receiving a second or third transplant, have high, panel-reactive antibodies, and those with high degrees of HLA mismatch.

These studies were not designed to specifically enroll high-risk patients. Only patients receiving their first renal transplant were enrolled and patients who required antibody induction therapy were excluded. And these patients may be considered those at highest risk.

Thus, to perform a meaningful subset analysis with the information we had, a high-risk group was defined using factors that are recognized as having a predictive value on acute rejection from registry information that is widely known.

In this definition, a patient was considered to be at high risk if they received a cadaver donor organ and would satisfy at least one of the following: had a cold ischemia time greater than 24 hours; a PRA greater than 50 percent; or more than two HLA mismatches.

In Protocol 301 there is a decrease in the incidence of efficacy failure rates for patients to be

considered at high risk treated with either sirolimus dose when compared to azathioprine, but this difference is not statistically significant.

In Protocol 302 there is a statistically significant decrease in the incidence of efficacy failure rates for patients to be considered at high risk, treated with either dose of sirolimus when compared to placebo.

Patients not to be considered at high risk treated with either dose of sirolimus had significantly lower efficacy failure rates than the control. We realize that there are some limitations with this definition of a high-risk group. Around half the patients fall into the high-risk group.

In Protocol 301 the high-risk controls have lower efficacy failure rates than the non-high-risk controls. And the numerical advantage of sirolimus 5 compared to sirolimus 2 should be assessed in view of different toxicity, which Dr. Tiernan will discuss.

There is a growing body of data showing the consequences of early to late rejection on long-

term patient and graft survival. Thus, to go along with the overall rates of efficacy failure during the first six months, it is also informative to see where the events occurred. Also, please keep in mind the following plots when Dr. Tiernan discusses some of her safety analyses.

In this plot we had the time to efficacy failure in each treatment group during the first six months of treatment. The time to efficacy failure is significantly longer in the sirolimus 2 and the sirolimus 5 groups compared to azathioprine. Azathioprine is the lower curve and the 5 mg sirolimus group is the upper curve, with the 2 mg being in the middle.

From this plot we see that the majority of the events occur within the first 30 to 60 days post-transplant, and the majority of the events that occurred following 60 days occurred in the two sirolimus treatment groups.

This slide shows the number of first biopsy-confirmed rejection episodes that occurred after 60 days from the time to transplant and the

severity of the rejections. A first biopsy-confirmed rejection episode occurred after 60 days from time to transplant in 27 total patients; 13 in each of the sirolimus arms and one in the azathioprine group.

A majority of these rejections were mild in nature. And all of these patients were alive with a functioning graft at 12 months.

Now we have the plot of the time to efficacy failure at six months for Study 302. Again, we see that the two sirolimus groups have longer times to efficacy failure than the placebo group, which is at the bottom; sirolimus 2 and sirolimus 5 is the upper curve.

In Protocol 302 there were 24 patients with a first biopsy-confirmed rejection episode after 60 days from time to transplant. They include 12 patients in the sirolimus 2 group, ten patients in the sirolimus 5, and two in the placebo group. The events were mild to moderate in nature with only one sirolimus 5 mg/day rejection being severe.

Three patients with a rejection after 60 days had a graft loss following the rejection that

occurred within one year post-transplant. There were two sirolimus 2 mg, which one was a mild rejection and one was a moderate rejection, and one sirolimus 5 mg per group, which was mild.

To summarize the efficacy of sirolimus, both doses of sirolimus show efficacy by significantly reducing overall efficacy failure at six months. However, there are some inconsistencies across subgroups.

There is a modest, numerical advantage in favor of sirolimus 5 in certain subgroups of patients and overall patient and graft survival is good. You can exclude a decrease of no more than 4.8 to 6.3 for sirolimus 2 mg, and 5.2 to 7.1 percent for sirolimus 5.

The significance of these two bullet points needs to be assessed by taking into consideration some of the safety concerns the Division has regarding sirolimus, which Dr. Tiernan will now discuss.

DR. TIERNAN: The safety perspective will be divided into three main sections: the first

section on deaths, graft losses, and discontinuations; the second will deal with some of the common hazards that result from the use of transplant immunosuppression, such as first transplant lymphoproliferative disease infection, and post-transplant diabetes mellitus; and then we'll finish with a discussion of the treatment emergent adverse events such as thrombocytopenia and leukopenia, but spend a little bit more time on the hyperlipidemia and renal function issues.

I have two tables here, one for 301 and one for 302, which are basically just a summary of the deaths and graft losses at 12 months as presented as the sponsor as well. And as you can see going across for the different groups for sirolimus 2, sirolimus 5, and azathioprine, there's no significant difference in death and graft loss.

And again, this is also the case in Study 302. Looking across this time at sirolimus 2, sirolimus 5, and placebo. No significant differences here in death and graft loss.

With death, the most common reason for

death was vascular, cardiovascular, or cerebrovascular, or infection. The overall death rates is just seen at 12 months in 301 and 301 were 1.9 percent for azathioprine, 2.8 to 3.5 percent for sirolimus 2, four to five percent for sirolimus 5, and 5.4 percent for placebo.

Discontinuations. The most frequent reasons for discontinuation were unsatisfactory response in azathioprine, placebo, and sirolimus 2; and with sirolimus 5 it was adverse event.

Okay, we'll start with the hazards of post-transplant immunosuppression. Post-transplant lymphoproliferative disease, the rates of PTLD were essentially similar to that found in other trials. Please keep in mind that despite this decreased use of anti-T-lymphocyte antibody that was found in the sirolimus arms, the highest incidence of PTLD was 1.4 percent and it was found in the sirolimus 5 arm.

When we looked at post-transplant lymphoproliferative disease please keep in mind that we did not know the EB virus status of donor and recipient.

Infection in studies 301 and 302. Across the treatment groups there were no increases in the rates of sepsis, pyelonephritis, wound infection, or pneumonia. For azathioprine and placebo these were groups that had higher rejection rates and an increased requirement for immunosuppression. However, in those groups there was no difference with respect to serious infection.

Regarding opportunistic infection, in the sirolimus 5 mg arms, as previously stated by the sponsor there was a higher incidence of mucosal herpes simplex. This is rather difficult to explain because many of these patients were on a cyclovirin and cyclovir prophylaxis; two antiviral drugs that have excellent efficacy against herpes simplex.

So this is a difficult thing to explain. But again, as pointed out by the sponsor, this is a diagnosis that's not necessarily culture-confirmed.

There was a decreased incidence of CMV infection and disease that the sponsor feels may have been explained by the mandated CMV prophylaxis that was utilized for high-risk patients; that is a CMV-

negative recipient of a CMV-positive kidney. And that certainly contributed to the decreased incidence of CMV infection and disease as compared to the MMF trials and the tacrolimus trials.

But also keep in mind that with CMV infection it's also very important to be cognizant of the donor recipient's status and the mismatch for CMV, and there were only 6.6 percent high-risk Black patients and 22.1 percent high-risk non-Black patients in this trial.

Post-transplant diabetes mellitus. The definition utilized in this trial: there was no prior history of insulin-dependent diabetes mellitus or non-insulin-dependent diabetes mellitus, and they had to require insulin for greater than or equal to 30 consecutive days with less than five days interruption to maintain a normal fasting blood sugar.

Overall, the incidence of PTLD was uncommon in this trial, even in the control groups which were treated with steroids for higher rejection rates. There was no significant difference in PTLD when we looked at the subgroups, be they Black, non-

Black, female, or male.

Okay, regarding treatment emergent adverse events. These are the events that occurred with a frequency that was greater than or equal to 20 percent. And the statistically significant increased incidence of the side effects seen with sirolimus 5 versus sirolimus 2 were fever, diarrhea, anemia, leukopenia, thrombocytopenia, and hyperlipidemia.

For the treatment emergent adverse events that occurred with greater than five percent and less than 20 percent frequency, again there was a statistically significant increase for sirolimus 5 versus sirolimus 2 with these side effects, which were chills, facial edema, hypotension, hypokalemia, increased LDH, skin ulcer, lymphocele, tachycardia, insomnia, and epistaxis. The cases of epistaxis were not necessarily associated with thrombocytopenia. I think only one case was.

Hematologic adverse events. Thrombocytopenia as already discussed, was dose-dependent. It was reversible. The mean counts were still in the normal range with no count being less

than 50 X 10^9/L. There was no increased incidence of bleeding.

For leukopenia, also dose-dependent, reversible. No cases of neutropenia. There was no white count that was less than 1000 mm^3. There was no increased incidence of infection.

Hemolytic uremic syndrome, thrombotic thrombocytopenic, also called HAS/TTP. There were 43 cases of HAS/TTP reported in the studies for 301 and 302. There were higher rates of HAS for sirolimus 5 and there were no patient deaths due to HAS. There were three patients who had graft loss: two in the sirolimus 5 group and one in the sirolimus 2 group.

For the liver function tests, we did not have data on hepatitis B virus and hepatitis C. The liver function tests that were evaluated were AST, ALT, and Alk Phos. There was a low percentage of patients with elevated LFTs to five to ten times the upper limit of normal. This was equally distributed among the study groups and there were no significant trends that were identified by race or gender.

Okay, hyperlipidemia I'll spend a little

bit more time on. Hyperlipidemia was a major side effect that was noted in the Phase II and Phase III trials. We did an analysis at the FDA. We looked at a transplant recipient cohort that actually started with normal fasting, pre-study, total cholesterol, and triglyceride levels, and then we looked at them to see if they developed new elevations on study drug.

Please keep in mind we didn't have lab tests such as HDL and LDL because those weren't mandated to be collected in this study.

This is the analysis of that cohort of patients for Study 301; again, keeping in mind azathioprine is the control here and sirolimus 2 and sirolimus 5. The group in the pre-study with less than 200 mg/dL of cholesterol coming in.

Azathioprine, 72 percent of the patients were starting the trial with a total cholesterol fasting less than 200; sirolimus 2, 71.8 percent starting the trial with normal cholesterol; sirolimus 5, 71.2 percent coming in with a normal cholesterol.

On study, you can see the percentages that developed a total cholesterol that was greater than

240. For azathioprine it was 47.4 percent as opposed to the sirolimus arms which were sirolimus 2 at 64.2 percent and sirolimus 5 at 68.2 percent. And these were significant increases with the addition of sirolimus 2 and sirolimus 5.

We looked at Study 302, again, keeping in mind that placebo was your control here. At pre-study, the percentage of patients who started the study with less than 200 mg/dL of cholesterol: 73.1 percent in placebo; and the sirolimus 2 arm, 71.8; sirolimus 5, 75.3.

On study, for placebo 41.1 percent of those patients developed a total cholesterol elevation to greater than 240; 75.5 percent for sirolimus 2; 72.7 percent for sirolimus 5. And again, these increases with sirolimus were found to be significant.

Bear with me. We did the same thing for triglycerides; the same set of tables. I won't go through the whole thing but I think basically you can see our parameters. Pre-study were 200 mg/dL for the triglycerides, and we were looking at the on-study development of greater than 500 mg/dL triglycerides.

Again, most of the studies were enrolling 72, 75s, 83 percent, starting with normal triglycerides. And you can see, on azathioprine for 301, five percent developed elevated triglycerides to greater than 500; as opposed to the sirolimus arms which were 14.5 percent and 17.9 percent developed elevated triglycerides. And again, these were significant.

Okay, Study 302 again, the same sort of table. And again, looking at the development of elevated triglycerides on-study, placebo in Study 302, 2.2 percent as opposed to sirolimus 2 and sirolimus 5 -- 15.5 percent for sirolimus 2, 23.5 percent for sirolimus 5. And again, significant changes.

We looked at the use of lipid-lowering drugs in the treatment on new onset hypercholesterolemia. And in this cohort of patients the percentage who required lipid-lowering agents included: for placebo, 15.8 percent; azathioprine, 21.6 percent; sirolimus 2, 45.6 percent for Study 301, 42.3 percent for Study 302; sirolimus 5 you can see, 51.8 percent for Study 301, 46.7 percent for Study

302.

When we looked at who continued on lipid-lowering agents, greater than 63 percent of those who were initiated on a lipid-lowering agent for high cholesterol continued on therapy at six to 12 months. And I think we've already discussed the difficulties with trying to assess the use of lipid-lowering agents.

People generally follow the National Cholesterol Education Program Guidelines. Those are based on LDL which was a value that we didn't have in our risk factor stratification; depending on smoking, hypertension, diabetes and their history. So it's a difficult thing to get a handle on.

Renal function. We struggled -- we tried to reconcile this problem with sirolimus being an efficacious drug for prophylaxis of rejection and yet at the end of 12 months this drug does not do as well as the controls as far as renal function. And it's believed that sirolimus lacks nephrotoxicity, but why is sirolimus effective at preventing acute rejection?

But at 12 months the renal function again,

is measured by keeping in mind these are the criteria we use to measure Nankivell GFR, serum creatinine is significantly worse than that of azathioprine and placebo.

When you are evaluating the assessment of renal function please keep in mind that the investigators were blinded when they made their decisions to discontinue study drug because of acute rejection and decreased renal function, but the cyclosporine doses and the whole blood cyclosporine trough concentrations were similar across treatment groups.

There were more rejections in the control groups and we were concerned, was this possible that we could be eliminating a significant proportion of patients who had poor renal function and thus unfavorably weighting the analysis of GFR at 12 months against sirolimus?

So once again, we did an exploratory analysis attempting to minimize bias and get a better handle on this renal function problem. We tried to capture all the patients for the study visit at 12

months, including those who discontinued study drugs. And even at that, 11 to 14 percent of the study population were still not included in our analysis.

When we attempted, and I think we were fairly successful, at ensuring that the analysis population was representative of Study 301 and Study 302 populations by trying to demonstrate similarity in the rates of rejection and the time to first rejection.

This slide shows the Study 301 mean GFR results at 12 months. We used a window of 337 to 393 days. And you can see for azathioprine that the mean GFR at approximately one year was 65.9 cc/min, and for sirolimus 2 it was 57.4 and for sirolimus 5 it was 55.1. So these are significant differences with azathioprine coming out with better renal function as measured by mean GFR at one year.

If you look at the N, the observed and total number of patients that we enrolled, you can see that that ranges from about 78.9 percent to 82.5 percent. So we're still missing patients in this analysis. It was actually rather than 20 percent of

the patients missing we took an additional look at those patients.

Some were losses for graft loss and for death, so we really feel that only about 11 to 14 percent of the population is missing in this analysis.

Let's go to Study 302 again, a very similar table. I'm sorry, 301; we'll do the serum creatinine first. For Study 301 the serum creatinine at 12 months, again, the same window: 337 to 393 days. Azathioprine is the control.

You can see the mean serum creatinine at one year is 1.6 mg/dL and sirolimus 12 is at 2.17 and sirolimus 5 at 2.09. And again, these are significant differences in favor of azathioprine.

Again, looking at mean GFR at 12 months, Study 302, the placebo with a mean value at 61.7 at 12 months at opposed to the sirolimus 2 and sirolimus 5 groups at 54.9 cc/min and 52.9 cc/min, respectively. Again, significant differences in renal function in favor of placebo.

A little bit different for the evaluation of serum creatinine at 12 months. For Study 302

again, placebo control versus sirolimus 2 and sirolimus 5. Placebo with a mean serum creatinine of 1.96 mg/dL; sirolimus 2, 2.11; sirolimus 5, 2.11. And these were not significant differences.

So the summary on the exploratory renal function analysis is essentially that the mean GFR at 12 months is significantly better for azathioprine and placebo in Study 301 and 302. And the mean serum creatinine at 12 months is significantly better for azathioprine in Study 301 but not for 302.

The differences in GFR and serum creatinine were in the opposite direction to what one would expect based on the differences that we see with sirolimus in prophylaxing acute rejection. And cyclosporine exposure we feel could not explain these differences.

So as usual, another analysis was undertaken to try to answer some additional questions. And it became of interest to evaluate GFR among those who did not experience a rejection episode to see if there was an underlying difference that might be independent of rejection.

Because the mean time to acute rejection in sirolimus arms was greater than in the azathioprine and placebo groups, it became of interest to compare the GFR at 12 months in patients who had experienced at least one episode of acute rejection.

And I'll just review the setup for these tables because you're going to see about four of them. This is Study 301; again, mean GFR measured at 12 months using the Nankivell equation; window 337 to 393 days. And again, the three main groups: azathioprine, sirolimus 2 and sirolimus 5.

You can see the patients are broken out into non-rejectors and rejectors, and you can look at the mean cc/min at one year. And the non-rejectors definitely have better renal function than the rejectors: azathioprine, 67.5 as opposed to 61; the non-rejectors for sirolimus 2, 60 versus 46 in the rejectors; and sirolimus 5, the non-rejectors at 56.3 cc/min as opposed to the rejectors in sirolimus 5 with 45.7 cc/min.

When you compare the non-rejectors across study groups, the non-rejector for azathioprine has a

GFR of 67.5 cc/min at one year as opposed to the non-rejectors for sirolimus 2 and sirolimus 5, which are 60 and 56.3. And these are significant differences in the non-rejector group.

And then we compared the rejector group, and once again it's the same trend. The rejectors for azathioprine have a GFR of 61 cc/min as opposed to 46.7 and 45.7 cc/min for sirolimus 2 and sirolimus 5 at one year.

And again, Study 302 a very similar setup for these tables. This time the placebo group is being studied against sirolimus 2 and sirolimus 5 and again, the non-rejectors have better renal function than the rejectors: placebo group non-rejectors, 62.9; sirolimus 2 non-rejectors, 57.29; sirolimus 5 non-rejectors, 55.2. So for the non-rejectors the placebo group definitely has a better GFR at one year.

When you look at the rejectors, placebo group, 59.7 cc/min as opposed to the rejector groups for sirolimus 2 and sirolimus 5. And then come in at 46.9 and 43.5. And again, significant differences.

And lastly, we looked at serum creatinine

and broke that out also as rejectors and non-rejectors. And again, across the treatment groups, generally the non-rejectors are doing better and when you look at azathioprine versus sirolimus 2 and sirolimus 5, the sirolimus non-rejectors at 1.97 and sirolimus 5 non-rejector at 2.01 have higher values than the azathioprine non-rejectors at 1.51. And again, significant differences, significant trends.

For Study 302 again, we're looking at serum creatinine and breaking it out by rejectors and non-rejectors. These differences are not significant in this trial. Again, placebo non-rejectors, 1.84 versus sirolimus 2 and sirolimus 5 non-rejectors at 1.9 and 1.96. And for the rejectors again, placebo at 2.17 versus 2.83 and 2.72. So not significantly different when looking at Study 301 for renal function when evaluating serum creatinine.

So in summary, in all treatment groups patients with at least one episode of biopsy-proven acute rejection had lower mean GFR and higher serum creatinine at 12 months, compared to patients without rejection. Among the patients with acute rejection

the mean GFR was decreased and the mean serum creatinine was increased in patients assigned to sirolimus versus those assigned to azathioprine or placebo.

Among the patients without acute rejection the mean GFR was decreased and the mean serum creatinine was increased in patients assigned to the sirolimus versus those assigned to the azathioprine and placebo arm.

And finally, our safety conclusions for sirolimus. As you're well aware, there are dose-dependent adverse events as previously noted for sirolimus 5 versus sirolimus 2. There's a lower GFR and an elevated serum creatinine at 12 months and we look to the Advisory Committee to tell us, number one, is this of any clinical significance? Were the correct tests used to assess renal function?

Hyperlipidemia. This is a consistent finding. It requires careful monitoring and treatment but we do feel that this can be managed. The long-term implications still remain to be seen. We don't feel that one year or two years of monitoring may tell

the whole story as far as cardiovascular complications.

And finally, we would recommend that if there are any recommendations for higher sirolimus dosing for African-American patients, please interpret these with caution if they're based on the assumption that no increased incidence of CMV, PTLD, or opportunistic infection is equivalent to saying they're under-immunosuppressed.

Because the development of infection and malignancy such as PTLD in a post-transplant recipient are dependent on so many different factors, including the epidemiology of the prior exposures that the patients had as well as the level of immunosuppression.

Do you want me to present the questions? Okay.

CHAIRMAN MASUR: Before proceeding to that it looks like there are a few members of the committee that have some questions for you, Dr. Tiernan. Larry.

DR. HUNSICKER: I would like to make two comments about some ways in which you present the

statistical analyses, and then finally initiate a discussion about the GFR issues which you may understand, I'm very interested in because I've been very interested in the impact of various effects on inter-sepsis, the rate of loss of GFR.

The two first questions -- maybe these are very broad policy issues, but when you're talking about what is in essence, an equivalence study and you've presented the range of possible or credible differences in survival of either the kidneys or the patients, you've done this study by study.

Now, when you're looking at positive outcomes in terms of P-values or something like that, it probably -- I'm going to make a statement and then have you respond to it. This gets back to the age-old question for all you folks. Is one big, combined study the equivalent of two studies, each of which is half the size of the big, combined study?

At least one position is no, they're the same. You just have to combine the two. Another is that you do get a different sense of consistency by looking at two separate studies.

Now, my assertion would be that when you're looking at P-values that the person is going to take out a very different conclusion -- I'm sorry, will take out the same conclusion saying that this is a study that is significant -- in both cases the study is significant at the .001; that is to say, we've got very heavy evidence that this is effective.

But if you show the confidence intervals as including as much as seven percent loss in each of two studies at the extreme of your 95 percent or whatever it was, confidence intervals, in fact, you're overstating the thing. Because in fact, to be that far off you'd have to be in the far extreme in both dimensions of a 2-dimensional thing.

I would propose to you -- and I ask for your comments on this -- that to get a confidence interval, really to be fair you have to combine your data in some fashion or another. Because the likelihood that we could be as far off from equivalence as seven percent in both of these studies simultaneously is very small.

A second and parallel thing has to do with

the issue of how to present subgroup analyses. As you have said in your presentation on several occasions the study was not really powered to look at subgroups.

There are two ways in which you can fail at significance in subgroup analyses. One is that the relative reduction in risk or change in risk is precisely the same, but N is smaller. That probably has a very different implication from where the relative decrease or change in risk is very different and the probability doesn't exist.

So some people would say that if you're going to say look, I'm a little troubled that there's no consistency here, that you should show that in addition to the fact that the P-values are no longer significant, that actually the size of the effect is different.

In most of the cases of the subgroup analyses here the size of the effect is comparable. In some cases that's not yet true. But I would just -- I ask you about this because I feel that the way this was presented raises more questions than maybe is fair to have raised.

Then I'd like to get back to the issue subsequently, of the GFRs.

DR. TIERNAN: I may not be able to answer your question statistically. I may refer those to the Statistician. But the reason that we separated the studies was basically because the randomization was different. For instance, with Study 302 that population may have had more delayed graft function in it.

DR. CAVAILLE-COLL: I'd also like to help her answer that study, too. That in addition the problem is, when you combine the two studies, how do you handle the controls? One of them was a placebo arm and one of them was a triple arm with azathioprine.

Finally, we expect that there are some geographical differences between studies that are essentially run in the U.S. and Global studies. This has been a consistent finding across clinical studies of similar designs. So that combining a U.S. study with a study that was largely non-U.S. and that had a different kind of control arm, different randomization

at baseline, and probably different ways of treating acute rejection -- patterns really between U.S. and non-U.S. countries -- I think created more problems. And I felt that we had to present the studies as they were.

DR. HUNSICKER: Let me respond to that. I think, as I go back, if you look at the issue of the -- if you're just presenting P-values that's fine. You keep your studies separate. But when you give confidence intervals, what you presented at the end was that the lowest, reasonable negative difference in, let's say graft survival, is -7 to -5 percent, or something like that -- looking at the seven percent from one study and the five percent from the other study.

But if you look at this as a joint distribution, even if there are two independent studies, they are two independent studies. The chances that you would have that much difference in both of the studies would be extremely small.

So that I just feel that if you're going to present confidence intervals you really have to --

I think you have to correct for the fact that you've got two cracks at this data and that they are complementary.

DR. CAVAILLE-COLL: Well, basically, this was the primary analysis. We had to present what was the prospective primary analysis as defined by the data analysis plan. And it's customary to do that before we do things such as combining.

DR. HUNSICKER: Well, then maybe you should do the combining. There are ways to combine. I don't want to beat this dead horse but I just want to say that I think that the -- to suggest that there is a reasonable, plausible chance that there would be as much as a five percent difference in outcomes for either patient or graft survival is small. It's just very small.

DR. CAVAILLE-COLL: Well, these are the 97.5 percent confidence intervals. So basically the way this has to be interpreted is that the maximum decrease we can exclude was the 97.5 confidence -- are the ones that we have stated.

DR. HUNSICKER: On a per-study basis?

DR. CAVAILLE-COLL: On a per-study basis, yes. Individual studies.

DR. HUNSICKER: Combined however one can combine those things, the chances are smaller.

Let me get to the other side. This is as I say, a philosophic thing that I am concerned about that we be fair about this. With respect to the analysis of GFR, first a question to you and that is that it looked to me as I looked at those data and going by quickly and on this sheet -- this is the fist time I've seen these put out this way -- it looked at though the effects of being sirolimus and having a rejection episode were independent.

That is to say, if you were to do an analysis of variance putting the three treatments and then with or without rejection, that you'd find that there was no interaction. Did you actually test that? Because if you could, that would make things just a little bit simpler to state; that you have a certain effect related to the treatment and a certain effect related to the rejection.

DR. DIXON: We didn't do an analysis of

variance breaking it down by rejector or non-rejector.

DR. HUNSICKER: Well, okay. let's just assume for a moment that those two are independent, because they looked to my eyes as though they were. The data on a rejection episode are very constant with the data that I presented at the AST meeting this past spring dealing with the impact of rejection from the humans database.

That is to say, a single rejection episode as I recall, cost about 8 cc's of GFR when you looked at six months. And that was very comparable. You have differences of somewhere between 6 and 14 with an average of about 8 to 10. That was the cost of a single rejection episode.

If in fact, there is no interaction -- and I think there probably is not -- there is also a similar sized adverse effect of being on sirolimus. Now, the question that was raised is, what is the clinical significance of this? Well, at the moment that that happens, probably none. That is to say, this year I don't much care whether my GFR is 56 or 64.

But if the rate of loss of GFR subsequently is equal in the two groups -- something we do not know -- but if that is the case, since there is an average rate of loss of GFR over time following kidney transplantation of about 2.5 mL/min, a difference of 8 mL/min at whatever time interval you'd take it, is the equivalent of three years of graft survival. So yes, it would be significant.

This is something that will not become apparent until very late. Now what does this mean in terms of the particular plan here? I think from the beginning the question when this issue was raised before is, is this rise in creatinine that we see in this particular study, the consequence of the way in which cyclosporine was handled by protocol, as opposed to the freedom that one would have had -- they would have had if they had done it differently?

Or is this in fact, a nephrotoxic effect of sirolimus when it is taken together with cyclosporine? In my mind remains an open question. Dr. Kahan has presented animal data suggesting that once you correct for the cyclosporine level in the

tissues that you can't see an impact of sirolimus.

The data that you have presented which suggests that the cyclosporine levels were equivalent as far as we can see in this group, would re-open that question. And I think because of the size of the difference in GFR at one year, and my interpretation of what that impact might mean, it has to be a very important question to answer; whether in fact, there is an interaction between cyclosporine and sirolimus that causes an adverse effect on renal function, or whether there is not.

It would seem to me this is an important thing for us to find out in the future. But what this is going to turn out to be I don't know. It depends upon whether this is replicable in other studies once the cyclosporine management is freed up.

CHAIRMAN MASUR: Any reply to that?

DR. CAVAILLE-COLL: I think this is very well noted. I think we'd like to hear more about this, too. I think we did show you some slides that overall, if the rejection occurred or if efficacy failure occurred, it occurred later in the Rapamune™

arm than in the sirolimus arm -- I mean, in the sirolimus arms than in the control arms.

We don't know to what extent that may be part of the explanation. We'd be interested in your thoughts, too.

DR. HUNSICKER: Well, I'm not enough of an expert, but lots of people have presented data to the effect that late rejection episodes are more expensive in terms of GFR than earlier ones. But you don't know whether the late rejection episodes you have in this case are typical late rejection episodes are simply early rejection episodes that have been deferred. And so you don't know.

The way to find this out would be to look at the difference in GFR between the non-rejectors and those who reject early and those who reject late. If they're the same then all you've done is to defer your rejections.

I tend to think that you're going to find out that they're the same simply because there looked to be no interaction between the size of the rejection effect and whether it was in the sirolimus group or

the other. But that's a very fast looking at it; non-mathematical look.

CHAIRMAN MASUR: Other questions or comments for the presenters? Courtney.

DR. FLETCHER: This would be a question on Dr. Dixon's presentation. My first reaction is on slide number 20 where you've compared the efficacy failure rate by race -- Blacks and non-Blacks. I just want to ask, in the sirolimus 5 mg group whether those rates are different from controls or not?

You don't have it indicated that they are, but I just wanted to make sure.

DR. DIXON: No, they're not different. Statistically, they're not significantly different.

DR. FLETCHER: My second question for you would be at slide 22 where you've looked at efficacy failure rate by gender. And a question as to whether it be appropriate to look at the pooled 2 and 5 mg doses for females and compare that with controls?

Simply just thinking, would that be a way to increase the sample size to ask the question of response of what looked to me to be the sex difference

in response?

DR. DIXON: No, we didn't look at that but it would be a reasonable way that you can look at the data to try to interpret some more of the differences.

CHAIRMAN MASUR: Terry.

DR. STROM: I want to pursue a bit the points and issues that Dr. Hunsicker just talked about. I think that the possibility that there's some subtle drug interaction of the sort that Larry's pointing to looms is a strong possibility, and perhaps the most likely.

But there is another possibility that I think ought to be considered, and the possibility that I'm going to talk about may be considered as controversial by some.

But I've been impressed with these series of studies that have been done by a consortium of Canadian transplant units showing the presence quite often, of substantial lymphoid infiltration in kidneys that have had stable kidney function at the time that the biopsies were obtained.

And they have gone on to produce data

showing that these kidneys are ones that deteriorate over the long haul and some recent data showing a rather dramatic effect by anti-rejection therapy. The numbers are small, the effect dramatic, and some people have objected therefore, to the interpretations that are rendered.

But one of the possibilities is -- and while I don't think it will turn out to be the answer, I think is possible -- that rapamycin has pushed from overt, clinically detectable rejection episodes into a format in which rejection is more subtle and is not easily seen and it is, you know, a grinding kind of beneath the surface, immune reaction that is causing the differences in renal function.

And I think that in any analysis that wants to come to grips with what is this all about, this latter, albeit less likely possibility, should be taken into account.

DR. HUNSICKER: May I respond to that? There is a problem in that not all of the patients were included in this final analysis. But if your hypothesis were correct Terry -- that is, you took all

of the patients including the rejectors -- the ones in the sirolimus arm should at the very least, not worse than the ones who are getting less immunosuppression. But they were.

DR. STROM: I'm not sure, Larry. I'm --

DR. HUNSICKER: You'd have to assume that there were more rejection episodes that had been suppressed and therefore not seen and not adequately treated in the Rapamune™ group, then even occurred in the control group. And that doesn't make sense.

DR. STROM: Yes. You know, while I favor your explanation I think that these sub-clinical rejection episodes are common and if an effective therapy is making clinically overt rejection episodes tilting the balance toward things that are more subtle -- and I'm, you know -- and much more easily repairable.

If you knew whether this is a subtle drug interaction you might go one way with cyclosporine. If you know that it was sub-clinical rejection episodes, you would do something entirely different. So I think that the implications for therapy are

important. And while I favor your interpretation of the data, I think that the other possibilities should remain on the table.

CHAIRMAN MASUR: I guess the question is, Larry if will allow me the last word, your point is an important issue but whether or not we can come to consensus is in a way that is relevant to our decision.

DR. HUNSICKER: This is really relevant to question 3 which is, what more do we need to know? And I think I come out of this meeting not knowing whether there is an adverse interaction, or as Terry suggested, some -- which I think is very unlikely -- sub-clinical rejection which is doing this.

Or as the presenters have suggested, simply that this is the consequence of being locked-stepped into a certain cyclosporine dose. I don't know, but we need to find out the answer because it does make a difference in the long haul.

CHAIRMAN MASUR: Darrell.

DR. ABERNATHY: Yes, I think Barry actually presented some data, the animal data that may

help us a little with that, because if we do hypothesize that sirolimus is a PGP inhibitor, seeing tissue exposure to cyclosporine enhanced as a function of that is not terribly surprising.

And I agree with you that certainly in the future you would want to know answers to those questions because then one would do something quite different with an adjustment cyclosporine dose.

CHAIRMAN MASUR: Steve.

DR. PIANTADOSI: Yes, thank you. I have a couple of questions for the FDA and then a couple of gripes, also.

I'd like to ask you the same two questions I asked the sponsor this morning. The first being, was the FDA involved at all in the decision to revise the sample size and the timing of that decision?

DR. CAVAILLE-COLL: No, the FDA was not involved in that, although we did advise the companies that they would need to have an adequate safety database.

DR. PIANTADOSI: I understand.

DR. CAVAILLE-COLL: But this was actually

prior to initiation of the studies.

DR. PIANTADOSI: Okay. Did the FDA perform any analyses that attempt to control this multiplicity of fairly strong prognostic factors? We've seen analysis by every subset imaginable one at a time ignoring all of the other factors that the other subset analyses demonstrate are important.

And I'm wondering if anybody has done, either within the studies or combining studies, analyses that attempt to simultaneously control more than one prognostic factor?

DR. SULLIVAN: Hello; Nancy Sullivan, Statistics, FDA. We did that for GFR. The sponsor has already addressed the answer to that question for the 6-month efficacy endpoint.

And I'll have to ask Cheryl -- I don't remember the exact details but there were still treatment differences in GFR accounting for, you know, risk factors like race, gender, number of HLA mismatches, and donor source of the organ -- whether it was living versus cadaver. We didn't look at whether people had a rejection or not in that model,

though.

DR. PIANTADOSI: I think that's extremely important information that part of my gripe is that kind of information should probably be up-front. It certainly would help me in thinking about some of the questions that have come directly from the agency.

But trying to make inferences from subset analyses that don't control for other important differences I think is at best, confusing, and potentially misleading. This gets into my general gripe which is that the emphasis on these kinds of analyses that ignore the simultaneity of risk factors is very problematic and the emphasis on percentages and differences in P-values is also unhelpful.

And I think we've heard from some of our clinical colleagues very important criticisms in that regard. There are better methods, for example, looking at odds ratios and attempting to adjust those odds ratios for the differences that we've all talked about, I think would be helpful.

They also can facilitate studying interactions and there may be some very important

clinical and possibly statistically significant interactions going on here that we can't see from the views of the data that both the sponsor and FDA have presented.

Furthermore, these subset analyses, if someone were to come to an Advisory Committee like this with a claim of efficacy and a desire for labeling based on a subset analysis, I'm not sure that effort would ever even get to the Advisory Committee, and I find it odd that we would consider basing a modification of the labeling on a subset analysis without considerably more exploration and prospective design on the part of this sponsor.

So there seems to be a double standard here about exactly what we do with that. And then finally, to complain a little bit about the confidence interval and return to the point that was made earlier, we look at these confidence intervals and we look at the very tip of the interval, down somewhere around five percent, and worry about whether we're near that five percent cutoff or not.

But I think the point is well taken that

that's partially an inappropriate thing to do. Aside from technically being an inappropriate use of the confidence interval, there's probably no support whatsoever for values that happen to be on the very edges of those confidence intervals.

The support is in the center of the interval, and to base a rejection of a hypothesis just because the tip of the confidence interval is near some pre-specified limit, is I think, totally inappropriate. And we need a better method for summarizing not only across studies, but for deciding what the definition of equivalence is.

And I don't think that just having the tip of the confidence interval touch some null hypothesis value is an appropriate basis for deciding on equivalence or non-equivalence. Those are some gripes. Thanks.

DR. SULLIVAN: Let me just clarify that the FDA didn't specify a five percent delta in terms of defining equivalence for that 12-month endpoint.

DR. STROM: I understand that, and my point is really not so much about whether it's five

percent or anything else. My point is that there's no support practically speaking, for values in the tails of the confidence interval. And therefore one should not look at what the tail touches and worry that that somehow represents reality.

DR. SULLIVAN: Well, that's similar to doing a non-inferiority test though. So where the lower bound is does tell you what type of a non-inferiority test you would be able to reject.

DR. STROM: Yes, but the problem with the tail of the interval is that if you look at a measure of support or evidence, the likelihood ratio is about seven or eight; even a tail of that confidence interval. And if that tail just touches some value and then you're going to say, well because it overlaps that value I'm afraid that that value may be the right one and therefore I can't declare it to be equivalent.

I'm saying it's inappropriate because the support for the values at the tip of the confidence interval is only about one-eighth of what it is at the center of the interval. And you don't want to base definitions of non-equivalence on such weak support.

That's the point. Not whether it's five percent or seven percent or anything else.

DR. SULLIVAN: Right, I think we essentially agree with you about that.

CHAIRMAN MASUR: As we discuss our three questions we're going to come back to the opportunity to make some more comments. Were there questions specifically for the presenters that we ought to do before we come back?

DR. STROM: It's a question that I probably should have asked at the earlier session, and with this foregoing discussion about the statistical analysis -- something of which I know very little -- I probably should keep my mouth shut.

However, in the past when we've considered other treatments there are a number of circumstances where we know that patients are placed at high risk for immunologic graft failure. They include race as we've discussed today, very young patients who aren't included in the study, and a number of other circumstances where patients are largely excluded from the study at hand.

And in the past, patients across all of these high-risk groups have responded relatively uniformly to other therapies. And the question that I'm posing is, there's a one-size-fits-all dose recommendation for high-risk patients at 5 mg. It seems from the data that we've seen that both efficacy and toxicity are dose-related.

So I'd like to come back to the question. Are all of the high-risk groups equally benefitted by the higher dose or are there subgroups that are not receiving benefit from the higher dose and if so, what are they?

CHAIRMAN MASUR: Larry, are you going to answer that?

DR. HUNSICKER: I am going to start an answer. I actually had thought that we were going to get to this when we got to question number 2. However, I strongly object to the global concept of a high risk because in fact, within the data presented to us there were three high-risk groups.

There were the group of patients with increased numbers of mismatches in which the risk was

just as high as they were in the African-Americans as I recall. And in fact, 2 mg did just as well as 5 in that group.

There was the group of patients who received cadaveric as opposed to living donor transplants who were at higher risk. They did on average, just as well with 2 as they did with 5.

And I saw no global evidence that any identifiable "high-risk" group did better with 5 than with 2, with the sole exception of the African-Americans. And that is not absolutely solid from within the data that we have from this study.

So my answer to you Terry is that the only group for whom we have seen evidence that there may be superiority of a different dose from 2, is African-Americans.

DR. STROM: I mean, that's my recollection of the data, too. You just have had more in the way of assertiveness training than I have.

(Laughter.)

CHAIRMAN MASUR: On that note, maybe we ought to get to the questions, although Dr. Lipsky has

also been taking assertive training here.

DR. LIPSKY: No, just a question for the FDA. Is there any statistical evidence that there's a dose-related increase in toxicity -- any toxicity -- that was statistically significant?

DR. SULLIVAN: I believe Rose covered -- there were several adverse events that were significantly higher in the 5 mg versus the 2 mg.

DR. LIPSKY: Then in the two.

DR. SULLIVAN: We could put those slides back up.

DR. LIPSKY: That was what? That was lipid mainly?

DR. SULLIVAN: There were two slides: one for adverse events greater than 20 percent, I believe, and then one for adverse events that occurred between 5 and 10 percent.

DR. LIPSKY: But not some global -- I mean, a whole list of things? But if you took --

DR. SULLIVAN: For each of those there was a significantly higher rate on the 5 mg versus the 2 mg.

DR. LIPSKY: For each item in the list?

DR. SULLIVAN: Yes.

CHAIRMAN MASUR: Okay. You can take a quick look at that while Dr. Goldberger poses questions to us. Mark, do you want to run us through the questions?

DR. GOLDBERGER: Yes. I was just going to wait until they put them up on the screen, actually, and make a few comments here.

Our first question: is sirolimus safe and effective for the prevention of acute rejection in patients receiving allogeneic renal transplants?

And again, obviously the assessment of safety and efficacy -- particularly the assessment of safety, takes into account the disease being treated and the benefit being shown. It's also important that, as one thinks about this, to be certain that the product can be adequately labeled for safe use.

That is to say, if there are issues that come up in the assessment of a product and one has a sense about how to deal with it but they can't be translated into wording for a label, that poses some

problem that needs to be specifically addressed.

If the answer to this question is "yes", we would like an initial recommendation as to what dose you would recommend. And keep in mind that the dose must be safe and effective. It need not be optimal. There's been an enormous discussion about that issue this morning.

I think everyone has come to recognize that the dose here may very well not be optimal, but that's really not the issue for approval. It needs to be safe and effective.

If the answer to question 1 is "no", what additional data would be required? And we would in particular in that circumstance, like you to distinguish between new analyses of data that has already been submitted, versus the need for new studies of some type. And I think it's very important to distinguish between the two of those.

All right. As to question number 2: is there a need for an alternate dose in specific populations? And obviously as a starting point we would need some definition of who those specific

populations would be. And of course, they ought to be definitions that can be clinically used; that is, markers that can be assessed easily, clinically.

If "yes", is there sufficient information to support such a dose, and if not, what additional studies would be needed? And again, that would be either new data or new analyses on already existing data. And again, it would be very important for you to define and distinguish between the two of those.

And our last question is: what additional Phase 4 studies would you recommend? And I would enlarge that in the following way; that this could mean both new clinical trials or specific recommendations about follow-up on clinical trials, for instance, already underway.

As you've heard, follow-up is still being collected, at least for some parameters, on the Studies 301 and 302. If you feel it's important to gain additional information on certain other safety issues -- for instance, in those studies beyond what the applicant may already be doing -- then those should clearly be defined.

CHAIRMAN MASUR: Okay, thanks very much. Why don't we start with the first question and maybe we could ask our non-voting members first who are to my right, then we'll start around the table and get comments on question number 1 from members.

Sue, would you like to volunteer to start?

DR. McDIARMID: I think that the data that is being presented does give support that this is both safe and effective. I'm still struggling with the dose issue. Certainly as the sponsor said, 2 mg worked, and maybe this is not such a bad starting point.

However, I think that there are caveats to that and it gets back to the discussion that we've had before here, that whether or not there should be a recommendation regarding monitoring.

And it would seem to me that because we are at the moment, stuck with data that gives us only one dose, at least if we accept the 2 mg except for the question about high-risk patients, that perhaps they should be the caveat that monitoring should be included in some way or another in the use of this

drug.

So I think that the safety and effective question has been answered except, this is of course, short-term data. I think that most of the data we have is at six months, some is at one year. And I think I personally have a great deal of difficulty in saying that a new drug is safe at the end of basically, a 6-month or maybe a 12-month period.

So I think that, given the time constraints it's safe so far, but I think the long-term issue is particularly in regards to hyperlipidemia and effects on cardiovascular complications, the effects on malignancy and potentially PTLD is still unanswered.

CHAIRMAN MASUR: Well, presumably we learn in each decade that drugs are safe only as far as we have data, so I guess that is the perpetual problem.

During the follow-up -- do we have enough information on which to project the package insert could recommend a particular long-range strategy, or does that still need to be obtained?

DR. McDIARMID: I think it probably still

needs to be obtained. We really didn't see a lot of data from the sponsor in regards to monitoring and levels. They have a sense, I think, of what is probably within the range of where we should be aiming. The number I heard was being five and 25.

And there's an analysis in the data that we were given from them that projected that levels should be somewhere between 10 and 15. But to put these kinds of numbers into the labeling at this point when we have not a lot of information I think might not be the best thing.

However, I think part of what needs to still happen with the development of this drug is a better understanding of monitoring and levels and their implications. And this is particularly I think, applicable to those populations that may have variables in their pharmacokinetics.

CHAIRMAN MASUR: I guess we would have to presume that monitoring would be available to clinicians if someone could come up with schema. Terry, on question number 1?

DR. STROM: I have very little to add. I

think that we learned today that two seems to be efficacious and within reason, safe. I think issues concerning the recommendation of 5 mg for certain high-risk patients need to be sharpened up.

I agree with Larry. I saw data only about African-American recipients for whom that claim can be made and I think that warrants some discussion. I think that there are many other issues that will come out of the subsequent questions.

CHAIRMAN MASUR: Blanche.

DR. CHAVERS: I think the drug appears to be efficacious in reducing the incidence of acute rejection. As a Pediatrician however, I don't feel I have any guidelines on management of adolescents who might receive this medication. And I think there needs to be some subset analysis of the adolescents who receive the drug in this study. I think it would also be appropriate to recommend monitoring of adolescents who are on the drug.

CHAIRMAN MASUR: Okay. Lynt.

DR. JOHNSON: I think that when used in combination with cyclosporine and steroids as this

study was done, this drug appeared to be very safe and effective. I don't particularly see the need for additional monitoring when used in that combination in the adult population.

I think that there probably needs to be some mention and caution regarding not necessarily monitoring for drug levels in this population but for the lipid issues that were brought up.

I think that that really needs to be part and parcel of this because as Sue mentioned, I think that the side effects of that are not going to be seen in one year but further down the road. So we need to be certain that those are being followed.

CHAIRMAN MASUR: So is it we need more information or we should be recommending we provide guidelines for management?

DR. JOHNSON: Guidelines for management is what I am suggesting, with additional information.

CHAIRMAN MASUR: All right, why don't we start around with the voting members? Suthan, you can start.

DR. SUTHANTHIRAN: I'm glad I'm going now

because if everyone had spoken I wouldn't have too many new things to say. I think that we have been presented with very convincing data, that in primary HLA mismatched transplants the sirolimus 2 and 5 mg improves outcome as defined by some of these endpoints.

The question really is allogenic renal transplantation. It is more broader than what we presented today. For both drugs which work in this kind of situation would be expected to be useful in repeat transplants and perhaps even in HLA identical.

I think the drug safety profile that was presented to us is also quite reassuring. So I would say that the answer to the first question is "yes".

In terms of what dose, I think this is true for any immunosuppressant. We never know what's really the optimum drug doses for any drug because the types of experiments you need to perform is beyond what we can do clinically.

I think the data we have is that 2 mg is effective and that's all we can go by. So I think the current recommendation would be 2 mg of sirolimus.

Now we run into this difficult issue of whether we should recommend 5 mg for so-called, high-risk patients. I think when one talks about clinically high-risk patients I think they classified them correctly; you know, the one with the repeat transplants, high PRA, HLA mismatches, African-American recipients.

But the data we really have as it has been pointed out already by this group, we really have data in African-Americans, we don't have data in highly-sensitized patients or repeat transplant patients. And in fact, in HLA mismatch there is no clear benefit between 2 and 5.

So what do we decide in this situation? I know the difference in survival and the difference in terms of the reduction in the risk in African-Americans did not reach statistical significance. Nevertheless, as a clinician taking care of patients, to me it looks like going from a 30 percent, 18 percent, is quite reassuring.

So I'm comfortable but I will certainly look forward to getting additional data. Again, this

is a point that has been made before. I think this is just the beginning understanding of this drug as we have all done with cyclosporine, tacrolimus, and mycophenolate, and other drugs which we have improved.

So I'm not uncomfortable about saying that at the present time African-American recipients may be considered high-risk and may support the suggestion that maybe 5 mg will be a more appropriate dose in this patient population.

And I'm sure we can add on certain things to say that the recent dose-dependent adverse effects and add those qualifiers in the package insert.

Do you want me to answer the rest of the questions?

CHAIRMAN MASUR: Why don't we come back to that. We're doing a loop and we will come around again.

DR. SUTHANTHIRAN: Okay. Thank you.

CHAIRMAN MASUR: Ron.

DR. SHAPIRO: You want the drug to be safe and effective and that be at 2 milligrams. Obviously there are concerns about elevated lipids. And not a

very good prediction incidence of rejection of at the 2 milligram dose in cadaveric recipient which are sort of rare. Everything else is relatively straight forward transplants. But I believe we have that for the 2 milligram dose beyond that I think we would need more information.

CHAIRMAN MASUR: Robert.

DR. MANN: I would reiterate what has been said up to this point; that I think at six months it certainly has been proven to be safe and effective in reducing the incidence of acute rejection. I do obviously, as others have voiced, have some concerns about the long-term effects of hyperlipidemia, and I am certainly concerned about a drug which may potentiate the nephrotoxicity of cyclosporine.

This is not a trivial matter in patients who have undergone a renal transplant and as Dr. Hunsicker has suggested, may in fact potentially shorten by a significant amount, the long-term survival of the graft. I think we'll need certainly, long-term data before that question can be appropriately answered.

I also would reiterate what others have said in that the only high-risk group in which we've seen data to support, potentially support, suggestion of a 5 mg dosing would be in African-Americans. And we have insufficient data about which to make appropriate recommendations for pediatric population.

CHAIRMAN MASUR: Larry.

DR. HUNSICKER: I wish I could bring myself to a terse answer. I did once just simply say "yes" and everybody was astonished.

If this is the vote, my vote is "yes" for safe and effective at 2 mg. I have two or three caveats. One is that we do not have any significant toxicity data beyond one year. You are correct that we always know that we don't know how safe a drug is much beyond -- but a year is a very short lead-time.

And I will tell you, based on my long experience in transplantation, that roughly a year and two months -- if it takes that long for you folks to get this drug approved -- roughly a year and two months everybody will be asking what do we do now?

And the fact is, we haven't the foggiest

idea. So one of the things that has to be put on as a caveat is that we do not know the safety of this drug beyond one year.

Now, when mycophenolate was presented I almost lost all my friends by proposing that we actually put a one-year limit on the labeling. And I was talked out of it by my friends who told me that if they didn't talk me out of it they'd outvote me anyway. So I'm not going to make that recommendation.

But I think that we need to make it very clear that we need prompt recording of toxicity data for two years and three years and so forth, because this issue will be right in front of our nose before you can turn around. So I'm not willing to just say well yes, we've got to know more about it; in time we will.

The second thing is, as to use in -- I'm going to take these special populations aside and I'm going to say that I do believe that we are not totally orphans with respect to the issue of what the appropriate dose is. I referred before to an analysis that's in this book here that we have not discussed,

which relates in a logistic regression, the likelihood of rejection to the actual plasma levels of the drug.

We do know something about this, and presumably we can use this in many of the populations that we don't understand right now. I do not believe we can apply that necessarily, to African-Americans. I think that may be a different question where we need to be on a different slope.

But I think we have -- very potentially -- we have information we can give to Blanche about her teenagers or to Sue about either her kids or even her liver patients if she wants to use this thing on labeling patients who are recipients of liver transplants.

Because I think we know what the relationship is between plasma levels and the likelihood of prevention of rejection episodes. And since we have not had that presented here we can't say anything intelligent about it.

But I think we can tell the FDA that that information is known and that they ought to work this out with the sponsors of the drug and see if they can

come to some useful recommendations about dosing based on plasma levels in those patients who do not fit into the relatively bland, you know, 70 plus-or-minus 30 kg, white, Anglo-Saxon males -- whatever the heck.

So my comments about those are that we can probably do better than just simply say 2 mg, even based on today's data, and that we really need to know about toxicity after a year. And I'll talk more about what kinds of things we need to know later.

CHAIRMAN MASUR: I think just to follow up on that, I think we do need to be specific as we go along with questions 2 and 3 for what particular studies need to be done as opposed to what can be learned from the current database. Roy.

DR. FIRST: I think the data presented clearly shows safety and efficacy for the 2 mg dose. I come back to what was said about monitoring. I think more data is needed and more guidelines for monitoring because certainly little exists for pediatric patients.

And whether you like it or not, patients on sirolimus are also going to receive calcium channel

blockers and they're going to have fungal infections and microbacterial infections and have seizures. So I think there have tc be guidelines as to how to modify doses when you have an interacting drug.

The other thing that I remain concerned about is the dose scheduling and the recommendation that it should be four hours from the cyclosporine. Because clearly I think it's been shown that the more complex a dosing regimen the lower the adherence.

And you're now talking about asking patients to take an additional drug at around one o'clock, 12/1 o'clock. It's an unusual time in the transplantation's regimen and I worry about increasing the complexity and having less compliance or less adherence.

And then finally, of the dose and recommendation of 5 mg, there is certainly a trend in the Black patients but I think it's not clearly established. Why not 3 mg, why not 4 mg? And this wasn't studied. And I think dose escalation studies with greater detail need to be done in the future in Black patients to establish the correct dose, and that

there should not be a recommendation for 5 mg at this point in time.

DR. ABERNATHY: I would say "yes" to the safe and effective at 2 mg for a period of six months. I think that's what we have data to support. I think in terms of thinking through more carefully what the dose should be, I think we've seen nothing today that didn't suggest a dose response and a concentration response relationship for efficacy, and we've seen nothing that didn't suggest a concentration response relationship for toxicity.

So I simply do not understand why that data hasn't been developed already and I think it has to be developed.

DR. PIANTADOSI: Yes, 2 mg.

CHAIRMAN MASUR: There are many people who appreciate such short answers.

DR. WOOLSON: Yes, 2 mg. I do really, like the gentleman three down mentioned, I do think we need more information on the African-American population with regard to dose. And so I think -- I support the 2 mg but the 5 mg I do not support. I do

not believe the data are adequate there.

DR. FLETCHER: Yes. And based on the available data 2 mg but I, like all, I think everyone else, I don't believe that that's the optimal dose. I think there's a better dose. I think we have to remember how many individuals that took this dose failed, or the therapy failed them: 19 percent in the 301 study, 30 percent in the 302 study.

So there is a substantial proportion of patients that will receive this drug that will not derive the benefit from it. And so like others that have commented I think there's a clear need to -- I think we ought to talk about this more when we get to question 2 about the need for alternative dosing studies.

But going back to as to whether there should be information communicated in the package insert, on what the available data did tell us about concentration and effect relationship, I do clearly think there needs to be some information to that effect in there.

We have been led to believe by the sponsor

a test to measure -- is going to be problem, and if it's going to be used people are going to have to look somewhere for this type of information, and I think we know something that now can be communicated in a package insert.

DR. LIPSKY: I think on the efficacy issue, I think that's clearly "yes". On the safety issue, yes, and now you'd say, well what dose? Well, I've berated at least -- I shouldn't say berated but raised questions about why the dose was used in that and what we have done. And we have the same issue with safety.

Everybody seems to have said 5 is no and 2 is yes. But look at the data. What is that definition of safety? If we look at a relative risk and benefit situation and going back at the individual percentages of the exposure, looking at endocrine system -- this is page 73 of the brochure -- eight percent for 2, ten percent for 5.

Thrombocytopenia occur at two percent for 2, five percent for 5; ALT increase, eight percent for 2, seven percent for 5; AFT increase, four percent for

2, six percent for 5. Do I need to go on and on? I'm not so sure that if we're worried about, you know, if we're not worried about the 2 mg dose what is our definition that makes us worried about the 5 mg dose?

At the same -- I think we ought to be as scientific as we can about that and say what is our definition? What is it clear about 5 mg that is inappropriate? Then you say, well what is the dose? I say, well we don't really know for sure what the dose is but have a package insert that details the experience or what has been done with a clinical trial.

But I mean, I need to ask you what about those comparisons, etcetera? How were the two doses different in the safety, I would just ask, well what is the definition you are going to have of safety and how can you clearly apply it?

I realize the sponsor felt that felt a little bit afraid I think that was on the 5 mg dose. Maybe that should be clarified. And I think in the presentation there was some phrase that was, maybe you shouldn't use the five, or be careful of safety. But

I mean, I'm not necessarily downing the 5 mg dose.

CHAIRMAN MASUR: At this time, before we go into questions 2 and 3 and explaining what more information we need, I think we need to take a vote of the voting members who are to my left. I guess we're looking for a hand vote in response to the question -- and I'll read it just to be sure what we're going on.

Is there sufficient information to support that sirolimus is safe and effective for the prevention of acute rejection in patients receiving allogeneic renal transplants?

So all those who would vote "yes", raise your hand.

All those who would vote "no".

And is there any abstention? No.

We had a number of people state that additional information was needed and as we answer questions 2 and 3 it would obviously be useful to indicate what new phase ought to be done as opposed to what can be monitored.

We mentioned a variety of issues. Clearly, everybody wants more information on how to

manage high-risk patients, particularly African-Americans. We need more information about drug interactions, about how to manage, recommendations on how to manage lipids, how to manage adolescents, patients with hepatic insufficiency, more information about the causes of nephrotoxicity.

There are probably a dozen issues which we've detailed. So today, questions 2 and 3, hopefully we'll get some comments on what new studies need to be done and which of that should be Phase 4.

DR. GOLDBERGER: One issue that would be very helpful for us, if you would. Those committee members, guests, etcetera, who really believe for instance, that therapeutic dose monitoring or the option of that would be important to have available, please make that as clear as possible in your recommendations in terms of, you know, what type of availability, etcetera, there ought to be.

Because I think that's sometimes very helpful for us in some of our discussions with the company. So we would ask, if this is believed to be something that's important for this drug that you make

that as clear as possible.

CHAIRMAN MASUR: Do you want to make any comment? You know, we were presented data here in terms of the study that did not use drug monitoring. Is it within our province to recommend that the package label advocate drug monitoring when there hasn't been a study shown that's beneficial in terms of the experience?

DR. GOLDBERGER: Well, there would be a couple of issues. The first I guess, practical issue is, the package insert could not recommend this until we were satisfied of course, that the assay was widely available. And I mean, the question would come up, if you were to -- if such a recommendation would be made, would there have to be a delay in the approval of the drug in order to have this available?

It's not my impression from what I'm listening to that that's what people are saying. On the other hand, there is a great concern about this, but we cannot, you know, make statements about therapeutic drug monitoring in the package insert until everyone is satisfied that there is a reliable

assay that would be widely available.

And I think that would be one issue. The other issue I suppose is, I'm not sure how much -- whether we would need to do some additional review of some of the data that the company has put together. I will say it would probably have been more helpful to have had than a Board discussion of some of the modeling, etcetera, that in fact the company has done, which all of you have seen in the materials that they've submitted but which were not discussed here.

So I think that makes it a little difficult about what we could put in the label now. However, for instance, if you were to make a strong recommendation about the need for this, then I think that that would influence obviously, what the Phase 4 recommendations would be, and what we would try to achieve in subsequent trials and subsequent revisions in package labeling.

So I think at this point in time that's probably what would be the most important approach to doing this.

CHAIRMAN MASUR: As we go along if you

have any reason to indicate if an alternative dose should be recommended for a particular population.

DR. GOLDBERGER: Yes.

CHAIRMAN MASUR: Most that the comments have been fairly negative about that. Would anyone like to make a strong plea then we need to consider that as a group.

DR. GOLDBERGER: And just remember that to put it in the package it has to be something that we can translate from an idea into words to put into a package insert. So although there are many people sitting around the table who are very experienced clinicians, who would, when faced with a variety of patients probably have a feeling about how to use an increased dose of this drug, that's not necessarily helpful in terms of putting it into the package insert. So it needs to be able to be put into words that we can put clearly into a package insert.

CHAIRMAN MASUR: So with that very broad call for comments, Lynt do you want to start, and particularly about the issue as to whether we should be recommending a higher dose and if so, for whom?

DR. JOHNSON: I think, to answer your question, I think there is probably a need for an alternate dose. I don't think that the company has provided us with the information to determine what that alternate dose should be, from my personal opinion.

I think it's hard for me to be in favor of recommending the 5 mg dose without any real scientific basis for doing so, and then it turned out to be that that was the dose that was studied and that seemed to work in those patients. But on the other hand, why should we recommend 3 mg or 4 mg?

So the answer to the question, I think there is a need for an alternate dose but I think that we need to have some dose escalation studies in the sub-population to recommend what that dose should be.

CHAIRMAN MASUR: Are there any other additional analyses or Phase 4 studies over and above what has been recommended?

DR. JOHNSON: The other area I think that we need to focus on more is this distinction between living donors and cadaver donors. As you know, we

have a very high population of living unrelated donors that are probably a different kettle of fish than the living related donors.

And so I think that we have to really be careful in terms of our insinuations of those two populations because there are actually probably three, separate populations: cadaver, living related, and living unrelated donors. And the living, unrelated donors are becoming a higher percent of the patients that are being transplanted.

I think that the other high-risk groups, you know, have been identified here and have not been sufficiently studied to make a recommendation in those groups; particularly those who are high PRA and repeat transplant patients.

CHAIRMAN MASUR: Okay. Blanche.

DR. CHAVERS: I don't think there is sufficient data to support a recommended dose in pediatrics.

CHAIRMAN MASUR: Okay. Terry.

DR. STROM: Yes. I just want to underscore what Blanche has said because kids,

particularly under ten years old, constitute another wealth of high-risk group for immunologic graft failure. And insofar as we have no information on kids of this age I think this group needs special study.

DR. McDIARMID: Well, I can only echo the concern about pediatric patients. I would actually like to ask for some clarification. In the study, the age range was greater than 13 but the sponsor told us that they excluded patients less than 40 kilos. If that's correct then I think that the recommendations should be based on weight. Because if you start using an age I think you're going to have a problem.

This data that we have is greater than 13 years of age so in theory you could say it could be approved for those patients greater than 13 years of age. But I'm quite concerned about the issue of age and particularly weight with these very small adolescent patients that could be transplanted.

So maybe we should discuss whether we need to actually have an age range or weight range in the labels. That's one issue.

In regards to the issue of recommending a different dose for high-risk populations, I don't think we can for high-risk populations in general because we've only got data on one. But I think from a practical point of view the information that's being provided regarding the 5 mg dose and the African-Americans, it seems to me should be in the label so that people can at least just see that information.

As a clinician, it seems to me that it's rather important to know that. And whether you act on it or not, because it's not given as an absolute recommendation but is given as information, I think should be up to clinical judgment.

But a great deal of time and effort is being put into look at that question and this is one population which, at least in this country, is about 20 percent I understand of the renal recipients. And I think it's too important an issue to just ignore it. So I would actually favor at least presenting information in the label and letting the clinician decide.

In terms of the question about whether or

not we should recommend monitoring, again, perhaps the best way of approaching this is again in the label to just allow the information that has been provided so far from the modeling from the sponsor, at least have it in the package so that people can use that information.

The availability of getting the livers is actually becoming I think, reasonably widespread, and at least people have the information to start making clinical judgments on.

And in regards to additional studies I think that, I'm not a nephrologist but everything I was ever taught told me that you really ought to be talking about true GFRs and not basing changes in monitoring renal function on creatinines and calculated GFRs.

So in regard to what seems to be a very important issue regarding long-term renal function and whether or not there's a nephrotoxic effect of combination of cyclosporine and Rapamune™, it would seem to me that such new studies should have as their gold standard a true GFR and not calculated GFRs or

assumed creatinines.

There's obviously very wide weight ranges in these patients, these moles and Cmoles, and the estimate of GFR based on creatinine is always going to be skewed by that.

And finally, in regards to the lipid question, I think this is very important and should be a very high priority focused for the Phase 4 studies. And I think that this body needs to hear what those results are, particularly in terms of long-term effects, the use of lipid-lowering agents, and how often they use, etcetera. Thank you.

CHAIRMAN MASUR: Thanks. Jim.

DR. LIPSKY: Okay. On issues of what more needs to be done, obviously we want to get the numbers for the adverse effects at 18 months and two years, etcetera.

I mean, if you read the data in the background information that are now presented for why fixed dose was used in the Phase III studies, and it would seem we ought to review that again, carefully, to see if now that what we know of how the results

came out, if that model permits or what we have put together, to see if dose and concentration response relationships might be useful.

And I think that if that had been done with titer of rapamycin and mechanism of action, but it almost seems like the fact that it may be something else, or the metabolite in small amounts in whatever is being produced and it's V_{max} that is causing the effect.

Because, at the flat end of the rectangular hyperbole, the dose response relationship looking at the toxicity and efficacy it appears certainly being a subgroup maybe, because something else is being produced. Now the problems are probably more complicated here than straightforward.

But I think we have to review it again already -- repeat myself -- review up to now for the fixed dose. And maybe that could be a guidance that instead of cumulative to determine concentration effect if they need to be done without reinventing the wheel.

If that turns out to be the case then it

might be very useful to have a reproducible assay.

DR. FLETCHER: With regard to question 2, I think that we have to be clear with alternative dosing in specific populations, the three major concerns that I have are the potential for sex-related differences, for racial differences, and in pediatrics.

The gender to me is very important, as Dr. Dixon pointed out in her review, she showed in both 301 and 302, the critical mass. And while the difference, there's about a 50 percent reduction for male and about a 20 percent reduction for females. And I also think this is a very important issue that must be explored.

When I talked about the potential racial differences there may not be pharmacokinetics but there may well be pharmacodynamics. that needs clarification. And third, the pediatric issues do as well.

I think I would probably give my strongest support there. We have a very serious risk if we under-dose this drug and if we overdose this drug.

We know that it may be better affected by several factors including age, including concomitant drugs. If we put all of those factors together it seems to me the only way in which we're going to get the maximum benefit of this drug is with the right degree of other factors. If we do that when it calls for further study.

CHAIRMAN MASUR: So you would advocate a Phase 4 study that looked at strategy based on concentrated guided doses?

DR. FLETCHER: Absolutely. I prefaced the comment with that. I don't think we could recommend something that couldn't be done but we need to do that, absolutely.

CHAIRMAN MASUR: Okay. Robert.

DR. WOOLSON: The answer to the question, is there a need for an alternate dose in specific populations, I think in the African-American population I think the data suggests that there may be a need for an alternate dose. I do like the idea of putting that in the label, the results for the 5 mg that we did see in Study 301 for the African-American

population.

I don't think the data are complete enough on the pediatric population for the reasons that were given earlier, so I think that's the other point.

And with regard to what additional Phase 4 studies, I think the need for longer-term monitoring is evident. I would like to see additional information gathered longer-term on the lipids; particularly since cardiovascular deaths might be a cause for concern in this population as well.

CHAIRMAN MASUR: Steve.

DR. PIANTADOSI: With regard to the question of the need for an alternate dose, I think the answer for need is likely to be yes, and that whatever information we convey should go in the label. But I'd like to be very careful about the attribution of the effects that go into the label.

For example, the way the data have been presented suggest that the racial composition is the important factor, but in fact, I heard the company say in one of their analyses not shown on the slide, that it wasn't the racial composition but instead it was

the number of mismatches.

And I think we have to be very careful about what we attribute the effect to. There may be some analyses that are important to do that will help reflect on this question that we've not been presented with.

This touches on the question I asked earlier and the way to define those specific populations that may require an alternate dose. We have to be careful not to use the reciprocal definition of high-risk; that is to say that high-risk is defined by those patients who are benefitted by a high dose but not by a low dose. That's not the correct definition of high-risk.

High-risk is something that's defined a priori, much in the way the question about Blacks versus non-Blacks was defined. And then one investigates whether or not there's a difference in outcome based on that a priori definition of high-risk. And that definition of course, ideally would be not driven by the data in the study.

That gets to the need to know the

independent contribution of each of the risk factors that have been mentioned, and there's an assortment of them: the source of the donor, the mismatches, repeat transplants, possibly gender, and so on and so on. And I find myself swimming in one at a time risk factors and not knowing what's independent of what.

So yes, I think there may be a need for alternate dose but I'd like for the agency to be extremely careful about the factor to which they attribute risk or the factor that they name as being definitive for that population.

CHAIRMAN MASUR: Is there any particular study that other panelists think that needs to be done? Is there any particular Phase 4 study that you would like to see other than what we have been talking about? Concentration dependent study looking at some of the populations where we have a dearth of data?

DR. PIANTADOSI: No, is the short answer. I think that we've already mentioned everything I could think of that would need to be done.

CHAIRMAN MASUR: Okay. Darrell.

DR. ABERNATHY: Yes. With regard to need

for an alternate dose, I believe I understood that this drug is given as a solution, so we really have the luxury of thinking more openly than you usually do when you're trying to figure out how many pill sizes to make.

That's correct. I guess I would support what's been said earlier. We need to really not think about an alternate dose. We need to define what the therapeutic concentration range is and then with that data figure out dosing regimens and populations.

With regard to additional studies, not surprisingly I would think there are a series of drug-drug interaction studies that need to be specifically focused on.

To simply say that one can predict because it's a 3A this or that or the other thing, for potentially critical interactions I'd argue that's not necessarily so because it simply has to do with affinity for the enzyme and so on, and just because something is an inhibitor doesn't mean it's a potent inhibitor, or what have you.

Therefore, I would suggest that we need a

careful look at the potential interaction with HMG reductase inhibitors and to look at that one seriously. There's been a drug taken off the market within the last year, year-and-a-half because of that interaction. We need to look at erythromycin, other macrolyte antibiotics.

CHAIRMAN MASUR: Ron.

DR. FIRST: Thank you. Coming back to the dosage issues, I think the situation is similar to what occurred in the mycophenolate mofetil studies where lower rejection rates occurred with higher doses in Black patients. And that didn't go in as the recommendation in the package insert, but if my memory is correct it was added.

And I strongly support what Sue says; that the data should be available in the package insert. That in the sub-population of Black recipients a lower rate of rejection was seen with a higher dose.

The therapeutic drug monitoring issue, coming back to that, I don't think it in any way should hold up approval and that should go into Phase 4 and future studies should be done so that some

recommendations are available.

And then finally, we've heard a lot and I think one of the major concerns of everyone is the long-term effect of the hyperlipidemia, both the combined hypertriglyceridemia and hypercholesterolemia. And nothing has been said, why does this occur, and I think some basic studies, some more basic research needs to be done or perhaps the company does have this information.

There's been some very interesting work from Ian Hutchinson in Manchester where he shows that sirolimus mediates a dose-dependent inhibition of the glucocorticoid receptor, which is responsible for breakdown of the various lipids that we are talking about.

And he's convinced this is the mechanism. But I think when one understands the mechanism then one may be able to attack it in a more effective manner.

DR. HUNSICKER: I suspect that there will be a need for more than one dose but I don't think we know what the other doses are. And I don't want to

delay. I think Ms. Kory and Mr. Zylwitis have both emphasized the sense that we ought to get on with this, get it out and available to be used.

As to the labeling, I agree with Dr. Suthanthiran that we probably should say something in the labeling to the effect that there was some evidence that some populations might do better with a higher dose, but not be terribly precise because we haven't the foggiest idea what the higher dose is.

Again, as to the labeling, I don't think it makes a heck of a lot of difference what you put in there because the people that are going to use this are going to be from the transplant community. They're probably not going to read the labels anyway and they're going to listen to each other in conference.

I'm fairly, I'm meaning what I'm saying here; that this is going to be used by an expert group of people who are going to depend more upon their expertise, and so the precise way in which this caution is put in there is probably not terribly critical.

Ultimately, I agree with those who believe

that this should be related to concentration and I believe that ultimately, maybe sooner rather than later because I'm given to understand that there are already some good studies that have been done that may suffice -- I haven't seen them so I can't say that -- may suffice to give us a very good idea of what kind of dose guidance, you know, plasma level guidance there should be.

And at such a time as the FDA has those in-hand and knows what the reasonable dose is, and if there is an assay out there it's easy enough to change the labeling.

With respect to African-Americans I think the issue here is whether the African-American has a different slope in its relationship of dose to the likelihood of preventing rejection, and I think that needs to be explored more explicitly.

It may be that those data suffice already to do that but if it doesn't then that should be done and find out. Is in fact, the African-American a group that needs a higher level for the same pharmacodynamic effect? We don't know that.

Then finally, additional studies that ought to be done, I actually would like to reiterate something that my good friend, Roy, said. I would like to see at least a very brief study on simultaneous versus spaced therapy. I think it is utterly unrealistic of the company to think that patients are going to take this stuff four hours after their cyclosporine and I think it would be much better for us to note what's happening rather than to extrapolate what's happening.

This agent needs to be tested together with other agents that are currently being used in immunosuppression, such as mycophenolate and induction agents. And my understanding is that's being done but certainly the FDA is going to be interested in that, both from the point of view of efficacy, but particularly from the point of view of safety in terms of over-immunosuppression.

Finally, with respect to long-term things, I reiterate we don't know the safety of this drug in long-term so we need to get simple things like the usual kinds of toxicity ratings.

But in addition we need to know specifically about lipids, whether the tendency for the lipids to fall -- the cholesterol and maybe even the triglycerides to fall back towards the baseline in the patients receiving sirolimus for a longer period of time, whether they continue or whether that plateaus out.

In other words, do these patients continue to have high levels of lipids after the first year? And along with that, do they in fact, have evidences of increased cardiovascular events? And finally, what happens to their renal function? Not just graft failure but renal function, long-term. We need to know those things.

CHAIRMAN MASUR: Okay. Richard.

DR. MANN: I'll start by saying I don't think any of the recommendations that we're making right now should delay approval, but I do think that there are a number of things that we need to know. I agree with what Dr. Abernathy said earlier, that ultimately I think we will be guided by levels and that once we have what we believe to be an effective

level we should then do appropriate studies to determine what is appropriate dosing.

Specific populations that I think may in fact, likely will require different sort of dosing in order to achieve comparable pharmacokinetics as well as pharmacodynamics include pediatric population, Blacks, as well as women perhaps.

I think that one group that was clearly excluded from this study that we have no data about are diabetes, and in particular when it comes to hyperlipidemia and the long-term complications of that I think we need to know more about what this drug does in diabetics.

And certainly we need to know more about the long-term consequences on GFR in a drug that's being used in renal transplant recipients. I'll stop there.

CHAIRMAN MASUR: Ron.

DR. SHAPIRO: In terms of approval of the drug, the answer is probably "yes". Do we have sufficient information, probably not. These trials were done in relatively straightforward transplants.

We don't have a lot of information about the liver function of African-Americans. We need more in the way of research with regard to that.

I don't know what I'd put in the package insert with regards to that. All that would have to come in Phase 4 trials.

DR. SUTHANTHIRAN: I believe it is a general consensus for the 2 mg dose but I think we would make a mistake if we exclude the 5 mg dose, for the following reasons.

I think we talked about the African-Americans but I think there is an even more important group here which Ron alluded to, which is the donor source. The majority of transplants in the United States and elsewhere are cadaveric donor source. And if you can look at the data in slide 21 from the FDA group, sirolimus at 2 mg is numerically better but is not statistically different from the control group.

Now, the cadaveric group did best or significantly better only with the 5 mg. So I think it's inappropriate for us when we recommend 2 mg. Because the majority of transplants, if you take the

data, how it was presented to us, will not benefit from 2 mg alone.

I think a large segment of patients like the liver transplants and some other groups would benefit from 2 mg, but when you're talking about cadaveric donor transplant, the most common type of transplants found in the United States are going to require 5 mg of sirolimus. And this is -- Ron pointed this out to me and mentioned it in his talk.

So I believe that absolutely we require more than one dose. We should talk about I think, 2 mg is fine. I think we should have the opportunity to use a 5 mg dose and as was pointed out, the toxic effects are not that really different between 2 and 5.

If you're talking about efficacy in terms of defining a reduction in certain predefined endpoints, we ought to allow people to, physicians to -- yes, unlike Larry Hunsicker, some other physicians do read the package and read about what doses should be used.

I will say that we do need an alternate dose and we could all have feelings about what the

right dose is but we have to go by what the data is we have in front of us. And the data here in front of us is for 2 mg and 5 mg and that's what we need to support at this point.

In terms of what other things should be done, I'm very concerned about the defeat that you have found in both the non-rejection group and in the rejection group. And I think that Terry's point is well-taken. It is possible there is a subliminal, subclinical rejection that contributes.

I think that it would be very important in this patient to consider protocol biopsy maybe at 12 months, at 18 months, and to define whether what is going on in these grafts. How do we obtain important long term data on these patients like 36 months. We talked about cholesterol but we don't know whether it's HDL or LDL. We need to look into it.

There may be polymorphisms that may predispose the patients to respond to the drug in different ways. I think these are some of the other things that ought to be done. But I think the dose -- I'm not obsessed about it but I think that dose effect

is very critical and we would make a mistake if you were just to recommend 2 mg.

CHAIRMAN MASUR: Well, that's an important issue here. How would you propose that we recommend that the two different doses. If you're saying that's right for cadaveric well are you saying you'd recommend 2 mg for living related and 5 for unrelated. Or there are obviously other parameters involved -- how would you sort that out?

DR. SUTHANTHIRAN: I think I would recommend the 2 mg dose, and I would also put it in the package insert, the data, and let people decide on the basis of data. You know, again, Professor Hunsicker said how expert the transplant physicians are, and perhaps the surgeons, too.I would put the data in the package.

CHAIRMAN MASUR: I want to hear some comments on it. Does anybody want to say anything more? Any more recommendations, could the wording be more specific? Jim.

DR. LIPSKY: Yes, I think what we could say is -- we could say something based on the data