

DR. SUTHANTHIRAN: In terms of the high cholesterol, their data in terms of HDL versus LDL, do we know in terms of --

DR. CAMARDO: Yes, we do. We actually have data from the psoriasis portion in which it was very clear that LDI, VLDL and HDL were not (Inaudible.) From a metabolic study that we're currently doing with our colleagues at Baylor we actually have a more lipid subfraction analyses than I'm sure you care to see, but if you'd like I can ask one of our consultants to review that a bit. It's up to you.

But the LDLs are elevated, the VLDLs are elevated, the HDLs are unchanged. And interestingly enough, if you look at the triglycerides and stop the Rapamune™ in about 72 hours or six days, the triglycerides come back to normal. This was a contrived situation. These were patients who already had had lipid elevations; were given a high dose for the specific reason of looking at lipid metabolic parameters.

So we do know a little bit about what's going on here. I think the key thing is that it looks as though clearance of the LDL and VLDL remnants are delayed. But HDL doesn't seem to go down, which is

good.

CHAIRMAN MASUR: Does anyone feel strongly that they have to see that data? Well I guess we'll pass for the moment. Anyone else? Dr. Mann.

DR. MANN: Have you any data beyond 12 months as to what happens to the GFR?

DR. CAMARDO: No, we don't have it.

CHAIRMAN MASUR: Larry.

DR. HUNSICKER: I actually have several minor I think, short questions. First of all, with respect to the potential interaction of cyclosporine and rapamycin on GFR, you've suggested two possible explanations. One is that the cyclosporine doses may simply have been higher because they couldn't have been reduced. But the other that you just referred to on running is that there may actually be an interaction.

Since you can't really look at this very cleanly in humans I was wondering whether you have actually had the opportunity to look in animals at the impact of RAPA added to cyclosporine when the cyclosporine is being given parenterally, or at least

you make sure that the levels are comparable, to see whether there is a renal effect of RAPA in combination with cyclosporine that is not attributable to the level of cyclosporine?

DR. KAHAN: Larry, at the AST meeting in May, Herman Potter, one of our graduate students, presented this data, and what he found was that -- well, there was a previous observation that we found which was that whole blood levels did not reflect renal tissue levels of rapamycin very well.

And indeed, the pharmacokinetic interaction was exacerbated in renal tissue where the renal tissue level was very high, even relative to the whole blood level. And I think this is quite consistent with the proclivity of this drug to partition into tissues.

When we did a median effect analysis which accounted for a concentration in kidney, we found that the interaction wasn't even additive. So there was no effect of sirolimus above the effect of cyclosporine by itself.

Now, in Bill Bennett's previous work as

you may recall, they gave the drugs intramuscularly. They measured trough level concentrations which were extremely high, but they didn't measure kidney concentrations and they didn't correct the results for the increase in trough concentrations with the combination.

So we feel that appropriate dose concentration control will mitigate this effect based on the rat model.

DR. HUNSICKER: Okay, so to summarize that, at least in your fellow's case, once he had corrected for tissue levels of cyclosporine there was no effect of rapamycin?

DR. KAHAN: Exactly.

DR. HUNSICKER: Okay, the second question is a practical one related to the timing of the dose of rapamycin versus cyclosporine. Compliance goes down when you have to separate doses as you well know. It looked at though one could achieve a similar effect by giving a slightly lower does together because the effect was relatively consistent.

Do you want to comment of whether this is

a reasonable extrapolation from your data, and do you have any data on this?

DR. CAMARDO: I would agree that's a reasonable extrapolation of the data. I think it's also reasonable to give the same dose simultaneously. But that would take a long time to demonstrate why because of all the therapeutic monitoring that we had to do in Phase III --

DR. HUNSICKER: I'm more interested in the -- that one does not have to insist in the labeling and in the education that these must be kept separately because this will markedly, adversely affect compliance.

DR. CAMARDO: The short answer is that we're doing a study to see that we can make sure that compliance isn't an issue with the dosing separation. But unfortunately on the basis of these results I can only recommend what we did.

DR. HUNSICKER: No, I understand that.

DR. CAMARDO: I want to remind you that Rapamune™ is very linear, sirolimus is linear with dose, and one could extrapolate reasonably, easily I

believe, around -- you know, to make it easier on the patients.

DR. HUNSICKER: A third question really goes to whether at least your book here is suggesting we may be going in the future, which is lower doses of cyclosporine in order to reduce renal toxicity. One of the concerns is if you're -- you have a very wide variability in bioavailability from individual to individual. And if one is using both low cyclosporine dose and you happen to trip across an individual who is one of the low absorbers, one might get into trouble.

The question that I have is since there is fair consistency between the trough level and the area under the curve and at least some modicum of consistency within patient over time, would it be a reasonable thing to think that one might want to check the trough level at least once after achieving a steady state to make certain that one is in the therapeutic range?

DR. CAMARDO: Actually, that sounds like a quote from the current version of the labeling that

we were discussing. But it would be reasonable to check a trough level, which makes it more convenient, obviously. Especially in circumstances where the dosing of cyclosporine is being changed. We will advocate that.

But my point is that when given with full dose cyclosporine the variability is relatively inconsequential. But as soon as the cyclosporine is lowered or removed remonitoring would be required. What we think currently is that monitoring would be less difficult to do in terms of just the trough level, and it wouldn't be needed as frequently because the half-life is much longer.

Now, I see my colleagues have put up a slide here. I don't know if we want to show this, but you've asked a couple of questions that we could answer, but this is not data in the NDA and I want to make sure -- I mean, you've obviously said it's okay. I just want to make sure we can review this. I think you've seen it. Is that okay?

Briefly, I'll take a minute. You mentioned the question of the interaction of

cyclosporine with rapamycin, with Rapamune™, sirolimus. I tried to make the point we don't really know what is happening here in patients but the only way we could test it is to test the hypothesis that it is related to cyclosporine.

We have two studies going on now: one with 200 patients, one with 550 patients. And we have reduced those data from Study 203. I want to quickly do this. It will address your question. Could you run through these slides for me? Just show the next one.

This is a study in which patients are randomized to standard dose cyclosporine in 2 mg of Rapamune™. This is just like the Phase III program. In this group patients only get cyclosporine therapy for three months and then they get concentration controlled Rapamune™. We're looking at graft loss acute rejection and patient survival, but we're also looking at creatinines at six months.

Quickly, this is the first time we've ever shown this. This is the mean creatinine at six months for the dose group. That's identical to the

Rapamune™ Phase III program. Creatinine is 1.69. For a small number of patients the creatinine is 1.36 after cyclosporine withdrawal. This is the significance.

More impressive is the fact that in the next slide these study sites did actual, real measurements of glomerural filtration and they're clearly higher. It doesn't reach statistical significance but the trend is going in the right direction.

If you keep going, the next slide shows this is the Phase II dose ranging study from 203. I went through that very quickly. We decided to use standard dose cyclosporine but if you look at the creatinine measurements, here is micromole, here is mg/dL. For the control group at 12 months it's 142. At the one mg/m^2 dose of Rapamune™ that's about 2 mg.

Creatinines were higher in the standard dose versus the reduced dose group and that's also true for the Rapamune™ 3 mg/m^2. For obvious reasons we didn't look at the Phase III. The obvious reason is mostly related to blinding and the other issues

that are related to clinical trials and their demands.

But you know, these data -- any piece of data in and of itself is probably not as convincing as the weight of the evidence that seems to be coming together. Do we have any other slides here? Another one?

And this is a single center experience in patients converted from cyclosporine to Rapamune™. The mean creatinines were decreased. These were patients in whom there was some cyclosporine toxicity. If you go to the next slide it goes this graft over time: creatinines from six months prior to conversion, the conversion to Rapamune™, and then the gradual decrease in the creatinines over the next 12 months.

These patients tolerated Rapamune™ at these doses. The side effects had to be managed obviously, but the effect on the kidneys of cyclosporine seemed to have been eliminated by the transition. I've probably said more than I should on that, but this is -- I mean, these are the data currently.

DR. HUNSICKER: The final question if I can is, I'm intrigued by the fact that hyperkalemia was less common in the RAPA patients fairly consistently. In the face of other things suggesting more cyclosporine effect which would be expected to go the other way, this raises the question of whether there is an effect on potassium handling of rapamycin. Does it induce akaleuresis?

DR. CAMARDO: I can state unequivocally that there is an effect on Rapamune™ on potassium handling, and there are some handling of other electrolytes that are consistent with some tubular effect of Rapamune™. It actually is good when you use it in combination. On its own when we used Rapamune™ at higher doses patients did in the early phases, require some potassium supplementation. It was a bit of a surprise but it's consistent with the tubular effect.

DR. FIRST: Just one quick question. In terms of concomitant drug administration, what about the other calcium channel blockers and the anti-epileptics? Do you see a similar effect dependent on

their effect on the cytochrome oxidases then as you see with cyclosporine?

DR. CAMARDO: You know, I'm going to defer -- Jim? While I didn't study it you would expect the calcium blockers to behave like diltiazem, which is one we studied. And in fact, we did an extensive series of in vitro cytochrome for 50 enzymes, and it looks as though 3A4 is the major one that's affected. So I think that gives us the information to extrapolate to other drugs. That's what my colleagues are telling me.

CHAIRMAN MASUR: Let me go back and then coming back to Darrell. Go ahead.

DR. SHAPIRO: (Inaudible.)

DR. CAMARDO: No, I don't. And I could ask one of my surgical colleagues to comment on that. I mean, we've been glibly ascribing it to an effect on the wound healing of the internal -- you know, the wounds internally. But I -- you know, Barry you stood up. You ought to address this.

DR. KAHAN: There is no question that there is an increased incidence of lymphocele and this

was observed very early. Fortunately, the majority of cases respond to just catheter drainage percutaneously; don't recur and don't require surgical intervention.

You know, we normally attribute the lack of a lymphocele to sealing of the lymphatics around the iliac vessels and it's possible that some of the growth effects just empower that sealing of the lymphatics. But it doesn't constitute a serious clinical problem.

DR. MANN: In your lethal presentation you showed us some Phase II trial data that suggested we reduce the dose of cyclosporine; that much of the beneficial effect in terms of reduction of acute rejection was lost, particularly in the Black population.

You've just shown us some additional data regarding --

DR. CAMARDO: The renal function, right.

DR. MANN: -- that renal function improves, but are you finding that when you reduce the dose of cyclosporine that in these studies you're

seeing data similar to what you showed us in the initial presentation; which is to say that you're having a higher rate of acute rejection?

DR. CAMARDO: Well, I think we're being a lot more careful, first of all with the -- I mean, we learned in Phase II how to deal with Rapamune™ and cyclosporine in Black recipients. We didn't know that a priori. If you recall that slide, in non-Black recipients reduced dose cyclosporine is equally effective with standard dose cyclosporine.

Unfortunately, those analyses are complicated by the fact that the numbers in patients get very small. The short answer is that we're not seeing any issues when we reduce cyclosporine but we're doing it after the first three months. So we're taking a conservative approach in the earlier phases when rejection risk is highest and then we're reducing later on.

But it seems to be working. I hate to be talking about data that's in process because we're not really here to discuss that. But even in Phase II in non-Black patients cyclosporine was effective in

combination with Rapamune™. It was really the Black recipients who didn't tolerate the reduced cyclosporine.

CHAIRMAN MASUR: Darrell.

DR. ABERNATHY: Yes, I'm trying to understand the synergism between cyclosporine and rapamycin in particular. Both these drugs are substrates for CYP3A4 and are apparently both binding to P-glycoprotein which I think has not been sufficiently explained to me at this point.

The first question would be, what are the K_Ds or K_Is of cyclosporine versus sirolimus for P-glycoprotein?

DR. CAMARDO: Jim, you're shaking your head. Does that mean you don't know or you --

DR. ZIMMERMAN: I don't have that data --

DR. CAMARDO: Stand up so I can hear you. And it really has to get on the record. So why don't you just come up? I'm afraid the answer is, we don't know. But I'm not --

DR. ZIMMERMAN: Basically, we did substantiate the number of drug interactions. Some of

these drugs served as both substrates of CYP3A4 and PGP and I'd just like to put up slide B-42, PKZ.

CHAIRMAN MASUR: For the record, could you state your name?

DR. ZIMMERMAN: Yes, James Zimmerman. I am the Clinical Pharmacokineticist on this project for over seven years so a lot of the investigators know me.

As you can see here we did document for all the drugs that we studied, that they were either a substrate for 3A4 and also PGP, or just one or the other. We have a reference for each one of these so it is documented.

Now in terms of actually giving you a K_I for the interaction I don't have that. Obviously these studies were done from all different types of sources of biological material and so I don't even know if that information -- you know, if we were to compare, whether they would be relevant for the two drugs.

DR. CAMARDO: Joanne, can you answer that from animal studies? Is that -- I'm sorry to cut you

off but I saw our metabolism person here.

CHAIRMAN MASUR: Can you identify yourself please?

MS. SCOTINA: Joanne Scotina, Drug Metabolism. Slide 29. We've done some studies, or studies have been conducted using human liver microsomes where we've looked at the inhibitory rate constants with regard to the potential for inhibition of cytochrome P4503A for dependent metabolism of Rapamune™.

So what's being looked at here is whether any known 3A4 substrates have the potential to inhibit Rapamune™ metabolism. And in fact, K_I values have been determined and they range from 10 to 120 micromolar. And on the second bullet it's indicated that clinical relevancy -- that is, whether these effects are likely to extrapolate into the clinic -- is dependent on the systemic circulating concentrations relative to the inhibitory K_I values.

And indeed, we see that for drugs such as ketoconazole where the K_I value is low which is an expected finding because it's a potent inhibitor of

3A4, but not nifedipine which has a higher K_I value, there was an increase in Rapamune™ whole blood AUC in healthy subjects.

DR. ABERNATHY: I still want to come back to the thought of a combined PGP inhibitor and CYP3A4 inhibitor to better understand, because ketoconazole obviously blocks both of those processes, not just 3A4. So I guess with regard to the prediction I was a little surprised that there weren't some clinical interaction data with the drug like erythromycin, for example.

Because I'm trying to not isolate on, this is a drug that appears like it's a CYP3A4 inhibitor. It's a drug that has a complicated, both PGP and 3A4 effect. And the concern is, how important will that be when it's co-administered with other drugs that are either inhibitors or are going through both of these processes?

That's kind of a partly question, partly statement.

DR. ZIMMERMAN: Yes, Darrell. When we chose to investigate the interacting drugs, certain

drugs were just taken as a given. We expect interaction with erythromycin. We chose the strongest inhibitor. I think usually you chose the strongest inhibitor and the strongest inducer and that's just what we did in these studies.

We couldn't study them all. But I'm of the opinion that you really can't tell what's going to happen with the 3A4 PGP combination. I'm not even sure that in vitro studies can help you predict what's going to happen. I think they can give you an idea, but as far as I'm concerned you just can't predict it.

However, if a drug is known to be a fairly strong inhibitor, like erythromycin and cyclosporine and ketoconazole, I think those will come across. You just don't know the quantitative degree -- you don't know the degree to which they would be inhibitors.

But I would expect -- like I said, I expect effect for erythromycin for other drugs which are not either strong inducers or strong inhibitors. You really don't know. You just have to do the experiment to find out.

DR. ABERNATHY: One last query, a little

along the same line. You presented, there was a synergistic effect between rapamycin and cyclosporine. If you correct for AUC rather than simply looking at dose, is that a pharmacokinetic synergism or do you think there's a pharmacodynamic synergism as well?

DR. CAMARDO: This is another question that could be answered with more data. Is that okay to show a little more data? Dr. Kahan has a few slides; five slides, maybe.

I mean, this typically addresses the issue of a pharmacodynamic synergy related to concentrations of rapamycin, sirolimus, and cyclosporine that was performed in the Phase III studies, and Dr. Kahan can present it in about two minutes. So you'll be able to see that there's actually a dynamic interaction, not just a kinetic interaction.

DR. KAHAN: B-73; my B-73. As you know, the way in which -- or, the reason why I got interested in the development of rapamycin was because based on the model of the median effect analysis we identified rapamycin as the only one of the available immunosuppressive agents that act synergistically with

cyclosporine.

So it was of course, important to see whether or not we could extend that observation to the clinical data. And basically as you see here, what we have here is the median effect equation which is on the left-hand side, which basically is interpreted in this analysis as the fraction of people full of rejection over the fraction of patients who have rejection at a given concentration *X*.

It is equivalent to that concentration *X* over the median concentration, or 50 percent of patients free of rejection to an arbitrary power M. This equation was first described by Chew and Talloway and has been extensively used for anti-virals, antibiotics, and immunosuppressives. And this is the logarithmic conversion.

And since we had a protocol stipulated, a trough concentration of neoral, and since we had concentrations that were being measured surrounded by protocol, we measured concentrations every day for the first five days; once a month and then for one month, 3, 4, 6, 12. And we used those concentrations and

incorporated them into the model.

And this particular plot shows the cyclosporine concentration, of course on the log scale, versus the fraction of patients who are free of rejection versus those with rejection on a log scale.

The line on the right-hand side shows the data from the two control groups; namely the ones that got placebo or azathioprine. The line on the left-hand side shows the line from the patients that are in the treatment group.

And what you can see there is that the 90 percent reduction level -- 90 percent of patients free of rejection -- that there's a 2.2-fold cyclosporine trough level necessary to achieve freedom from rejection.

Now if we look at sirolimus, we took the data that was in that 207 study and even though that study which used sirolimus, azathioprine, and prednisone was small, the data fit or the equation fit the data very well, and the correlation coefficient was 0.97.

Now, this shows the sirolimus,

azathioprine, and prednisone line when sirolimus was combined with cyclosporine at the 90 percent effect level. Again, we had a reduction by about 5-fold.

So in the next slide which summarizes -- well actually, this just shows you the values for Rapamune™ 90 percent free. In the presence of cyclosporine 13.5 ng/mL; in the absence, 61.5. Cyclosporine in the absence of Rapamune™ 509; in the presence, 231.

And then we use the combination index equation also devised by Chew with the concentration when one is used in the presence of the other with the concentration of that drug alone, plus the concentration -- the second combination versus the concentration of that drug alone.

Same that if we had a value that was less than one with adjusted synergism. And the next slide summarizes that calculation. Again, we have the 241 and 509 with the 13.5 and 61.5, and the end result is 0.65. which shows the combination index less than one and suggests from our clinical data that we have synergy, although this will have to be tested in a

prospectively designed study.

Thank you.

CHAIRMAN MASUR: Steve?

DR. PIANTADOSI: Thank you. I have two questions. The first has to do with the sample sizes for this study. The original design specifications as I understand them, did not require a sample size as high as that which was used in either study, including the overadjustment for the Type 1, the restricted Type 1 error.

Can you tell us a little bit about how the decision was taken to increase the sample size from the original specification to the final number?

DR. CAMARDO: They were really just practical considerations. The one was the need for additional safety data above and beyond the efficacy requirements. And the second one was the inability to really stop a study the day you find out you have enough patients. You always need additional time. The combination of those two gave us the number.

But the real driver was the safety. I mean, in particular we were not -- I mean, I don't

know if you're interested in it but I'll just answer it. We were not looking at the data to see what was going to happen. It was blinded and we just decided we needed about 1,000 patients on Rapamune™ to start with.

And rather than enrolling another study we just expanded the size of the one study. That's what happened.

DR. PIANTADOSI: So those decisions were made near the planned end of the original study?

DR. CAMARDO: They were made about -- they were actually made in advance of the decision to start enrolling -- the actual number. But it was -- again, I want to emphasize again, it was based on safety. And then as time went by we realized how people were enrolling and which study centers had started. We terminated the study when we thought we would have about 1,000 patients on Rapamune™. That's what happened.

DR. PIANTADOSI: Thank you. My second question deals with the analyses. You analyzed a number of factors in the presentation as well as in

the written report that affect the primary efficacy failure endpoint. And those included things like which study you were on, the treatment, the dose, race, mismatched donor origin, and so on.

And the many analyses were presented of those factors individually or one at a time. Did you perform any analyses looking at those factors simultaneously in an attempt to sort out the relative importance and any interactions between them?

DR. CAMARDO: Yes, we did, and I showed that data. But I think the results showed that really the major effects on efficacy failure related to treatment and HLA mismatch. Those were the major effects, and I believe race was in there as well.

Robert, I've got to ask you to help me on this one, though.

DR. GOLDBERG: I'm Robert Goldberg. In that analysis if I understand correctly, race was entered and did not prove to be significant.

DR. CAMARDO: Okay, so it was treatment in HLA mismatch?

DR. GOLDBERG: That's correct.

DR. CAMARDO: Thanks, Robert.

CHAIRMAN MASUR: Bob.

DR. WOOLSON: Back to the sample size question. Insofar as you knew that the Blacks were a high risk group to begin with, did you have target number of Blacks for this study that was based on power considerations?

DR. CAMARDO: No, I wish we had, but in fact, we did not.

DR. WOOLSON: And back to the sub-group of the Black population. If I'm reading the data correctly the recommendation for Blacks at the 5 mg dose is largely based on approximately 100 patients: 60 or so in the 5 mg and 40 in the azathioprine -- at least from Study 301.

And I was wondering if you could just give us an overview or give me an overview of the safety profile for those individuals -- the 60 and the 40?

DR. CAMARDO: Yes, actually the -- I mean, the safety analyses have the same disadvantages of the efficacy in that there is a small number of patients. But what I did mention is that graft survival were

good in those patients who had above 90 percent. There was no decrement.

There were no lymphomas or PTLD in those patients suggesting that the additional immunosuppression was tolerated. The rate of serious infections, sepsis in particular, was no different for the 5 versus the 2 mg dose in Black patients. The rate of CMV for example, was extremely low because a lot of the Black patients were at low risk for CMV anyway.

So we couldn't really tell for sure but there was nothing very big that appeared to make this a high risk proposition for serious infection. Actually, these are shown here just to illustrate what I said. In the Black patients the rate of CMV is actually zero. With the non-Black recipients, I believe in the reviewer's -- Dr. Tiernan's analysis in the FDA's review she'll point out that a lot of these were low-risk patients anyway.

But the numbers are the numbers. They were higher in non-Black patients. Sepsis is lower in the azathioprine group but not really different for

non-Black patients versus Black patients in the 5 mg group. These rates, as percentages they're relatively low.

The only other information we have is that when you look at a category called treatment failure, which is withdrawal or efficacy failure, it actually looks as though the 5 mg dose has a lower rate of treatment failure for Black recipients, which I believe represents the efficacy rate as lower and the number of discontinuations is a little bit lower.

If you look here at the treatment failure rate for Black patients versus non-Black patients there is no difference here in azathioprine. If you look here it's 49 percent for the 2 mg group reflecting a low efficacy failure rate, but actually 37 percent for the Rapamune™ 5 mg group in terms of withdrawals or efficacy failure.

I mean, we infer that this is somewhat better tolerated and the only other bit of data we have are the triglyceride and cholesterol measurements which are shown -- I'm sorry -- on the previous slide. Again, these are small numbers but the mean

cholesterol for example, in 22 patients followed for one year, Black patients was not really even any different from the cholesterol azathioprine group. The triglycerides are elevated.

There's no way I can get around the fact that the numbers are small. And the result was a bit of a surprise. I mean, we weren't sure what would happen so we respectively stratified. When it came out in the analysis we've been, as you'll see, been dealing with this over the last year to figure out what it actually means.

DR. WOOLSON: Thank you.

DR. CAMARDO: You're welcome.

CHAIRMAN MASUR: Courtney.

DR. FLETCHER: My first question is about the confidence with which we can conclude that 2 mg per day is the optimal dose of rapamycin for most patients. Page 62 of the briefing book you talk about a pharmacodynamic analysis where you show that the optimal concentration of rapamycin combined with cyclosporine is between 10 to 15 ng/mL.

In the work that Dr. Kahan just discussed,

this same concentration of 10 ng/mL came out in that analysis. The average trough concentration achieved with a dose of 2 mg/day however, is 8.6 ng/mL. In fact, you have in most patients concentrations below 10 ng/mL.

DR. CAMARDO: That's really an excellent question. Let me go back just to basics. The best data that the 2 mg dose is optimal I think really are that the results are statistically significantly lower in the two studies when the fixed dose was used.

I mean, I can't get away from that; that's the basic data that we have. Now, the therapeutic monitoring that we did is (Inaudible.) and I think that the simplest conclusion is that in fact, when you look at the rejection rates above and below, for example, 8 ng/mL, there are still patients at 5 ng and 4 ng who do not have rejection.

What I believe is that we're seeing the beset rejection rate which is better than cyclosporine alone with a fixed dose. I can't stand up here and tell the community where we know what pharmacodynamics means, that one couldn't hopefully improve that rate

if you could bring some of those patients who are poor absorbers up into the higher range.

And indeed, I expect that to happen over time. But frankly, we're not ready to make a recommendation yet because we don't really know if it's 8, 10, 15, or 20, and we're still within a wide range. I mean I -- you know, your question is exactly correct and you've inferred, you know, the appropriate steps I think.

But right now I don't want to discount the fact that in blinded studies with a fixed dose we got a very significant result that we can rely on and that we believe -- you know, in practice this dose will be acceptable for most patients.

DR. FLETCHER: What of the availability of an assay to measure concentrations in the community?

DR. CAMARDO: We've been working for several years. We have a very good IMX-based assay that is sensitive and specific enough, doesn't interact with the metabolites to any great extent, is reliable, reproducible, satisfies all the criteria.

Our colleagues, the company that makes

that assay, are currently in the stages of the same negotiation as we are to have it approved and marketed. We're doing everything possible to cut down the time between the availability of Rapamune™ and the availability of the assay.

We have a number of interim solutions that we believe will be useful. But eventually, hopefully, over the short-term rather than the long-term, physicians will have an assay in place and we'll be able to make better recommendations.

DR. FLETCHER: Just one last question -- actually a drug interaction question. You showed the possibility of using statin cholesterol lowering drugs or fibrate drugs in combination. Do you have any information on drug-drug interactions between those compounds and rapamycin?

DR. CAMARDO: We have a study performed with atorvastatin which we chose because it seemed to be the one most comparable. There is no interaction either way. It doesn't interact. I could show that but I think I've shown enough slides already for the morning.

These data aren't in the NDA so they haven't actually been reviewed by anyone on our counterparts at FDA. But the simple conclusion is that the ratios of sirolimus and sirolimus plus atorvastatin are unaffected by the addition of atorvastatin. And if you look at the plots of atorvastatin with and without sirolimus you don't see any difference. So they don't elevate the atorvastatin concentrations.

I expect that we'll be doing some kind of a fibrate study as well. We don't have that data yet.

CHAIRMAN MASUR: Jim.

DR. LIPSKY: Yes. Some questions on again, the rationale for the one-dose-fits-almost-all phenomenon. In the brochure you provided you stated that -- this is on page 20 -- or someone stated that intersubject normalized oral dose clearance varied sevenfold. And so it seems there's a great deal of variability here.

So am I understanding the rationale for the one dose is -- the 2 mg dose for virtually everybody is that it simply worked in most people? I

mean, were you tying your hands behind your back?

Could it have worked much better if it were concentration controlled? Although you state other times that concentration control didn't seem to matter. Yet the Chew-Talloway plots seemed to say they did. So what's going on here?

DR. CAMARDO: I mean, I hate to trivialize the results to say it just worked, but in fact, it just worked. But remember, we didn't tie our hands behind our back to make it more difficult. We decided not to do concentration monitoring because we chose blinding as a more important criteria than concentration control.

And so we were forced to use a fixed dose. I mean, you can think about running a study with unblinded third party observers but to do that for a year is very difficult. So we did the best we could to pick a dose. Now, I believe that -- well, I'm sorry, I lost my train of thought.

Over time I believe that physicians will learn to compensate for the variability in Rapamune™ but the fact is that the fixed dose really worked.

Had we gone to a higher dose it might have worked, but had we done concentration control in these studies, I frankly can't predict what would have happened.

It might have been better but frankly I don't know that. And you're proposing really, the idea of comparing a randomized study with concentration control versus 2 mg of Rapamune™. I frankly don't know what the results would be if we do that.

DR. LIPSKY: No, I'm not necessarily suggesting that. I might suggest that maybe basically one would say gee, levels associate with an effect but go for that level and just sort that out initially. You know, what is the dose response relationship. And I think you sort of imply that. You now have a recommended dose for high-risk patients, mainly African-Americans, that says it would be 5 mg. Well, is there a kinetic rationale for that dose, or did it also just work?

DR. CAMARDO: No, there's not a kinetic rationale. I mean, what happened in the study was that the efficacy failure rate was reduced at 5 mg but

as I showed you in Black patients the pharmacokinetics is identical, the troughs were exactly the same, there's no difference in the trough; how you see relationship with Black patients.

DR. LIPSKY: But is it the trough that counts? You also said interesting things about the kinetics. You said steady-state or presented; that steady-state was achieved in one week. You either had a half-life of -- or that 90 hours or 62 hours. So I presume that half-life does not account for much of the elimination of the drug? Or what's going on here?

DR. CAMARDO: The half-life there was based -- that one statement was based on patients receiving the dose twice a day. In fact, we're using loading doses for every patient now. We have eliminated waiting for the steady-state to be reached. So every patient is getting a loading dose of Rapamune™.

DR. LIPSKY: And the loading dose is based to achieve a theoretical steady-state or --

DR. CAMARDO: To achieve the theoretical steady-state for that dose of Rapamune™ in the

population -- it was just based on a calculation of the clearance and the volume steady-state distribution.

DR. LIPSKY: So if you had like a patient who weighed 60 kg and another weighed 120 kg, you thought about recommending the same dose for both those patients?

DR. CAMARDO: Well, just let me see the slide you're showing me here. In fact, we are, and the reason we are is because we never adjusted by weight, we adjusted by body surface area so it doesn't change that much.

If you look at the basis for the oral dosage and mg/m^2 for one mg/m^2, 3 or 5, basically what we did here is calculated what would happen if this patient received the 2 mg dose or 5 mg dose, and then moved it over to this line. And what happens is, you would just sum things up a little bit; some patients would go down. But around the body surface area of 2 m^2, the dose is so small that it doesn't make much of a difference. In fact, the clearance is more of a variable than the body surface area.

So the short answer is yes, we're comfortable with using this dose; based on these calculations and based on the fact that it was proven to work in Phase III.

DR. LIPSKY: And toxicity was not level or dose-related in any way? Well, you computed that 5 mg had greater toxicity than 2.

DR. CAMARDO: No, there's no question that the side effects are dose-related. This is true for the lipids, the cholesterol, for some of the other side effects like arthralgia. Again, we didn't tie our hands behind our back but we did blinded studies and so we were forced to ask those doctors to reduce the medication based on clinical effects. That appeared to work.

Now, there are clearly dose-related side effects, and those will have to be managed by dose-reduction or elimination if they occur. But they appear in the studies to be manageable without knowledge of the actual drug level.

DR. LIPSKY: So if you were asked to give a therapeutic index for this drug, could you?

DR. CAMARDO: I can give a target range. And in fact, we've been working on that and it's a bit of a wide range and it's one you've probably seen for other drugs like this: between about 5 and 25 ng/mL. But can I tell you what would happen if we did a study that was targeted? I still can't answer that question -- I can't answer the question -- what would happen if we did a target concentration controlled study instead.

Now, we have done that. I mean, I don't want to seem like a Philistine here, not interested in therapeutic drug level monitoring. The fact is, all of our cyclosporine withdrawal studies include monitoring, all of our studies of Rapamune™ alone include monitoring.

I think what I'm saying is that in the presence of an adequate dose of cyclosporine the additional benefit of Rapamune™ can be achieved with a fixed dose because in this case it's really the combination that we're worried about, not about any single drug alone, or we were concentration controlled cyclosporine.

I believe that once we get to the end here and we look at patients who are withdrawn from cyclosporine, we will in fact have to compensate for the variability of Rapamune™. I would not intend to have a fixed dose of Rapamune™ become the norm and try to set transplantation back to the late '80s or wherever it was before we had good assays.

So I hope I'm answering your question. You're hitting the right points.

DR. LIPSKY: The question is, has the dose been developed that is optimal and is it optimal for both safety and efficacy? I realize you can't redo trials and you went with what works. It just seems a little unusual that here's dose A for this condition, here's dose B, and it doesn't matter if you're dealing with a 50 kg or whatever body surface area.

I mean, to have a higher dose for high-risk patients and a lower dose for non and say we're not dosing just doses otherwise, just doesn't appear to be rational. Something isn't totally adding up.

DR. CAMARDO: I'd hate to leave on the note that you're saying it's not rational. Maybe it's

not the best that could be done, but I'd hate to think that this was the end of the development program for the new product. I think it's more like somewhere in the middle and I mean, we are here today to find out if we have the dose. So you've asked actually, one of the questions so I guess we'll have to get to that.

I mean, if anyone would like to make a comment I guess it would help.

DR. ZIMMERMAN: I would just like to comment that to dose on either mg or mg/m^2 I don't think it very pertinent because you simply don't know how much drug an individual patient will absorb when they are a site 304 PGP. I mean, it can vary from a factor of 5- to 10-fold. So fooling around with minor changes really wouldn't get you any better results.

DR. LIPSKY: Well, obviously, this draws a very high first-pass effect. But what about levels? I mean, when you're saying that it's 5 mg for a high-risk and 2 mg for low risk, what are you trying to achieve between the two? Are you getting more into the person? Is that what it is? Are you getting the same comparable level for the high-risk patient?

What's really going on there?

DR. CAMARDO: No, the high -- no, the kinetics are the same in Black and non-Black recipients. We concluded from the study that higher immunosuppression was needed to achieve a low rejection rate. Now you could argue, is that low rejection rate a goal of therapy for that individual?

But the data simply suggests that at the higher dose there was a better result for sub-group of Black patients, but it was not related to the trough level or the exposure of Rapamune™, sirolimus, and it wasn't related to the exposure for cyclosporine either because those were really identical.

DR. LIPSKY: You talk trough level. What about area under the curve or other measures of exposure?

DR. CAMARDO: Well, they're directly, linearly related. They correlate in -- I mean, in contrast with cyclosporine they correlate very, very well. I mean, that's not just a small study; that's over all the studies we've done from Phase I to Phase III.

DR. LIPSKY: So you have an explanation -- Henry, I'll end on this. So do you have an explanation -- cut me off -- what is the explanation of why 5 mg is better than 2 mg? A scientific explanation?

DR. CAMARDO: The only explanation is that in the Black recipients who were enrolled in the study the efficacy failure rate was lower for 5 than it was for 2.

DR. LIPSKY: And there must be an explanation for that. Do you have an explanation?

DR. CAMARDO: No, go ahead.

DR. KAHAN: It is well recognized that in the Black population there are dynamic factors that make them more at risk for rejection and graft loss, and they include the following. Number one, that if you do immune indices, mean tests of stimulation, they are more responsive.

Second, many of the Black patients have been pre-sensitized and it turns out that the majority of blood donors, just like organ donors, are Caucasian. And so there are several dynamic factors

that have been identified, even when you kinetically control for concentration.

And this probably relates to sensitivity of the targets to the pharmacodynamic action of the drug, and we believe that that's racially inherited and that's been found through virtually all transplantation studies in clinical transplantation and virtually all organs.

DR. LIPSKY: So the explanation of why a higher dose works in them is not because --

DR. KAHAN: You're putting in more drug and you probably need a higher concentration to inhibit the target.

CHAIRMAN MASUR: Did you have a follow-up question, Larry, quickly, before we move on to the right?

DR. HUNSICKER: I don't know how quick this becomes. I did want to say two things about this discussion that's been going on that gets back to skip 2. First of all, for somebody's who has been on this immunosuppressive panel, this is deja vu all over again.

We have gone through exactly this same development with respect to tacrolimus, with respect to mycophenolate. Both of these agents were introduced at fixed doses without monitoring and then -- well, tacrolimus is now monitored; mycophenolate is on the verge of being monitored, and I suspect this will come to be monitored.

So there's a part of me that says we've got to be consistent in what we are asking of the drug companies. We have gone this route all this while and this is how we've gotten here. And I share with the presenter -- whose name I've already forgotten -- which I do to everybody's name.

I share with him the sense that we're going to wind up monitoring this because it makes absolutely no damn sense that you're going to have two people with 7-fold different absorptions given the same dose. But the study was done the way it was done.

The second thing is that I would like to suggest at one point or another since you said a quick follow-up I will permit this to be deferred. Is that

in the briefing book you did speak about a secondary analysis of actually the rejection rate regressed against the actually achieved trough levels or whatever.

And I think that, as my recollection of what I read on this thing, was that that was fairly convincing; that higher levels are in fact, more immunosuppressive. And that therefore, serves as some basis for the assertion that 5 mg is likely to be more immunosuppressive than 2 mg because you've got a higher level under the curve, because it's dose-related, and because you can relate the frequency of rejection to the actually achieved trough level.

So that would be the thing that links the dose back to what Barry has just said. We know that Blacks are at greater risk for rejection, and for every immunosuppressive agent we've used, they have needed higher doses.

So I don't know whether that's an invitation to discuss that. You may want to do that later.

DR. CAMARDO: Well, we could do it now if

you want. It's up to you.

CHAIRMAN MASUR: Let's come back to this. Let's make sure we get all the questions because I have a feeling that we may not resolve this to everybody's satisfaction with the data that we have presented so far.

DR. McDIARMID: Thank you for your presentation. I had a couple of questions regarding the decreases of triglycerides in cholesterol over time. Obviously the individual investigators could make all kinds of advice about diet and exercise, and I also notice that about 40 percent or so, almost half of the patients in the Rapamune™ groups, did go on some sort of lipid lowering agent.

And I'm trying to understand how the effect of these different interventions made the curves come down closer at one year. How difficult is it in fact -- how much work do you have to do as an investigator to bring the levels down by various manipulations? Do you have some information on that?

DR. CAMARDO: Unfortunately not. Remember, that's the other downside of the blinded

study. The guidelines that we put in place were to lower the Rapamune™ by 50 percent if the triglycerides were above 750.

And our study from Baylor indicates that if you then wait about a week you'll be able to see an effect because the triglyceride elevation occurs very quickly after Rapamune™ is administered; goes away very, very quickly as well. So we know that happens.

But we didn't have strict, step-wise guidelines in place so I really -- what I think was happening is that in the first few months all that really mattered was the acute rejection and the infections, and the changing of the cyclosporine and steroid levels, and that the lipids really weren't managed very well because they weren't that important unless they were very high.

It seems like after that the management got better but I can't really comment on how hard it was because we didn't institute a program. What we think though, is that once the other patient cyclosporine and steroid levels have gotten to be stabilized it will involve either the use of an agent

either immediately, or an adjustment downward and a dose of Rapamune™.

Remember again, no one knew what dose patients were on, so they were actually reducing blinded medicine. I have to believe that it will be a lot easier to deal with this once doctors know what actual dose the patients are on and what drug they were on.

DR. McDIARMID: Do we not have information though, about how many patients or what percentage of patients needed a dose reduction now that the study is unblinded?

DR. CAMARDO: Yes, I do have that, actually.

DR. McDIARMID: Because of hyperlipidemia?

DR. CAMARDO: Yes, I do have that, actually, and it was not surprisingly higher at the 5 than the 2 mg dose. John, I think we do have a dose reduction slide for that if you could pull it up.

DR. McDIARMID: Perhaps while he's doing that --

DR. CAMARDO: Yes, actually, that's a good

question.

DR. McDIARMID: The other question I had in regards to that is that there's at least some consideration that the HMG cholase reductase inhibitors may have an effect on rejection. And now that the study is unblinded were you able to correct for that?

DR. CAMARDO: We did and there was no effect. It didn't matter. Can you show that John? We're going to see a discontinuation slide. This is it exactly. I mean, it's not -- it won't answer your question exactly, Dr. McDiarmid but here there were no patients above 750 mg/dL for triglycerides and placebo or azathioprine; 3.4 percent of patients had a dose reduction and 8 percent for Rapamune™.

It's very difficult to be sure that that's predictive over the population because we don't really know whether doctors were starting with statins or starting with fibrates, and some of them may have been discontinued earlier. But that's the rate we observed for this level of triglycerides in terms of reduction.

DR. McDIARMID: I had another question

about the effect of rising creatinine. In the 40 or so patients that had full pharmacokinetic studies, which I understand were for Rapamune™, were there full pharmacokinetic studies also for cyclosporine and was the area under the curve perhaps something that needed to be looked at rather than the trough to try and understand the effect on the rises in creatinine seen in the Rapamune™ groups?

DR. CAMARDO: Yes. That's a good question, too. We have a lot more data on the trough levels than we do on the area under the curve. We have -- I think those same patients had cyclosporine area under the curve done as well.

What came out of that analysis was a slight increase in the AUC for cyclosporine and the combination Rapamune™ 2 and 5 mg groups. The increase was somewhere between 5 and 10 percent for the AUC as opposed to azathioprine. And I discussed this at length with our kinetics group and it's not clear if that represents a sampling error, because in fact that was limited to a center or two or three rather than the population, or it represents a real

effect.

Nevertheless, it's a small effect; 5 to 10 percent in the AUC. So you have to just take that for what it's worth and see what it means in your own interpretation. But we did do those.

DR. McDIARMID: I also noticed in the data that you provided for us that with hepatic impairment you might need to decrease the dose by a third. I didn't see any information about that. I assume that at least some of these over 1,000 patients might have had hepatitis C or perhaps developed hepatic impairment post-transplant.

Do you have any advice for us regarding that in the real world in terms of this study?

DR. CAMARDO: Well, the data we have from -- the hepatic impaired patients were child Q Class I and II. I'm not sure any patients in the Phase III actually got that far in liver disease. So I'm afraid I can only refer you back to the data from the hepatic impaired study.

DR. McDIARMID: The other interest I had, although the numbers were small, is the question of

hemolytic uremic syndrome. It seemed to be a problem even though it was 5.4 I think, percent of the patients in the 5 mg group.

And I just wondered what your take was on this. Is this something that needs to be watched out for in the 5 mg group? I see there seems to be a center effect. Can you shed a little bit of light on the HUS situation?

DR. CAMARDO: The very odd thing was that there was both the center effect and it appeared to be consecutive patients at that one center. And of the cases that occurred I think more than half were clustered at three centers.

The very interesting result is that the combination of Rapamune™ at 5 mg with cyclosporine with regard to the rate of hemolytic uremic syndrome is in stark contrast with the effect of Rapamune™ when it's used as rescue therapy for patients with cyclosporine-induced hemolytic uremic syndrome.

I mean, I don't want to keep showing data but in fact, out of nearly ten patients who were switched to Rapamune™ most of them recovered, did not

have continued hemolytic uremic syndrome, and were spared rejection. Actually, it's shown here.

I mean, these are patients who had HUS and were switched to Rapamune™. Some of them have been on for more than one year. Some of them were discontinued for various reasons: rejection and nephrectomy.

But I do believe it's -- I mean, again, I mean I can't fall back on the blinded study when I want to and not when I don't want to. Based on the results of the blinded study if they are using 5 mg they should be aware of hemolytic uremic syndrome. It's clearly a higher risk.

But again, I don't believe it's related directly to Rapamune™ because that doesn't make sense with the other experience we've had. Does that answer your question?

DR. McDIARMID: Yes. Just one other -- actually, just two more quick questions. I was interested to know whether any of the centers, perhaps on a single center analysis, had done any protocol biopsies at a year or so to see if there was any

effect in regards to chronic rejection given the other properties that Rapamune™ may have on the endothelial cells and smooth muscle cells. Do you have any information yet on that?

DR. CAMARDO: We only have a little bit of the information. I mean, you know, we spent a lot of time putting together what we had for the NDA. One of the two studies is -- both of these two studies actually, are going on for two years. We probably won't have anything substantial until the end of two years and that's only if we can get a reasonable rate of protocol biopsies. So I really can't at this point, give you anything useful on that.

DR. McDIARMID: Are some centers actually doing protocol biopsies?

DR. CAMARDO: Yes. Yes there were centers -- actually in one study protocol biopsies at one year were mandated for follow-up. So the data should be available but I just don't have it really ready for discussion today.

DR. McDIARMID: And just one final comment. I was interested that the age range for this

study included age greater than 13. It actually turned out I think, to only be a handful of 13 to 18-year-olds.

DR. CAMARDO: Yes.

DR. McDIARMID: But it does bring to mind and perhaps reiterate some of the comments about dose. You can get some pretty small 13 and 14-year-olds who have got renal failure. Do you really think that we're sure about the pharmacokinetics and the dosing in these -- I think I probably still call them pediatric patients?

DR. CAMARDO: Well, as I say, with regard to Dr. Lipsky's previous comment, we actually excluded children if they were less than 40 kg because we didn't want to have really small children. We actually believe that you have to monitor in children. The clearance is unquestionably higher, the variability is going to be a problem in the children. We believe they need to be monitored.

I have a slide showing the clearances. It's one-and-a-half to two times as high in children under 11 and slightly lower than in children, in

teenagers, by comparison with adults. So we have that information available, and a recommendation we're going to make is a fixed dosing in children is not a good idea.

DR. McDIARMID: So you'll probably be recommending a weight rather than an age in regards to your current dosing recommendations?

DR. CAMARDO: You know, I think based on the clearance we might be recommending -- yes, I think we might be recommending a weight. Yes, that's a good idea -- I haven't thought about it that much I mean, but we're thinking about children being transplanted -- children or teenagers -- for monitoring to be recommended.

Because I don't really think I can even correlate the clearance with the weight, frankly. So I'd rather not get into the -- I mean, we'd rather just make a recommendation that these patients it's much less predictable. And frankly, we didn't study enough to be sure of the effect at a fixed dose.

So I'm just -- you know, slides go up without me even asking for them. But anyway, this is

the clearance. All you have to see is this number. This are seven patients from 5 to 11; seven patients from 2 to 18; 25 healthy adults receiving up to 10 -- actually up to 20 mg/m^2 squared.

There is a difference in the clearance. It's lower in the adults. It's 287 in the adults; 443 in the teenagers; and up to 550 in the children. And the variability here goes all the way up to 1,551. There's a 7-fold variability here. It's a little bit less there. So I don't think we can make a case to be forcing fixed doses on children.

DR. McDIARMID: Thank you.

DR. STROM: I'd like to frame a question about delayed graft function for a couple of reasons. One being, as rapamycin blocks the activity of growth factors in and outside of the immune system, and then growth factors that have been described in experimental systems that support recovery from acute renal failure.

The other reason for the question relates to the higher rates of efficacy failure in the Global as opposed to the US study, and one of the differences

being as there was randomization before surgery and as a consequence the incidence of delayed graft function is inevitably going to be higher in the Global study.

So the specific question is, in patients who experienced delayed graft function at the get-go, was there a difference in the duration or outcome of delayed graft function in those patients in the Global study? Has this been looked at?

And I guess it also raises the opportunity at some point to ask the question, since the Rapamune™ plus corticosteroid had a better profile with GFR than cyclosporine plus corticosteroids, has Rapamune™ without cyclosporine been used in a cohort of patients as a means to get around some of the problems related to delayed graft function?

But I guess the first issue, the outcome of delayed graft function in the global study.

DR. CAMARDO: Do we have the duration? I'm seeing here the rates of delayed graft function. That just confirms what Terry is saying, which is that the rates are higher in the Global study. We have the efficacy stratified by delayed graft function. I can

show you that.

I don't think that we're going to be able to show you the improvement in delayed graft function. These are the results from the US study for delayed graft function versus no delayed graft function in terms of efficacy failure. This is the Global study. Do we have the results with -- this is the overall patient -- all patients from all the groups from the two studies.

And again, without delayed graft function, Rapamune™ has the benefit of reducing efficacy failure. It's also true -- I mean, these are the rates of failure for delayed graft function. This Rapamune™ continues to be effective in those patients.

Now, the only slide I do have that indirectly addresses your question are the dialysis rates which would be reflective of delayed graft function to some extent, but I don't have the days of delayed graft function unfortunately. We can pull this one up. It will just show you that we've collected the dialysis data.

And these are combined for the two treatment groups. The percent of patients requiring dialysis was 16 and 17 for the Rapamune™ group, 17 for azathioprine, and somewhat higher in placebo.

Now, if that answers your question the answer to the second question is short. There are a handful of patients and Dr. Kahan has studied them. You may want to comment. I think there's a manuscript submitted to transplantation. If you want to just briefly comment, Barry.

DR. KAHAN: There is a manuscript in press which describes the initial six patients treated with an anti-IL2R monoclonal antibody and Rapamune™ from the get-go. No calcineurin inhibitor. Those patients who started on calcineurin inhibitors when their renal function approached normal, namely below two, we've now supplemented that with an additional dozen patients, which was also presented at the AST.

So we feel very confident that we can go for intervals of 90 days or potentially even 120 days without calcineurin inhibitors just using IL2R coverage with the Rapamune™, coming in with very low

of calcineurin inhibitors and getting better renal function in the long-term.

Particularly in high-risk -- this was done Terry, in high-risk kidneys that had been stored for more than 36 hours from donors over the age of 60. Or patients who had other risk factors like multiple lost grafts in the past.

DR. CHAVERS: For the handful of patients age 13 to 18 years who actually received Rapamune™ how many required dose reductions, how many were treated with lipid lowering agents?

DR. CAMARDO: Can we answer that or do we have to take a lunch break and go back to the NDA? I don't think I can answer that question for you. I mean, I can probably find it but I don't have it here today. Sorry.

DR. CHAVERS: For the handful of patients who developed HUS or TTP, how many had HUSs in their original disease?

DR. CAMARDO: I think none. None.

DR. CHAVERS: Okay. My third question is, what does the Rapamune™ rash look like? Is that a

reason for discontinuation, how you treat it?

DR. CAMARDO: Not a reason for discontinuation in the studies. Frankly, I don't know how to treat that.

DR. CHAVERS: What does it look like?

DR. CAMARDO: I have to ask someone who's in the studies.

DR. KAHAN: The cases that have been reported have looked very unusual, and actually Rapamune™ was only indicated because it was a study drug, it was that people who were suffering the rash had never before had an allergic reaction. We don't know that it wasn't a reaction to sulfa in some of these patients or other drugs that were started at the time of transplant.

So there's no characteristic pattern. It's just an outbreak that occurs in proximity to giving the study drug. But we haven't been able to identify any characteristics of it.

DR. CHAVERS: Thanks.

DR. JOHNSON: I have a little bit of trouble accepting the dose recommendation of 5 mg for

the Black patients based upon solely the premise that the 5 mg dose was chosen and it seems to work. And I guess since the side effects seem to be dose-related one of the questions I have is, has any consideration been given to a dose escalation study in this sub-population of patients that may allow you to achieve the maximal effect of the method of rejection while obtaining a safety profile that may be more in line with those patients that were given the 2 mg dose?

A reference was made to the need for higher doses or other immunosuppressives such as mycophenolate. But the comparative recommendation of that dose if you go by the standard doses, this is about 50 percent above the standard dose, while this recommendation is 150 percent above if you go by (Inaudible.) and about 200 percent above if you go by body surface area.

Any comment on that, please?

DR. CAMARDO: Well, I don't really believe that -- physicians will use a fixed dose and stay on it come hell or high water with regard to side effects. So what I strongly believe will happen is

that if the 5 mg dose is available and if the physicians use it they will be cautiously adjusting the dose with regard to avoid side effects.

And I suspect what will happen is it will be adjusted downward over the course of time, relatively quickly after the acute transplant period. The most acute -- the highest risk for acute rejection period has been the first three months.

That's what's happened in our studies; that's what I expect to happen. But frankly, I'd have to stop short of recommending that the dose be used for a certain number of months because it would just be an estimate on the basis of the data.

Now, we've actually been in discussions with regard to making this recommendation much more solid with a study that actually looks at different doses in Black recipients. That could be one outcome of this meeting today; that we receive a recommendation like that. But we haven't done it yet.

So I mean, currently I believe that -- well, I just come back to the same thing. The data stand for itself. The 2 mg dose was not -- you know,

there was nothing wrong with it in Black recipients. It was as good as azathioprine.

It might offer some advantages if patients who were on Rapamune™ get into some trouble with cyclosporine for example, in which case one could argue that it would give some leeway to adjust the cyclosporine doses. But that will all be empiric, unfortunately.

I do not think it would be valid at this point to make a recommendation that 5 mg be given to Black patients indefinitely, but I don't think it would be unreasonable to consider that early-on in the transplant period for patients who are Black and highly mismatched or fall into other risk categories.

I mean, I still have to leave some of this to the practice of medicine. But you have asked the question that the committee has to discuss; not me. I can't give you any more information than I already have.

What little data we have suggests that the 5 mg is somewhat better tolerated in terms of infections and certainly in terms of lymphoma in Black

patients versus non-Black. And also with regard to the survival, the 5 mg dose was actually very good.

But that's a judgment that has to be made today. I mean, I can just provide what we have and I would be the first to admit that we don't have a randomized study with all the doses studied appropriately in that sub-population. But we could not do that in Phase III. And Dr. Hunsicker said it best. We're doing the first things first and that's where we are.

CHAIRMAN MASUR: A couple of other issues. Looking at your 6-month endpoint that you presented, the question I had is, how one interprets the one-year results then, that at one year the results seem to come together? Why do you appear to lose some of the benefit between six months and a year if you look at patient survival, graft survival?

DR. CAMARDO: Well, in fact, the overall efficacy results were still significant at one year. We didn't show those; we just showed you the log rank test for efficacy failure. They are all statistically significant at 12 months.

However, I think you're alluding to the fact that at six months the 2 mg dose had a higher rate of graft survival and by one year that disappeared. There were some later graft losses. There were some rejections, there were other problems. I just think that that difference in six months was pretty modest.

I'm sorry? Yes, that's a good point. Actually, you brought this up, you can show it on the screen. It turned out that they're small numbers. When you look for example, for a specific -- these are the log rank tests for time to efficacy failure over 12 months for azathioprine, Rapamune™ 2, and Rapamune™ 5 mg.

You've indicated that at six months the success rate for graft failure was better for the 2 mg group and this seems to be coming down by one year. Now, this is efficacy failure and these are still different than placebo at one year.

The problem we have when we go back and look at the causes of graft loss, they do include death with the functioning graft and then when you

look at that you can't really find one cause of death that stands out, that could be attributed to Rapamune™.

I mean, all we do is really prevent rejection. There have been other side effects that have happened. Indeed for example, two patients happened to be transplanted with vancomycin-resistant enterococcus. The donor had enterococcus; wasn't picked up. They both were randomized to the 5 mg group.

We had three patients who were non-compliant in the 2 mg group. So when we get to these small numbers we just can't -- I just can't say what happened. But I mean, we're -- it's gratifying that the effect that we observe at six months did not disappear by 12 months. But the survival -- the patient and graft survival, like many other studies, it's very good anyway and making an improvement in one year is very hard.

I think most of my colleagues will support me on that one; that it just may take a longer time to see anything. And some of these patients -- these

patients will continue to be followed for a number of years further.

CHAIRMAN MASUR: Dr. Lipsky had another question about the follow up data.

DR. LIPSKY: Just one final thing. On the safety database there were a varying number of patients: 700 at 12 months and at 24 months, 60. Does that mean that patients stopped taking the drug, less patients for a follow-up? How long did the patients in the studies take the drug?

DR. CAMARDO: No, it just means we don't have the data. The results are still out there. We just collect the data for six months and one year. Now we're going to collect data again in another year. They are many more patients followed for two years than just 60.

DR. LIPSKY: But even at 18 months, 700 or 230, it's the same problem?

DR. CAMARDO: It's mostly the same problem. There have been some more dropouts between one year and 18 months but it's not 500.

CHAIRMAN MASUR: Are there any follow-up

questions?

DR. FIRST: Can you come back to an issue that Dr. Hunsicker raised? What are your intentions for the dosing recommendation relative to the time of administration of the cyclosporine in the package insert at this point in time?

DR. CAMARDO: We are recommending that it be administered separated from the oral.

DR. SUTHANTHIRAN: Now in many transplant patients receive cyclosporine with mycophenolate and steroid rather than cyclo, azathioprine, and prednisone as a triple regimen. From the published data how does a regimen of mycophenolate and azathioprine compared to cyclo or rapamycin?

DR. CAMARDO: I'm sorry, I didn't hear -- how does it compare?

DR. SUTHANTHIRAN: In terms of biopsy-proven, acute rejection. And I think you showed very nicely that when a patient is treated with a regimen that contains rapamycin that's clearly superior to a regimen that is cyclosporine, azathioprine or cyclosporine and placebo.

If the other group were to be treated with cyclosporine and mycophenolate --

DR. CAMARDO: Mycophenolate -- what would have happened?

DR. SUTHANTHIRAN: Yes.

DR. CAMARDO: Well, we didn't do that, obviously. Do we have the other study rates or we just have the infections? Because my recollection is that some of the mycophenolate investigators could actually -- John, could you comment on that? I mean, you were involved in the MMF studies. Maybe you could just compare the groups for us in terms of sort of the efficacy of mycophenolate compared with Rapamune™.

DR. NEYLAN: John Neylan. Well Suthan, of course the time the study was designed the use of mycophenolate was not possible. Going back post-hoc at this point and comparing some of the critical components of the two studies, you may recall that the endpoint or the composite endpoint for the mycophenolate studies was a combination of biopsy-proven acute rejection and treatment failure; that is, discontinuance from the study.

And it's a little bit difficult to separate out acute rejection from that composite endpoint because if the occurrence to the treatment failure endpoint occurred then we don't really know much beyond that about the incidence of acute rejection.

That said of course, the composite endpoint, when compared to the control arms of the three studies, was roughly 40 to 50 percent improved. Looking at acute rejection specifically, that was also similarly improved with the caveats I've just mentioned.

On the whole, acute rejection frequency for the 2 g BID dosage was of the order of 24 to 28 percent. So it was in the area that we see the biopsy-proven acute rejection frequency for this control arm.

Of course, additional caveats pertain. There was a use of antibody induction therapy. The cyclosporine preparation was the Sandimmune™ preparation. So all that said, I think you can say that these results are certainly comparable to what

was obtained in that earlier era.

And my suspicion is that in clinical practice the comparisons of the sirolimus in conjunction with the oral and corticosteroids, versus in a comparison with mycothenolate, neoral, and corticosteroids, these sorts of comparisons will likely occur in our very near future.

CHAIRMAN MASUR: All right. Let's try and close this up a little.

DR. ABERNATHY: In the studies which treatment was concurrent with the statin or other hyperlipidemic agents, do you have CPK data? I noticed there were no cases of arabdamyalisis but it would be more reassuring to see the CKs.

DR. CAMARDO: I can show you the CKs. They are actually within normal range for everybody. There's a slight elevation in the 2 and 5 mg groups but they stay within the normal range. Do you want to show those, A.J.? Do you want to put up the CKs since we were asked?

Just a second here. I'm seeing it so go ahead and put it up on the screen. This is the

US/Global combined study for month-1, -3, month-6. These are the CK units. Obviously this is post-operative. By month-3 these have declined; these are the values in Rapamune™ 2 and 5.

Again, I just want to emphasize they're within the normal range, and they're all within the normal range for CK, I believe, but they are a little bit higher for the Rapamune™ patients. I think the statistical significance here refers to comparison for RAPA versus azathioprine.

This one here, that are a little bit higher here in the azathioprine than in the placebo group.

DR. ABERNATHY: These are patients all concomitantly treated with statin or are --

DR. CAMARDO: I'm sorry. These are all --

DR. ABERNATHY: -- they hyperlipidemic therapy?

DR. CAMARDO: I'm sorry, I didn't directly answer your question. I don't have the patients treated with statins but there are approximately 40 percent in this group and approximately 20 percent in

the azathioprine and placebo groups. So this includes all patients in the study. I'd have to go back and look at the -- unless you can tell me we have that. I don't think we have that. No.

CHAIRMAN MASUR: Last question, Robert.

DR. WOOLSON: Obviously when you do enough sub-group analyses not everything is going to be significant. We often worry about the other side; too many things will be. But I was struck by one finding in the briefing book; namely, that there does not appear to be an effect among females in either study that was significant. And I was wondering if you could elaborate on that lack of beneficial effect there and in particular, whether that might have any relationship to the discussion that we had earlier about the dosing and body size and so forth.

DR. CAMARDO: Yes, the first point is, we could have underpowered the study for females. So that's one. There is a numerical difference, I believe, in both studies. It's very narrow in the studies, however.

There is a little bit of a difference in

clearance. I don't think that accounts for the difference. I think the major factor is that there was a slightly higher number of female patients randomized to azathioprine. They did extremely well by comparison to males.

In fact, if you look at gender, which is shown here, this is the rate of -- the primary endpoint. If you just look at the azathioprine group, the efficacy failure rate is 39 percent in males and 23 percent in females. So you know, I believe that for some reason this just worked better in the female population.

You know, I'm really at a loss other than that. But the fact is, we didn't specifically try to enroll enough female patients to accommodate this as the assumed efficacy failure rate. There is a difference from the placebo group to the Global study.

It barely reaches statistical significance for the higher dose group, but the trend is there for the placebo. I don't believe it's related to the, a) that females did better on azathioprine, and there was a slight misrandomization with excess females in the

azathioprine groups. Don't have any other explanation than that.

CHAIRMAN MASUR: Well, obviously it's not a burning question. We'll come back. We're now a little bit behind schedule but Dr. Camardo, you responded to all our questions with your data.

Instead of going to the FDA presentation now we'll take about a 45 minute break for lunch and at 12:45 we'll come back for the FDA presentation. So we'll see you then.

(Whereupon, a luncheon recess was taken at 11:53 a.m.)

A F T E R N O O N S E S S I O N

(12:47 p.m.)

CHAIRMAN MASUR: I think we have a quorum of the committee members.

DR. GOLDBERGER: I think we have sufficient staff to begin.

CHAIRMAN MASUR: Okay. So, Dr. Tiernan.

DR. TIERNAN: Good afternoon. My name is Rosemary Tiernan and I work in the Division of Special Pathogens and Immunologic Drug Products. And this afternoon I have the pleasure to present to you the FDA's review of NDA-21-083, (Sirolimus), Rapamune™.

This slide depicts the members of our review team, and we'd also like to thank Drs. Joyce Korvick and Rigo Roga for their input to this review.

Our FDA perspective will be divided into four major sections. I'll begin with an overview of the design of the clinical trials, then Dr. Cheryl Dixon our Statistician, will review the efficacy of sirolimus. I'll come back and discuss some important safety issues regarding the use of sirolimus, and then we'll present our questions to the Advisory Committee.

The study population for sirolimus consisted of de novo renal transplants. The ages of recipients as you already know, was greater than or equal to 13 years. The donors consisted of cadaver donors and living related and living unrelated donors. There were some notable exclusions.

There were no multi-organ transplants in the study, there were no re-transplants, and patients who required anti-lymphocyte antibody induction were not included.

There were several strengths of Studies 301 and 302 that I'd like to point out. These were randomized and double-blind control studies that allowed the unbiased assessment of endpoints based on acute rejection and an enhanced safety analysis.

There were standardized cyclosporine and steroid regimens that minimized a source of potential variability between the centers.

Additional strengths. Acute rejection was evaluated with standardized, histological grading system using the Banff criteria, and the pathologists were blinded to treatment assignment. There was

excellent representation of African-Americans in Study 301 and there was excellent follow-up; virtually complete assessment of graft and patient survival at one year.

As already outlined, there were some differences in US Study 301 and Global Study 302. US Study 301 obviously was conducted in the United States, and there were different ethnic populations that were in the U.S. and overseas in Europe, and this might contribute to differences in dietary habits and in the reporting of adverse events.

The randomization was different for Study 301 and 302. Because 301 was randomized within 48 hours after transplant it may have eliminated some patients with delayed graft function and surgical site complications. Hopefully these patients with delayed graft function would be included in the study designed for 302, which randomized before transplant.

Again, both double-blind. Azathioprine was the active control in 301, placebo control in 302. The stratification included race and investigator in 301, and in 302 donor origin and the investigator.

And 719 patients in 301; 576 patients in 302.

Immunosuppression, just to review this. Antibody induction therapy was prohibited; mycophenolate mofetil and tacrolimus were prohibited; acute rejections were initially treated with steroids and antibody therapy was utilized as needed.

We're already aware concomitant steroids and cyclosporine provided the background, and cyclosporine was managed with target cyclosporine trough levels.

Prophylaxis was for pneumocystis carinii. That was mandatory for the first year. CMV prophylaxis was mandated for high-risk patients; that is, CMV-negative recipients of CMV-positive kidneys. And this was mandatory in months 1 through 3 and recommended for other patients. Prophylaxis for urinary tract infection was for six weeks and it was center-specific.

There were co-primary endpoints and they included efficacy failure at six months which was defined as the first occurrence of biopsy-proven acute rejection, graft loss or death, and patient and graft

survival at 12 months. The study was powered to show superiority for the efficacy failure endpoints but it was not powered to show superiority for the patient and graft survival at 12 months.

And Dr. Cheryl Dixon now will review the efficacy and then I'll return and go over some of the safety points.

DR. DIXON: Good afternoon. As Dr. Tiernan said, I'm Cheryl Dixon, the Statistical Reviewer of the sirolimus NDA and today I will be discussing the FDA's perspective of the efficacy analyses.

In my presentation today I will briefly review the primary analyses which we essentially agree on with the results presented earlier by Wyeth-Ayerst. I will then further discuss some secondary analyses of the efficacy failure endpoint which include various demographic subgroups, a high-risk FDA-defined group, and the time to efficacy failure at six months.

The primary analysis of efficacy failure at six months for each study consisted of comparisons between each dose of sirolimus and the comparator done

by using the Cochran-Mantel-Haenszel statistics stratified by investigator.

All patients assigned to treatment were included in these analyses. And to maintain an overall probability of Type I error of .05, a Bonferroni-adjusted significance level of .025 was used for each comparison.

The overall rates of efficacy failure in both sirolimus treatment groups were significantly lower than the overall rate of efficacy failure in the azathioprine treatment group. Efficacy failure rates were 18.7 for the sirolimus 2 mg group, 16.8 for the sirolimus 5 mg/day group, and 32.3 percent for the azathioprine group. And there were no significant differences in results across investigator sites.

When the analysis of efficacy failure is stratified by race the other variable used, a randomization, the overall efficacy failure rates remained significantly lower for the two sirolimus doses when compared to azathioprine. However, there were some inconsistencies in this effect across strata with the sirolimus 2 mg group, which I will address

when I further discuss various subgroup analyses.

In Protocol 302 the overall rates of efficacy failure in both sirolimus treatment groups were again significantly lower than the overall rate of efficacy failure in the placebo treatment group. The rates were 30 percent for the sirolimus 2 mg group, 25.6 for the sirolimus 5 mg group, and 47.7 for placebo.

The sirolimus rates are slightly higher than those seen in Study 301 and this may be explained by the fact that the time of randomization was before transplant in Study 302. Again, there were no significant differences in the results across investigator sites.

In Study 302 donor origin was the second factor used at randomization. When the analyses is stratified by donor origin there are still significant treatment differences for both sirolimus groups when compared to placebo. However, there are some inconsistencies within strata for the sirolimus 5 mg placebo comparison, and I will discuss this further in a few moments.

The Division considers efficacy failure at six months and patient and graft survival at one year to be co-primary endpoints. This is to ensure that patient and/or graft survival is not adversely affected by reducing early acute rejections.

Similarity, with respect to patient and graft survival, incidence rates is assessed with confidence intervals about the difference in the rates, sirolimus minus the control.

Because of the multiple comparisons, 97.5 confidence intervals are reported rather than the usual 95 percent confidence intervals. And a difference less than zero indicates a lower survival rate for the sirolimus treatment group than the control group.

In Protocol 301 sirolimus 2 had a patient and graft survival rate of 94.7 percent, which was slightly better than the azathioprine rate of 93.8 percent, which was in turn, slightly better than the sirolimus 5 rate of 92.7 percent.

The lower bounds of the 97.5 percent confidence intervals about the difference in rates is

used to assess the maximum decrease in patient and graft survival rate we can safely exclude. The lower bounds of these confidence intervals are -4.8 percent for sirolimus 2 mg and -7.1 percent for sirolimus 5 mg. These rates needs to be taken into consideration when assessing the overall efficacy and safety of sirolimus.

In Study 302 both sirolimus treatment groups had slightly better patient and graft survival rates at 12 months than the placebo group, with rates of 89.9 percent, 90.9 percent, and 87.7 percent for sirolimus 2, sirolimus 5, and placebo, respectively.

The lower bounds of the confidence intervals about the difference in rates are -6.3 percent for sirolimus 2 and -5.2 percent for sirolimus 5. Again, these rates need to be considered when assessing overall efficacy in safety of sirolimus.

I will now discuss the results of some of the subgroup analyses performed for efficacy failure at six months. These includes race, which was the second factor used as stratification for randomization in Study 301, donor source which was the second factor

used for stratification in Study 302, recipient gender, and the number of HLA mismatches.

In the following tables, please keep in mind that the control for Study 301 was azathioprine and placebo for 302.

As I stated earlier, in Protocol 301 there were some inconsistencies within the race strata for the overall treatment effect of sirolimus 2. The efficacy failure rates are slightly higher, or could be considered essentially the same in Black patients treated with sirolimus when compared to Black patients treated with azathioprine.

However, non-Black patients treated with sirolimus 2 have significantly lower efficacy failure rates than non-Black patients treated with azathioprine. In both Black and non-Black patients treated with sirolimus 5 mg have lower efficacy failure rates than those treated with azathioprine.

There were relatively few Black patients in Protocol 302. Black and non-Black patients treated with either dose of sirolimus had efficacy failure rates lower than placebo. The differences seen for

Black patients in both protocols were not statistically significant, but it should be noted that these studies were not powered to detect a significant treatment difference in the various subgroups.

Both studies show that patients who received a living donor organ had significantly lower efficacy failure rates with either sirolimus dose when compared to control. Patients treated with sirolimus 5 and received a cadaver donor also had significantly lower efficacy failure rates compared to control.

Treatment with sirolimus 5 compared to control conferred a larger significant treatment difference in patients receiving a living donor when compared to a cadaver donor. The efficacy failure rate however, of 61.3 in patients who received an allograft from a living donor treated with placebo is higher than would be expected, and the 42.9 percent in patients treated with azathioprine may also be slightly high.

In patients treated with sirolimus 2 who received a cadaver donor organ, they only had numerically lower rates when compared to control.

In both studies female patients treated with either dose of sirolimus had numerically lower efficacy failure rates than those females treated with control. One needs to remember that the studies were not powered to detect significant differences in the subgroups and the number of females were small.

No patients treated with either dose of sirolimus had significantly lower efficacy failure rates than control. It is also interesting to note that females on sirolimus have similar or slightly higher efficacy failure rates than their male counterparts, but females treated with the control are doing better than their male controls.

The analysis for the number of HLA mismatches is slightly different from the one presented by the applicant. We used a breakdown of zero to two in three to six HLA mismatches, compared to zero to three in four to six used by the applicant. Our background was based on registry information which may show more favorable outcome with two or less HLA mismatches.

In both studies patients with three to six

mismatches have higher efficacy failure rates than patients with zero to two mismatches. Both doses of sirolimus show significant improvement in efficacy failure rates compared to control for the patients with three to six mismatches.

Patients with zero to two HLA mismatches were small in number and only patients treated with sirolimus 5 had numerically lower failure rates than the control. The difference in the 2 and 5 mg sirolimus dose groups shows a modest additional benefit for sirolimus 5, and this benefit is moreso for patients with zero to two mismatches than for three to six HLA mismatches.

The proposed labeling for sirolimus is currently recommending that both doses be made available for clinical use. It is being proposed that the 2 mg/day dose be considered for use in the majority of patients, but the 5 mg/day may provide an incremental benefit to patients at higher risk for acute rejection.

Patients that could be considered at higher risk include patients who are African-American,