DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

Monday, June 6, 2005

8:00 a.m.

5600 Fishers Lane
Room 1066
Rockville, Maryland

P A R T I C I P A N T S

Erik R. Swenson, M.D., Chairman
Teresa Watkins, R.Ph., Executive Secretary

MEMBERS:

Mark L. Brantly, M.D.
Steven E. Gay, M.D., M.S.
I. Marc Moss, M.D.
Calman P. Prussin, M.D.
Theodore F. Reiss, M.D., Industry Representative
Karen Schell, RRT, Consumer Representative
David A. Schoenfeld, Ph.D.

SGE CONSULTANTS AND GUESTS (VOTING):

Jeffrey S. Barrett, Ph.D.
Lawrence Hunsicker, M.D.
Allan R. Sampson, Ph.D.
Jurgen Venitz, M.D., Ph.D.
Mary Lou Drittler, SGE Patient Representative

GOVERNMENT EMPLOYEES (VOTING):

James Burdick, M.D.
Roslyn B. Mannon, M.D.
Michael A. Proschan, Ph.D.
John Tisdale, M.D.

FDA STAFF:

Mark J. Goldberger, M.D., M.P.H.
Renata Albrecht, M.D.
Marc Cavaille-Coll, Ph.D.
Arturo Hernandez, M.D.
Jyoti Zalkikar, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. SWENSON: Good morning, everyone. I am Dr. Erik Swenson, from the University of Washington, and I will be chairing this session. This is the meeting of the Pulmonary and Allergy Drugs Advisory Committee and today we are going to be discussing inhaled cyclosporine, a product to be presented by Chiron.

Let me begin with just a few items to keep us on schedule and for organizational purposes. One, I would request that everyone with cell phones, please turn them off or at least down to some vibrating or some innocuous mode. Then, we will go around and introduce everyone here at the table. I would ask that when you are questioning anything during this meeting to please identify yourself first. The transcriber will need to know who is speaking. We have microphones here. All you need to do is simply push down "talk" to go ahead and be heard but, please, turn it off when you have finished. If we get more than three

microphones on at one time things get confusing.

Without any further ado, I am going to turn the meeting over to Dr. Teresa Watkins for some introductory comments.

Introduction of the Committee

DR. WATKINS: Let's first go around the table, starting with Dr. Reiss, if you will introduce yourself and your affiliations, please?

DR. REISS: My name is Ted Reiss. I am vice president of clinical research at Merck Research Labs. I am the non-voting industry representative.

DR. BRANTLY: My name is Mark Brantly. I am from the University of Florida. I am a professor of medicine.

DR. TISDALE: My name is John Tisdale and I am in the intramural program of NIDDK.

DR. PRUSSIN: My name is Calman Prussin. I am a clinical investigator with National Institute of Allergy and Infectious Diseases.

DR. MANNON: I am Roslyn Mannon and I am a transplant nephrologist and medical director of the

intramural solid organ transplant program at NIDDK.

DR. GAY: I am Steven Gay, assistant professor at the University of Michigan, associate director of the lung transplant program and director of clinical support services.

DR. HUNSICKER: I am Larry Hunsicker, from the University of Iowa. I am a transplant nephrologist and professor of medicine, and I am a member of the Chemical Immunosuppression Advisory Committee but guesting on this one.

DR. VENITZ: I am Jurgen Venitz. I am a clinical pharmacologist and associate professor at Virginia Commonwealth University.

MS. DRITTLER: I am Mary Lou Drittler. I am a lung transplant recipient and I am a patient representative from here, in Silver Spring.

DR. BURDICK: I am Jim Burdick. I am director of the Division of Transplantation and Healthcare System, HRSA and a transplant surgeon.

DR. MOSS: I am Mark Moss. I am an associate professor of medicine at Emory University and section chief at Grady Memorial Hospital.

DR. BARRETT: I am Jeff Barrett. I am a clinical pharmacologist from the University of Pennsylvania and Children's Hospital of Philadelphia.

DR. PROSCHAN: I am Mike Proschan and I am a statistician from the National Heart, Lung and Blood Institute.

DR. SCHOENFELD: I am David Schoenfeld. I am a biostatistician and professor of medicine at Harvard Medical School and Massachusetts General Hospital.

DR. SAMPSON: I am Allan Sampson, professor of statistics, Department of Statistics at the University of Pittsburgh.

MS. SCHELL: I am Karen Schell. I am a respiratory therapist from Emporia Kansas, and I am the consumer representative.

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

DR. ALBRECHT: I am Renata Albrecht, director, Division of Special Pathogen and

Immunologic Drug Products.

DR. HERNANDEZ: I am Arturo Hernandez, a medical reviewer for FDA, Division of Special Pathogens and Immunologic Drug Products, and I am a transplant surgeon.

Conflict of Interest Statement

DR. WATKINS: With that, thank you. Welcome everyone. I am now going to now read the conflict of interest statement.

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Theodore Reiss is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Reiss' role on this committee is to represent industry interests in general and not any one particular company. Dr. Reiss is employed by Merck.

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

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms whose products they may wish to comment upon. Thank you. With that, we will have opening remarks from Dr. Albrecht.

FDA Introductory Remarks

DR. ALBRECHT: Thank you, Dr. Watkins. Good morning, everybody. On behalf of the Division

of Special Pathogen and Immunologic Drug Products and the Office of Drug Evaluation IV, I would like to welcome everyone to today's meeting.

We wish to thank the members of the Pulmonary Advisory Committee, the Chair, Dr. Swenson, and our consultants for taking the time out of their schedules to come to Rockville and join us here to discuss this application. I also wish to express our appreciation to Chiron and the investigators for the time and effort that they have put into developing this drug product and to the Chiron staff for their willingness and preparation for this advisory committee meeting. I would also like to recognize the dedication of the Division staff and the long hours they have put in for reviewing this application.

Let me speak briefly about this new drug application for cyclosporine inhalational solution and why we are bringing this application to the advisory committee. Could I have someone run the slides? I apologize, there are some slides that go with this presentation so that you may follow

along.

Let me continue. There are currently no FDA-approved products for the prevention of chronic rejection in patients with lung allografts. There are approximately 1100 transplants done in the U.S. annually and the survival at five years is lower than survival in other organ transplants such as heart, kidney or liver transplants. Prevention of rejection and increase in survival are critical and, therefore, there is a clear need for safe and effective therapy.

Next slide. Chiron has submitted the NDA for Pulminiq and requested that the cyclosporine inhalational solution be approved for the increase in survival and prevention of chronic rejection in lung transplant patients. The drug development program and the NDA for this product are not conventional. Unlike applications for immunosuppressants in kidney, heart of liver transplants for example, this NDA contained results from one single Phase II study conducted at one center. This trial enrolled 66 patients out of a

planned 136 patients. However, we learned that there was a survival advantage, 88 percent survival in patients who received aerosolized cyclosporine plus a tacrolimus-based systemic immunosuppressive regimen compared to 53 percent survival in patients receiving aerosolized propylene glycol vehicle in addition to a tacrolimus-based systemic immunosuppressive regimen.

Therefore, the agency agreed to file and review this NDA application. Based on the NDA review of the information in the application, we were unable to conclude that the observed difference in survival and chronic rejection was due to study drug. Therefore, we determined it was important to bring this application to the advisory committee for the following reasons:

This would represent the first drug for immunosuppression in patients with lung transplantation to garner FDA approval. This is a new drug application. Although oral and systemic cyclosporine are well characterized, cyclosporine inhalational solution is a new formulation of

cyclosporine. It is seeking a new indication. It is administered by a new route and it requests a new dosage regimen. As I mentioned, we weren't able to conclude that the differences in chronic rejection and survival were due to the study drug. For these reasons, we determined it was important to have this application discussed in an open public forum.

We have asked the help of the pulmonary product advisory committee because it is a standing committee with expertise in pulmonary disease. We have invited experts in statistics and transplantation to help with the deliberation, and we are very much interested in the committee's input regarding the adequacy of the clinical and statistical evidence whether aerosolized cyclosporine is safe and effective for the proposed indication.

This morning Chiron will present most of the background information, starting with Dr. Michael Scaife's presentation on the drug development program. Then Dr. Jeff Golden will

provide an overview of lung transplantation. Dr. Sarah Noonberg will discuss the results of the efficacy study, followed by Dr. Steven Dilly's presentation and Dr. Ron Helms' views.

The FDA presentation will follow the Chiron presentations and we will focus on those areas that proved challenging during the course of the review. Dr. Arturo Hernandez will discuss the study design, various clinical issues and outcome demographic characteristics and dosing. Dr. Marc Cavaille-Coll will provide a summary of the safety issues and Dr. Jyoti Zalkikar will give the statistical presentation.

Then, in the afternoon, we would like you to discuss, give advice and vote on a few questions. So, as you listen to the presentations this morning, please keep these questions in mind for later discussion. The first question: Is there sufficient information to make the determination whether the observed survival difference in study ACS001 is due to study treatment or some other factors?

In your deliberations, we will ask you to recall the statistical issues that were raised by the application; differences in baseline donor and recipient characteristics; whether the product demonstrated an effect on various clinical outcomes or things such as acute rejection, bronchiolitis obliterans syndrome, obliterative bronchiolitis.

Depending on whether you conclude that the answer is yes or no, we have a few additional questions, namely, if the answer is yes we would like you to talk about the generalizability or, more specifically, the labeling issues that you would recommend be put into a product label. If the answer is no we would like you to consider what additional studies you would recommend be conducted. In these discussions we would also like you to give us some suggestions regarding patient population, drug dosing regimen, as well as efficacy and endpoints that could be included in such studies.

The next question would be whether the safety of the product has been adequately

characterized for its intended use. Again, in this particular question we would like you to also consider the amount of preclinical and clinical information that is available in this application; infection about the cyclosporine and the vehicle, as well as the number of patients who have been exposed to the proposed dosage regimen.

If the answer to this question as well as the preceding one is yes, then we would like you to give us suggestions about what population the product should be labeled for; what information we should include in labeling on dosing regimen, dose preparation and administration, dosing intervals and duration of treatment. In addition, if you could give us guidance on what should be included in the labeling regarding the expected benefit on acute rejection, BOS, OB and so forth. If your answer to the latter question is no, then we would like you to give us some advice about what preclinical and clinical information would be needed.

With that, thank you and I will turn it

back to Dr. Swenson.

DR. SWENSON: Thank you, Dr. Albrecht. We will proceed now with the sponsor presentation and I would like Dr. Michael Scaife to go ahead and begin this, and I will let him introduce his colleagues and their different presentations.

Sponsor Presentation

Introduction

DR. SCAIFE: First of all, good morning, ladies and gentlemen. My name is Michael Scaife. On behalf of Chiron, I would like to thank the FDA as well as members of the advisory panel for this opportunity today to present to you on the safety and efficacy of an inhalable form of cyclosporine that will be referred to throughout the talk as either CyIS or the product's trade name, Pulminiq.

The first point I would like to make is that currently in the United States there are no drugs or combination of drug therapies approved for the treatment of chronic rejection following lung transplantation. The prognosis for these patients is really poor. Despite aggressive care, only 45

percent of lung transplant recipients will be alive five years following transplantation. This is much worse than for other solid organ transplant recipients. This is an orphan population in the U.S. On average less than 1100 lung transplants are performed each year.

We are here today to talk about certain aspects of Pulminiq, a medication that is an aerosolized form of cyclosporine dissolved in an inert vehicle, propylene glycol. As you all know, cyclosporine is not a new chemical entity. Cyclosporine was approved by the FDA in 1983 and currently has been approved in most countries of the world. It is available in oral, IV and ocular forms. In the U.S. it has been approved for the prophylaxis of allogeneic heart, liver and kidney graft rejection, and for the treatment of refractory rheumatoid arthritis and plaque psoriasis. In Europe cyclosporine is also approved for use following bone marrow and pancreatic transplantation, as well as for a variety of immune-modulated pathologies such as nephrotic

syndrome, atopic dermatitis and Bessay syndrome.

Pulminiq is simply an inhalable form of cyclosporine so, in essence, we are here today to talk about a well-known drug given by a new route of administration to enable delivery to the required site of action. As I mentioned, Pulminiq is a simple formulation consisting of cyclosporine dissolved in propylene glycol, with no other ingredients. Propylene glycol is also not new to pharmaceutics. Since the initial inhalation tox studies of propylene glycol in the '40s it has been widely used as a compounding agent for intravenous and oral pharmaceuticals, as well as foods. In fact, it is currently listed by the FDA as an approved inactive ingredient for use in inhalation products.

Several preclinical inhalation studies have been performed both with Pulminiq as well as with the vehicle alone. Specifically, you will see in the briefing book that we make mention of two one-month studies in the rat and the dog and a three-month study in the rat. I won't go into the

specific details but, as you will see, doses given in those animals were in multiples 15, 17 times the dose that we expected in man. The histopathological findings again are detailed in the book. You will find that aside from some small punctate findings in the larynx in a few of the animals, there were no long-lasting changes and, in our view, the results are not significant.

How did Chiron first become aware of the work on inhalable cyclosporine at the University of Pittsburgh Medical Center, which we will refer to from now on as UPMC? Well, in fact, from a sales rep who was detailing our inhalable topromycine product, TOBI, which is used for the treatment of pseudomonas infections in cystic fibrosis patients.

The slide here details the development activities at UPMC. The preclinical study started in '88, followed in '91 by human studies in lung transplant patients with chronic rejection. In '97 UPMC started a randomized, double-blind, placebo-controlled study of cyclosporine that ended in August, 2003. The results of this and other

studies will form the discussion of today's meeting.

You may ask why did Chiron want to acquire the rights to develop this product. Well, we looked at the results of 15 years of work at one of the largest lung transplant centers in the U.S. We asked ourselves the same questions, frankly, and had the same concerns as anyone would have had. It is a single-center study. It was being conducted by a single lead investigator. Has the study been conducted appropriately? Are the data robust? Are the striking effects seen on survival benefit real? And, if so, are they due to cyclosporine or some other factor or factors?

We did our initial due diligence of the data and how it had been collected and we concluded that the effect is real. Based upon our conviction, we acquired the right to file an NDA for the product. As you know, the FDA encourages the filing of applications for products that address a clear unmet medical need with a demonstrated significant clinical benefit and an

acceptable safety profile. We went to UPMC and we extensively audited the hospital records. We went in and we collected all of these data on standardized forms, and we analyzed the data in every possible manner, as you will hear later.

In may, 2004 we met with the FDA. We posed a very simple question, would the agency consider the positive findings from one clinical study, conducted by one principal investigator to be registerable? The FDA response, and I think Dr. Albrecht referred to it so she will forgive me for paraphrasing I hope, was assuming that the data are robust--and I happily stress the word "robust"--we encourage you to file. It is rare for us at the FDA to be provided with significant survival data for such a product. Based upon this positive meeting, Chiron filed an NDA for Pulminiq in October, 2004.

I would like to acknowledge the collaborative position taken by the FDA throughout the NDA process. We have been encouraged to maintain a dialogue with the reviewers and it is in

this spirit that we are here today.

The finding was accepted by the FDA and priority review status was granted in December, 2004. Ladies and gentlemen, Chiron is here today because we believe the data on survival benefit are real and clinically relevant, as well as statistically significant. We will present data that confirm that CyIS is safe and efficacious for the requested indication, which is to increase the survival and prevent chronic rejection in patients receiving allogeneic lung transplants in combination with standard chronic immunosuppressive therapy.

With that, I would like to introduce to the panel and the audience the agenda for the Chiron presentation as well as the speakers, their background and affiliation. The first speaker is Dr. Jeff Golden who is professor of clinical medicine and surgery at the University of California in San Francisco. Dr. Golden is also the medical director of the lung transplant program at UCSF.

We have asked Dr. Golden to speak to you today for two main reasons, firstly, because he is an eminent practicing physician and scientist who actually treats and cares for lung transplant patients, as well as being an active researcher into the mechanisms of acute and chronic lung rejection phenomena. Secondly, because he was not involved in the study and we wanted his independent views on the clinical findings. Dr. Golden will address the current status of lung transplantation.

He will be followed by Dr. Sarah Noonberg who is the clinical leader at Chiron for this project. Dr. Noonberg will present to you the clinical evidence for the efficacy and safety of CyIS.

Dr. Noonberg will be followed by Dr. Ron Helms, an emeritus professor of statistics at the University of North Carolina. Why did we ask him to be here today? As statisticians and physicians have analyzed the data from every possible angle and found the positive effect of Pulminiq on survival to be clinically as well as statistically

robust, the FDA statisticians expressed some concerns about our analyses and so we asked Prof. Helms to look at our approaches, assumptions and methodologies, as well as those of the FDA reviewers, and to let us have his candid opinion. He will share those views with you today.

The final presentation by Chiron will be given by Dr. Stephen Dilly. He is the chief medical officer for Chiron BioPharmaceuticals. He will review the case for approval of Pulminiq including a discussion of our proposed postapproval study. We will then hand over the meeting to the Q&A session that will be moderated by myself.

Finally, we have a list of additional experts, both internal and external. I would like to make the special point that we have the pleasure of having Dr. Trulock here who is a world renowned expert on lung transplantation and, again, as you know, you are free to ask any of our experts for additional information. With that, I would like to hand over to Dr. Golden. Thank you very much.

Current State of Lung Transplantation

DR. GOLDEN: Thanks. I am extremely delighted to be here as somebody who takes care of patients after transplantation. I am here really to give an overview of the current state of lung transplant.

Just a brief statement about myself, about 15 years ago I helped start a lung transplant program at the University of California in San Francisco. In the past few years we have been doing about 30 transplants a year, and this year we are on a pace for 40 transplants. Just to give you a perspective, this puts us in about the top 10 percent in terms of volume of annual transplants in the world.

About two years ago I was asked to visit Chiron and give a review of lung transplant. At that time I was first shown some data from the University of Pittsburgh on aerosolized cyclosporine. Subsequently, as some of you may know, I did attend the first FDA meeting in 2004 where I similarly presented an overview of lung transplant. Well, I am back and actually nothing

has changed.

I would like to summarize on the next slide the main points in terms of where we are in lung transplant. First, the long-term survival of lung transplant is 50 percent by five years. This is a poor survival. Second, bronchiolitis obliterans, or chronic rejection, is the primary cause of this poor survival. Third, the future of lung transplant really demands that we learn how to prevent bronchiolitis obliterans.

By way of history, before cyclosporine there had been approximately 40 lung transplants in the world. Looking at their survival, the median survival was somewhere around 10 days. One patient lived 10 months. After the introduction of cyclosporine there were one-year survivals, such that eventually there was 75 percent one-year survival in lung transplant. With this large improvement compared to the pre-cyclosporine era, the interest in lung transplant really took off.

As you can see from this slide, early on in 1985 there were about a dozen transplants and as

of 2003 there are somewhere around 1700 transplants in the world, about 1100 in the United States. These are done for various recipient categories you see listed here. Approximately half are for emphysema or alpha-1 antitrypsin deficiency, cystic fibrosis, and another large area is idiopathic pulmonary fibrosis. Although in this registry analysis it is 17 percent, at UCSF 60 percent of our lung transplant patients have idiopathic pulmonary fibrosis, a disease for which there is no therapy and a disease that has a five-year survival, somewhat similar to lung cancer.

However, despite this increased one-year survival and this tremendous increase in the number of transplants done around the world, we are, unfortunately, still stuck at a low 50 percent survival of around 4.5 to 5 years. Although one might say emphysema has a slightly better outlook at 4 and 5 years than idiopathic pulmonary fibrosis, in general lung transplant survival is about 50 percent at 4.5 to 5 years.

To give you some perspective, if you look

at kidney transplant at that interval of 4.5 years after transplant there is 90 percent survival. And if you look at heart and liver transplant it is about 75 percent survival. Not only do we have this 50 percent survival at 4 to 5 years, but this has not changed in almost 20 years. We have plateau'd in terms of poor survival in that period of time.

As I say, the problem responsible for this poor mortality clearly is bronchiolitis obliterans. In this histology section, with an artery here, the obliterative lesion that is established as a fibroplastic plug diminishes the airway diameter such that, instead of being this size, it is reduced and constricted down to this tiny lumen here secondary to this fibroproliferative process of the lesion of bronchiolitis obliterans.

Bronchiolitis obliterans or chronic rejection is diagnosed in two ways, histologically through a transbronchial biopsy or clinically. The problem with the histologic diagnosis of a transbronchial biopsy is that it is a specific

finding but it is not very sensitive. Transbronchial biopsy is simply not sensitive sufficiently to diagnose this chronic airway process. Therefore, over the years we have developed a clinical diagnosis in the absence of a histologic finding on the transbronchial biopsy such that we look at specific decrease in air flow when there is no alternative cause, and we label this bronchiolitis obliterans syndrome.

It is important to stress that obliterative bronchiolitis and bronchiolitis obliterans syndrome, or BOS, are really histologic and clinical manifestations of the same airway process. Patients develop progressive shortness of breath with this graft failure, progressive airflow obstruction and recurrent pulmonary infections. Regrettably, once this chronic rejection develops the airway damage is progressive and irreversible and patients die of graft failure and related infections.

The registry for transplant would say that somewhere around 5 years the percent of patients

dying from different etiologies would be bronchiolitis obliterans about 30 percent, but actually you cannot separate this from infections which are always present in the setting of this airway damage. Furthermore, in this registry setting where they describe organ failure, that is obviously bronchiolitis obliterans. So, when you add up these categories of bronchiolitis obliterans organ failure and related airway infections, including pseudomonas, aspergillus, etc., let me simply state that bronchiolitis obliterans complications relate to the vast majority of deaths at 4.5 to 5 years after lung transplantation.

No matter what we have done in the last 18 years, we have not prevented this development of chronic rejection, this airway process, whether we give tacrolimus, different combinations of cyclosporine, micofenolate, azathioprine, prednisone and, in fact, I could put rapomyacin up there and various other lytic therapies and various approaches to prednisone pulses for acute rejection, etc. Despite all this systemic

immunosuppression, we really have not changed the incidence of chronic airway rejection closely related, unfortunately, to the poor survival at 4.5 to 5 years.

We now appreciate that there are non-immune factors that relate to airway damage, be these infection or reflux disease. These non-alloimmune factors clearly relate to immune activation. In fact, I believe we are now understanding that when we see chronic airway rejection and we increase systemic immunosuppression we actually are helping to promote such non-alloimmune factors, especially infections which cause further airway immune activation and actually make the process worse.

We have always known that there are alloimmune factors such as acute rejection that relate to damage of the organ. We are now appreciating these non-alloimmune factors, again, be it early airway damage with transplant, various infections, reflux disease which is a very new concept in terms of what injures the airway--that

these non-alloimmune stimuli, in consort with alloimmune rejection, together damage the graft leading to progressive, additive epithelial injury, inflammation and fibroblastic repair culminating in the picture I showed you of bronchiolitis obliterans.

One newer concept in terms of immune factors is called lymphocytic bronchitis/bronchiolitis. One might call it airway rejection. This histology reveals lymphocytic bronchitis/bronchiolitis and airway disease wherein you have submucosal lymphocytes working their way into the mucosa. Let me point out that lymphocytic bronchitis/bronchiolitis has been highly related to the subsequent development of the more fibrotic bronchiolitis obliterans. This concept of an airway inflammation based on immune reaction in the airway, lymphocytic bronchitis, was not on the radar screen 15 years ago when the concept of inhaled cyclosporine was conceived.

We have always known that acute rejection is one of the factors that relates to the

subsequent development of bronchiolitis obliterans. However, I want to separate out the airway process from acute rejection which is a perivascular process diagnosed by transbronchial biopsy. I should emphasize that a transbronchial biopsy has variable adequacy for obtaining small airway samples to diagnose whether it is bronchiolitis obliterans or the early airway inflammation of lymphocytic bronchitis.

If I was designing a study today of any inhaled immunosuppressant therapy I would try to learn more about the biology of the airways. We, at UCSF, and some other institutions have been doing endobronchial biopsy. This is not standard but we are learning a lot more about the airway biology in terms of lung transplantation.

On my last slide I want to just emphasize that although I might expect systemic immunosuppression to clear up a perivascular process, I am suggesting that bronchiolitis obliterans, chronic rejection, is an airway process and it makes eminent sense to employ inhaled

cyclosporine to treat the epithelium. It is clear now that the epithelium is key to the development of bronchiolitis obliterans. Bronchiolitis obliterans is an airway disease.

Just to finish, my colleagues in the lung transplant world are very excited about the potential benefit of inhaled cyclosporine. As I say, the epithelium is key and it makes eminent sense to develop a system of local immune suppression to the airway and the mucosa. Frankly, given the poor survival of our transplant recipients which, as I already mentioned, has not changed in almost 20 years, I personally feel that inhaled cyclosporine fulfills an unmet need.

I questioned whether I was going to say the following but I think I will. On a personal note, for people like myself who take care of these patients, who see them terribly short of breath in various diagnostic categories who go on to have a lung transplant and then regain a normal life, including family life, going back to work--to all of a sudden see these patients once again slowly

develop progressive airway rejection, chronic rejection and shortness of breath is extremely disheartening to the patients, to say the least, their family and, frankly, for their physicians. Thank you for your attention.

Clinical Evidence of Efficacy and Safety

DR. NOONBERG: Good morning. My name is Sarah Noonberg and I am the clinical leader for the inhaled cyclosporine project. Over the next 45 minutes I will be reviewing the clinical data supporting the use of inhaled cyclosporine in lung transplant recipients.

I will begin with a brief discussion of early preclinical and open-label clinical trials of inhaled cyclosporine at UPMC. These trials generated a lot of interest in inhaled cyclosporine and really set the stage for the pivotal randomized, double-blind, placebo-controlled trial which we, at Chiron, refer to as ACS001.

I will then describe the study design and baseline characteristics of patients in ACS001 before moving into a discussion of efficacy,

focusing primarily on the endpoints of survival and chronic rejection. I will then switch gears and summarize the safety data that has been generated for inhaled cyclosporine from a safety database of 102 patients. Although the favorable safety profile is clearly an important aspect of the drug, I am going to be spending much less time reviewing safety listings as this is an area of general agreement with the FDA.

Finally, as with all studies, there are limitations to ACS001 both with respect to study design, as well as choice of the primary endpoint. I am going to end this presentation with a discussion of some of those limitations and how we view them in light of the clear strengths of the study.

As Dr. Golden has described, the introduction of cyclosporine as an immunosuppressant truly revolutionized lung transplantation and allowed for the possibility of long-term survival. Within a few years of FDA approval investigators at UPMC began to develop an

aerosolized formulation, and within five years they initiated preclinical trials.

In the first set of experiments non-transplanted dogs were given a single dose of inhaled cyclosporine. The dose was well tolerated and revealed that pulmonary concentrations were 10- to 100-fold higher than concentrations in other tissues. In addition, there was no change in lung function and no histologic abnormalities.

In a canine lung transplant model dogs were given single agent immunosuppression with inhaled cyclosporine and investigators reported a dose-dependent decrease in the frequency and severity of allograft rejection.

In a rat transplant model rats were given an identical dose of either inhaled cyclosporine or intramuscular cyclosporine. Inhaled cyclosporine was found to be at least as effective as intramuscular cyclosporine in causing a dose-dependent decrease in proinflammatory cytokine production, as well as a decrease in allograft rejection but with far lower systemic exposure to

cyclosporine.

These encouraging preclinical results led to the development of a series of open-label non-comparative trials with inhaled cyclosporine at UPMC. These trials enrolled two different groups of patients, both with established complications of lung transplantation. In the first set of protocols lung transplant recipients with documented chronic rejection were given inhaled cyclosporine in addition to their standard immunosuppressive regimen. Investigators reported improvement in rejection histology and stabilization of pulmonary function relative to pre-enrollment data. But, more importantly, these patients had improved survival both compared to contemporary UPMC unenrolled controls as well as controls from a historical lung transplant registry.

In the next set of protocols patients with refractory acute rejection, defined as acute rejection that failed to respond to immunosuppressive intensification--this represents

a step earlier in the disease process as acute rejection--as a risk factor for the subsequent development of chronic rejection and was the logical next population to study. When these patients were given inhaled cyclosporine, again, in addition to their standard immunosuppressive regimen, investigators reported an improvement in rejection histology, a reduction in proinflammatory cytokine production, and a dose-dependent increase in pulmonary function, all relative to re-enrollment data. Once again, these patients had improved survival compared to contemporary UPMC unenrolled controls.

Despite the non-comparative nature of these trials and their inherent limitations, they made quite an impact in the transplant community, and have led to unregulated compounding of inhaled cyclosporine by a number of U.S. transplant centers. In a survey of 2002, published in Chest, of transplant practices 10 percent of U.S. transplant centers already used inhaled cyclosporine. They compound it in their pharmacies

and they give it to patients with progressive chronic rejection.

These open-label trials were clearly provocative but their interpretation is limited by the lack of an adequate control group. However, they laid the framework for the very first and one of the only randomized, double-blind, placebo-controlled trials in the lung transplant population. Unlike the previous protocols that enrolled patients with established complications of lung transplantation, this trial was designed to test the efficacy of inhaled cyclosporine in preventing rejection and improving outcomes when given prophylactically to patients shortly after their single or double lung transplant procedure.

The trial had two phases. In a pilot phase, the first phase, 10 patients were given open-label inhaled cyclosporine and were followed prospectively. They formed a cohort designed to test the safety and tolerability of the drug in this patient population. In the second phase, the randomized phase, 58 patients were randomized and

56 were randomized and treated with either inhaled cyclosporine or placebo, which in this case was inhaled propylene glycol, the vehicle used to create the inhalation solution. The primary endpoint of the study was rate of acute rejection, and secondary, prospectively defined endpoints of survival, rate of chronic rejection and pulmonary function.

The criteria for enrollment into ACS001 were fairly straightforward. To be included, you had to be a recipient of a single or double lung transplant and be 18 years of age or older. Exclusion criteria included the presence of active fungal or bacterial pneumonia or anastomotic infections prior to the initiation of appropriate antimicrobial therapy. Patients with bronchial stenosis greater than 80 percent had to be treated with standard techniques prior to enrollment. Patients who failed to wean from mechanical ventilation and women of childbearing potential unwilling to use birth control were also excluded. It is important to note that all patients met study

inclusion and exclusion criteria.

All patients in ACS001 were treated with standard-of-care immunosuppressive therapy following transplantation, and all were randomized and enrolled within the first 7-42 days following their transplant surgery. A total of 26 patients were treated with inhaled cyclosporine and 30 were treated with placebo. All patients underwent an initial 10-day dose escalation period where they were initiated on low dose inhaled cyclosporine at 100 mg, and that dose or equivalent volume of placebo was gradually increased to a maximally tolerated dose up to a protocol-specified maximum of 300 mg. The dose or equivalent volume that they reached on day 10 was the dose that they continued 3 times a week for a period of 2 years.

After completion of dosing patients continued to be followed for study endpoints up to the study end date of August 21, 2003. This corresponded to 2 years after the last patient was enrolled and, therefore, could complete their 2-year period of dosing. Therefore, the total

length of follow-up per patient depended on the timing of enrollment and ranged from 24 months for the last patient enrolled up through 56 months for the first patient enrolled.

ACS001 was a randomized trial, and the randomization scheme was developed by the Department of Statistics at the University of Pittsburgh. The randomization was stratified by CMV mismatch, defined as donor positive/recipient negative, versus all other combinations. This was chosen because international registry data has demonstrated that patients with CMV mismatch have a 32 percent increased relative risk of death in the first year compared with other combinations, with a p value of less than 0.0001. Therefore, the assertion that the randomization was not stratified by any variables known to affect outcome is incorrect. The randomization was also stratified by enrollment period and distinguishes patients who generally had a less complicated postoperative course, were stable and met exclusion criteria by 7-21 days versus those that had a relatively more

complicated postoperative course and met exclusion criteria and were stable between 22 and 42 days after the surgery. In line with ICH guidelines, it is impractical and often counterproductive to stratify by more than 2 factors in a study of this size.

This slide illustrates the baseline characteristics of patients enrolled in ACS001. Overall, the two groups were well matched with respect to the majority of relevant baseline demographic characteristics. Donors were similarly well matched for clinically relevant variables. However, as can be expected from any randomized study, there were a few important imbalances. The two variables where clinically relevant imbalances existed were with respect to primary diagnosis and transplant type.

As Dr. Golden has demonstrated, the primary diagnosis leading to transplantation can have an important impact on survival. Patients with COPD have traditionally been associated with better outcomes, especially within the first year,

and this is statistically significant. Nearly twice as many placebo patients had this more favorable diagnosis. In addition, patients with idiopathic pulmonary fibrosis or IPF have historically had among the worst survival, both short-term and long-term, and this is statistically significant at one year and at five years, and there were far more patients with IPF in the inhaled cyclosporine group compared to placebo. Both of these factors together could potentially bias results for better outcomes in the placebo group.

By contrast, double lung transplant recipients have historically had marginally improved survival compared to single lung transplant recipients in the first several years, and this difference becomes increasingly pronounced with time but is not statistically significant at one year or at five years, the time period of interest for ACS001. However, there were more double lung transplant recipients in the inhaled cyclosporine group and this could potentially bias

results towards better outcomes in the inhaled cyclosporine group. Therefore, although imbalances exist, they are split between groups and would not be expected to strongly influence results in one direction or the other.

The protocol specified that patients were to continue study drug for a period of two years. However, due to the nature of the patient population with its high mortality rate, frequent complications and frequent hospitalizations, not all patients could complete the two-year period of dosing and this is not surprising. Roughly two-thirds completed at least one year of therapy and roughly half completed the full two years of therapy. As the protocol specified that dosing should be held temporarily in the presence of an infection not responding to treatment, not all patients had each and every one of their scheduled doses. However, this just reflects the protocol rather than any lack of compliance.

The median duration of dosing was comparable among the two groups. Of the patients

that did prematurely discontinue dosing, the primary reasons were adverse events in the placebo group and withdrawal of consent in the inhaled cyclosporine group. Of the six who withdrew consent, two were due to early tolerability problems; two were primarily due to unrelated medical problems; and one was due primarily to an unrelated social problem and for one the reason was unknown.

Although no patients were lost to follow-up, five patients, three in the inhaled cyclosporine group and one in the placebo group, were taken off the study, the randomized trial, and crossed over into an open-label rescue protocol of inhaled cyclosporine. Their data was censored at the time of crossover and the treatment groups remained blinded. In both groups there were patients that were withdrawn due to protocol deviations and violations that largely included medical non-compliance and smoking.

This slide summarizes the important efficacy and safety results from study ACS001.

Treatment with inhaled cyclosporine led to significantly improved survival and chronic rejection-free survival compared to placebo but did not affect the rate of acute rejection. Treatment with inhaled cyclosporine was not associated with increased risk of nephrotoxicity, infections, malignancies or any systemic toxicities known to occur when cyclosporine is given orally or intravenously. However, similar to other inhaled drugs, inhaled cyclosporine was associated with mild to moderate respiratory tract irritation and bronchospasm.

I will first discuss the effect of inhaled cyclosporine on survival. Using an unadjusted analysis, inhaled cyclosporine was associated with a significant survival advantage compared to placebo, with a relative risk of death of 0.213 and a p value of 0.007. This corresponds to a 79 percent decreased risk of death in patients treated with inhaled cyclosporine compared to placebo. This slide is the Kaplan-Meier plot of survival duration from the time of transplantation to the

study end date, and is the primary reason that we are all here today.

During the period of the study there were 3 deaths in the inhaled cyclosporine group compared to 14 deaths in the placebo group. The results are not only highly statistically significant but also clinically very important. This is the first time a cohort of lung transplant recipients has had survival comparable to recipients of other solid organ transplants and marks a major advance in outcomes for this patient population.

The importance of an unadjusted analysis rests on its robustness and how well it compares to analyses that control for other baseline characteristics that might affect outcome. Therefore, we performed univariate analyses adjusting for potential risk factors that might affect survival, and found that the relative risk of death and the p values were remarkably consistent.

This graph illustrates the relative risk of death and 95 confidence intervals when the

survival data is adjusted by a number of different factors that have been documented in the literature to potentially affect outcome. We also include two factors suggested by the FDA, ICU time after transplantation and the use of donors who at some point during their hospitalization prior to harvesting were treated with an inotrope. Neither of these two factors is supported by the literature or registry data as having an impact on survival. For the case of donor inotrope use, it is not considered in guidelines for optimal donors or marginal donors. However, the key message is that regardless of the baseline characteristic none of these factors appreciably impacts the relative risk of death and lends strong support to the validity of the unadjusted analysis, and this is what is meant by a robust endpoint.

In order to further test the robustness of the survival endpoint, we performed multivariate analyses which adjust for clinically relevant baseline characteristics simultaneously. As not all characteristics can ever be simultaneously

input into a single statistical model, the job of the clinician is to decide which of these are the most clinically relevant.

In order to determine the most clinically relevant factors we searched through the literature to determine those that had been documented to be short-term or long-term prognostic factors. We then reviewed registry data to determine the level of significance and, finally, we discussed these factors with transplant physicians who care for these patients. The general agreement was that the most clinically relevant factors were transplant type, CMV mismatch, primary diagnosis, early acute rejection--all shown in green. We also include in our model the variable of enrollment period as this was a randomization stratification variable and it is in accordance with ICH guidelines.

This slide also illustrates the relative distribution of 16 different baseline characteristics that have been documented in the literature to potentially affect short-term or long-term outcome. As is evident, the majority are

balanced or, if anything, would favor better outcomes in the placebo group.

This slide illustrates the results of the multivariate analyses when these factors are successively added into a Cox proportional hazards model. The key point is the consistency of the treatment effect. The addition of the five most clinically relevant factors into this study does not have any appreciable impact on the relative risk of death or the p values, and provides even further support for the robustness of the survival endpoint.

Robustness was further evaluated by performing a number of sensitivity analyses around the survival endpoint. When we did so, we found that the relative risk of death remained consistent. The top row illustrates the unadjusted analysis on the full data set. When we include patients who were randomized and treated the results are essentially unchanged. When we look at survival relative to first dose of study drug rather than time of transplantation, again the

results are essentially unchanged. When we exclude three placebo patients who had early mortality and died within the first three months--when we just take them out of the analysis and we only analyze the remaining 27, it remains statistically significant. When we take out 14 patients who did not receive at least 80 percent of the protocol maximum dosing adjusted for death, we lose 25 percent of the sample size but still maintain statistical significance and the relative risk of death is barely altered.

The FDA has raised concern about the effects of early pneumonia. So, if we remove from analysis 15 patients who had an episode of pneumonia within one month of initiation of study drug we have lost greater than 25 percent of the patient population and, therefore, expect that the p value is going to increase but the key point is that the relative risk of death, the treatment effect, is barely changed.

Questions have also been raised about the effects of ICU time after transplantation. If five

patients who were in the ICU greater than 14 days were removed from analysis, the results are statistically significant and in favor of the inhaled cyclosporine group. Therefore, we have looked at the survival data from a number of different angles and found the survival data to be robust.

To assess the duration of the survival benefit we collected additional survival data 10 months after the study ended, and we found that the survival benefit persisted. At that point there were 5 deaths in the inhaled cyclosporine group compared to 15 deaths in the placebo group, with a p value of 0.017.

This post-study follow-up is important and it is useful and supportive data. However, it has its limitations. The first is that the study had ended and it ended almost a year earlier. The data was analyzed and patients were unblinded; treatment groups were known. In addition, except for those patients who had crossed over into an open-label protocol, all patients were off study drug for a

substantial period of time, ranging anywhere from 10 months to a maximum of 3.5 years. When you consider that the median time to diagnosis of chronic rejection is 16-20 months, it is going to confound the results. Also, there were placebo patients that had crossed over and were now receiving inhaled cyclosporine so the net effect, as expected, is that it is going to trend toward the null.

This is what the FDA refers to as the five-year data and believes that it is the most appropriate time point to analyze the survival data, but for the reasons that I have just described we disagree and we believe that the data is best analyzed at the prospectively defined study end date.

In order to verify that the placebo population was representative of what would be expected in a larger U.S. transplant population, the placebo survival curve was compared with data from the United Network for Organ Sharing, or UNOS, that maintains a large transplant registry.

Placebo patients were matched with UNOS controls who were transplanted during the same period of enrollment as ACS001, and they were matched by the variables on the slide. Matching also excluded patients who died before they could have possibly enrolled into ACS001.

This slide illustrates the results and shows that both early mortality and late mortality in the placebo group are extremely consistent with what is expected in a larger multicenter patient population. Roughly 50 percent survival at 4.5 years is exactly what has been documented in the literature for years. Therefore, any analyses that exclude early deaths or late deaths or deaths due to particular causes have to be viewed with caution as they would no longer lead to a placebo group whose survival is representative. By comparison, when the ACS001 inhaled cyclosporine group is compared to the UNOS controls the relative risk of death of 0.252 is very comparable to what was seen in ACS001 where the relative risk of death was 0.213.

This is a busy slide but it makes a very important point and brings us into our next topic, namely, the primary reason for the improved survival in patients treated with inhaled cyclosporine is that inhaled cyclosporine prevented chronic rejection. This slide illustrates the timing and cause of death for both groups. As expected, early deaths were predominantly due to infectious causes. However, subsequently nearly all deaths are associated with chronic rejection. Of the five deaths that the agency calls attention to in the mid portion of the graph as driving the statistical significance, four out of the five had chronic rejection. By contrast, in the inhaled cyclosporine group the curve becomes flat and late mortality is not occurring.

One question that has been raised is why is the survival difference statistically different at two years when all patients would have completed their study drug. The reason, as evident from this graph, is that chronic rejection is the predominant cause of death in the first year so you wouldn't

expect to see early large separation of the two curves. However, after a year it is the major contributor, as Dr. Golden has demonstrated, to mortality.

To review, chronic rejection is an umbrella term for patients with histologic evidence of bronchiolitis obliterans, or OB, documented by transbronchial biopsy. It is also representative of patients with clinical evidence of bronchiolitis obliterans syndrome, or BOS, using a sustained and unexplained decline in FEV1 as a surrogate marker. It is not uncommon for patients to have bronchiolitis obliterans but, due to the progressive nature, they haven't met clinical criteria for BOS. It is also not uncommon for patients to have BOS but, due to the insensitive nature of transbronchial biopsy in making the diagnosis they don't have OB. So, these two groups, patients with OB and patients with BOS, are overlapping but they all represent patients with chronic rejection. So, looking at each group individually may be informative but it has to be

viewed as a subset analysis. Consistent with direct delivery to the airway epithelium, the site of chronic rejection, treatment with inhaled cyclosporine led to a 72 percent decrease in the risk of chronic rejection or death. As you will see, when we performed the same univariate and multivariate analyses, the results are even more robust.

This slide illustrates the Kaplan-Meier estimate of chronic rejection-free survival and uses a composite endpoint of first diagnosis of OB, first diagnosis of BOS or death. There are two important points here. One is that there is general agreement with the FDA that the rate of biopsy and the rate of pulmonary function testing is comparable between the two groups so that the difference isn't driven by increased testing in one group or the other.

The second is that the use of a composite endpoint of chronic rejection and death implies that patients who die and, therefore, can't go on to be diagnosed with chronic rejection are counted

as events rather than censored in the statistical analysis. To censor deaths in a statistical analysis of chronic rejection would require the assumption that there is no relationship between chronic rejection and death, an assumption that we know to be invalid.

The agency issued guidelines in April of 2005 endorsing a progression-free survival analysis for similar oncology endpoints to avoid a type of bias known as informative censoring. As with the survival endpoint, we found a remarkable consistency of the chronic rejection-free survival endpoint when we performed a series of univariate analyses. None of these baseline characteristics had any appreciable impact on the treatment effect or its significance, which speaks to the robustness of this endpoint as well.

This slide illustrates the result of multivariate analyses on the chronic rejection-free survival endpoint. Once again, the addition of the 5 most clinically relevant factors in this study--adding them into a Cox proportional hazards

model has essentially no real impact on the treatment effect of the confidence intervals and the p values remain highly statistically significant.

Valid questions have been raised about whether the survival benefit is so strong that any composite endpoint that includes survival would be statistically significant. Therefore, for exploratory reasons we performed an analysis of chronic rejection with death censored. This clearly biases results against the inhaled cyclosporine group due to the larger number of deaths in the placebo group. As mentioned, this is referred to as informative censoring. However that said, when we performed the analysis the results were still statistically significant and in favor of the inhaled cyclosporine group. Chronic rejection occurred in 50 percent of placebo patients and 27 percent of inhaled cyclosporine patients.

This slide illustrates the Kaplan-Meier estimate of time to chronic rejection with deaths

censored and clearly illustrates a statistically significant effect on chronic rejection independent of death despite the large bias inherent in the analysis. This analysis is important because it leads to the conclusion that treatment with inhaled cyclosporine prevents chronic rejection, the leading cause of late mortality in lung transplant patients.

However, the primary endpoint of the study was not survival or chronic rejection but rate of acute rejection and this endpoint was not met. Approximately 70 percent of patients in both groups had at least 1 episode of documented grade 2 or higher acute rejection prior to study termination. After the start of dosing rates were comparable between the 2 groups, with a p value of 0.73.

Dr. Golden has explained the paradigm shift that has occurred in the transplant community in terms of how acute and chronic rejection are now understood. Acute rejection is primarily a vascular process so an immunosuppressant with low vascular exposure would not be expected to have a

significant effect, and that is what we are seeing in ACS001. By contrast, chronic rejection is an airway process. It is mediated in the airway epithelium so an immunosuppressant delivered directly to the airway epithelium would be expected to have an effect, and that too is what we are seeing in ACS001.

Now I am going to switch gears and briefly discuss safety. This slide illustrates the relative systemic exposure to cyclosporine when given by an inhalation route compared to an oral route. A 300 mg dose of inhaled cyclosporine has been demonstrated to lead to a mean peak blood concentration of 206 ng/mL, roughly 11-14 percent of what you would expect in an oral dose. the levels at 24 hours are barely detectable by standard assays, and these numbers are reflected in the mean AUC, or area under the curve, which suggests a roughly 8-fold lower systemic exposure to cyclosporine when it is given by an inhaled route compared to an oral route. This low systemic exposure explains why no additional systemic

toxicities were seen in the inhaled cyclosporine group compared to placebo.

Data to support the safety of inhaled cyclosporine and propylene glycol come from multiple sources, and this is outlined in much further detail in the briefing book. The first are preclinical toxicology studies in dogs and rats, performed both by Chiron as well as referenced in the literature. These studies show that no unexpected toxicities were seen when animals were treated at many-fold higher doses than what would be used clinically.

The next source is the randomized, placebo-controlled ACS001 trial where safety data from 30 placebo patients were compared with safety data from 36 inhaled cyclosporine patients, the 26 randomized and the 10 placebo.

The next source is ACS002, which was a retrospective safety analysis of 70 patients enrolled in 1/7 different open-label protocols of inhaled cyclosporine in patients with refractory acute and chronic rejection. The ISS, or

integrated safety summary, is a combination of all patients treated with inhaled cyclosporine in either ACS001 or ACS002 and represents 102 unique patients in our safety database.

To summarize our clinical safety data, review of the adverse event listings in ACS001 revealed that inhaled cyclosporine was safe. There was no increased risk of nephrotoxicity, neurotoxicity, infections, malignancies or any other toxicities that occur with oral or intravenous cyclosporine. In addition, there were no new or unexpected systemic toxicities.

So, the key point is that treatment with inhaled cyclosporine led to a 79 percent decreased risk of death compared to placebo, with no systemic toxicity. However, inhaled cyclosporine was associated with respiratory tract irritation and bronchospasm and this will be discussed in the next slide. Review of adverse event data in ACS002 and the ISS confirmed the safety findings of ACS001, and no new safety signals were seen after review of the serious adverse event data.

After review of the ACS001 adverse event listings and case report forms, it became clear that there were two distinct but interrelated safety signals that appeared to be a direct result of inhaled cyclosporine. The first was bronchospasm manifested primarily by cough, exacerbated dyspnea and wheezing. The second was respiratory tract irritation manifested primarily by pharyngitis but also laryngitis and non-cardiac chest pain. In general, these events were mild to moderate. They occurred early in the patient's treatment course and diminished with time, and once they resolved it was rare for them to recur. But, most importantly, there was no progression to more serious respiratory complications such as acute respiratory failure or ARDS. The adverse event of lung consolidation was noted in higher frequency in the inhaled cyclosporine group but the clinical relevance of this finding is unclear as underlying causes such as pneumonia, lung mass, atelectases or other underlying causes were comparable between the 2 groups.

Having reviewed the most important clinical results for inhaled cyclosporine, it is appropriate to take a step back and take a look at some of the outstanding issues surrounding the data. Study ACS001 was conducted at a single center, and this was discussed with the FDA well before Chiron decided to move ahead and file the NDA. However, it is important to note that no other transplant studies or registry analyses have ever shown a survival benefit comparable to what was seen in the inhaled cyclosporine group of ACS001.

We also looked at the placebo group and found that survival was comparable to a multicenter matched database. Single-center trials are not ideal. However, they do have one important advantage. Because confounding due to differences in patient care is minimized, single-center trials are actually better at determining a treatment effect than multicenter trials of the same size. Finally, Chiron has committed to a multicenter postapproval trial to further study the efficacy

and safety of inhaled cyclosporine.

The sample size of N equals 56 for efficacy and N equals 102 for safety is small. However, the lung transplant population is exceedingly small, with 1100 lung transplants performed in the United States each year. Despite the small sample size, the survival and chronic rejection data are highly statistically significant so the sample size was sufficient to test the hypothesis that inhaled cyclosporine improves survival and chronic rejection-free survival.

Cyclosporine and propylene glycol are well-known and well-characterized, and the safety profile of inhales cyclosporine is extremely favorable, especially in light of the survival benefit. Again, Chiron has committed to creating a larger efficacy and safety database through a postapproval trial.

The randomization code was susceptible to unblinding and CRF assembly was retrospective. The randomization code used a patient subject number followed by an A, B, C or D designation, with A and

D referring to placebo patients, B and C referring to inhaled cyclosporine patients, and it is possible that the study could have become unblinded due to the simple nature of this designation. However, there are several factors that make this very unlikely. First is that the principal investigator was never exposed to the subject numbers. Second, the investigator removed 3 inhaled cyclosporine patients from the inhaled cyclosporine arm only to cross over into an inhaled cyclosporine open-label rescue protocol. In addition, the pathologist reading the transbronchial biopsies and making the determination of bronchiolitis obliterans was never exposed to study numbers.

The issue with retrospective CRF assembly is whether somehow in the retrospective nature of filling out these forms an assessment of an outcome is altered. However, when the outcome is death, or the presence or absence of bronchiolitis obliterans on an original histopathology report, or whether FEV1 has declined by 20 percent or more from a

post-transplant maximum, these are hard endpoints and would not be expected to be altered by retrospective CRF assembly.

Treatment groups were not balanced on each and every baseline characteristic. The purpose of randomization is not to eliminate all imbalances but, rather, to randomly distribute them between groups. The two treatment groups are comparable, and of the clinically relevant baseline characteristics we examined the majority are balanced or, if anything, would favor better outcomes in the placebo group.

Finally, when imbalances do occur in clinically relevant variables statistical models can be used to adjust for these both in univariate or multivariate analyses, and we have presented such analyses that show that the data is robust. So, we feel extremely confident in saying that baseline imbalances did not explain the efficacy of inhaled cyclosporine.

The study did not meet its primary endpoint of decreased rate of acute rejection.

However, scientific understanding has evolved since the design of ACS001 and the lack of an effect on acute rejection is consistent with low systemic exposure. The design of the study doesn't impact the assessment of survival or chronic rejection or alter how the data is obtained. It is also important to note that survival and chronic rejection were prospectively defined secondary endpoints. These analyses are not post hoc nor do they constitute data mining.

Finally, the survival and chronic rejection data are clinically important, statistically significant and scientifically sound. Inhaled cyclosporine is delivered directly to the airways, the site of chronic rejection. Inhaled cyclosporine prevented chronic rejection and, in doing so, markedly improved survival. The importance of this data is illustrated by the fact that physicians from 30 different transplant centers in the United States, which represents almost half of all active lung transplant centers, have requested early access to inhaled cyclosporine

as part of our early access program.

We have been advised to make it clear to the advisory committee where there are differences of opinion between Chiron and the FDA, and that is really why we are here today. So, this slide illustrates five of the most important areas where we disagree.

First, we believe that covariates in a statistical model should be chosen based on an association with the clinical outcome rather than because of an imbalance. In the case of ICU time, the use of ICU time greater than ten days, there is an imbalance toward the placebo group. However, this is not documented to be associated with survival. If an ICU time greater than seven days is chosen that imbalance is minimized, and if an ICU time greater than four days is chosen the imbalance is reversed. We believe that it is important to differentiate patients who had an earlier, easier postoperative course from those who had a harder postoperative course, but believe that this is best accomplished by the randomization

stratification variable enrollment period, early versus late.

In the case of donor inotropic support, we have yet to find a single reference that even considers this variable, much less finds it clinically relevant and the FDA has called this one of the most clinically relevant factors in the study.

We do have variables and we do have data on donor quality through other variables that have been documented in the literature to be clinically important, such as donor age, donor bacterial colonization, donor graft, ischemic time, and these are balanced between the two groups. The important point is that the use of a covariate that is imbalanced but not clinically relevant will always cause results to trend toward the null and that is what we have seen with the FDA analyses.

Second, in analyses of survival we disagree that patients whose use of donor inotrope or the donor inotrope data is missing--we disagree that these patients should be excluded from

analyses. In the FDA analysis, by excluding long-term survivors in the inhaled cyclosporine group, the treatment effect and p values are going to be altered inappropriately.

Three, we believe that survival is best analyzed at the prospectively defined study end date rather than one year after--or nearly a year after the study was over. I have already discussed our reasons for this.

Four, we believe that patients with bronchiolitis obliterans, or OB, should be included in an analysis of chronic rejection. The diagnosis of OB has a specificity of over 95 percent. Patients with BOS and OB represent overlapping subsets and, therefore, to look at either one alone, we believe, is a subset analysis.

Finally, five, analyses of BOS should not censor deaths. This is clearly informative censoring, and when deaths are not censored and BOS-free survival is analyzed the results are statistically significant and remain so when controlled for by CMV mismatch, primary diagnosis

and early acute rejection. Analyses that censor death can be informative but we have shown in our chronic rejection that although they can be informative they shouldn't be used as the primary analysis.

So, I would like to end with a summary of the clinical data that I presented. In the lung transplant population with no appropriate approved drugs, very few randomized clinical trials and a dismal prognosis that hasn't changed in almost 20 years, treatment with inhaled cyclosporine was associated with a 79 percent decrease in the risk of death. Treatment with inhaled cyclosporine was associated with a 72 percent decrease in the risk of chronic rejection or death. We have demonstrated that our efficacy results are robust through a number of different analyses. We have also demonstrated that the ACS001 placebo population is representative of a larger U.S. transplant population. We have demonstrated that treatment with inhaled cyclosporine was not associated with any systemic toxicities. Finally,

inhaled cyclosporine was associated with local respiratory tract irritation and bronchospasm, a relatively small price to pay in light of the profound survival benefit.

Thank you. I would like to end and turn this presentation over to Dr. Ronald Helms, Professor Emeritus of Biostatistics of the University of North Carolina, who is going to spend a few minutes discussing the statistical considerations of the study.

Statistical Considerations

DR. HELMS: Thank you, and thank you for the opportunity to come and address this group here this morning. My time is short so I am going to dive right in, if I may.

Why are we here? Well, this survival curve tells why we are here, the profound difference in survival in these two treatment arms, as has been discussed at length already.

A second reason I am here is that this is a very interesting project, a very interesting project. Let me first establish a disclaimer and

my conflict of interest issue. The views that are expressed in this presentation are mine alone and do not represent either the FDA or Chiron or Rho, my current employer, or the University of North Carolina, my former employer. It is possible that these views may represent the best interests of future lung transplant patients. In terms of financial conflict of interest, neither Rho nor I have any financial stake in the outcome of this submission. Less than half a percent of Rho's total income this year will come from Chiron. Chiron pays Rho an hourly consulting fee for my time plus travel expenses and, in fact, my board of directors told me they would prefer that I work on other projects that are more financially rewarding to the company.

[Laughter]

So, I am here despite that. Also, neither Rho nor Chiron has edited my presentation and I have reviewed the briefing documents that you have seen from both the FDA and Chiron, plus some other more comprehensive documentation. So, I feel

unconflicted here.

So, why am I here? Well, coming back to the results of this study and the fact that it is a very interesting project--it is a very interesting project and we have a problem. By "we" I mean the professionals sitting here around the table, the FDA professionals, the Chiron staff--we have a problem.

This Kaplan-Meier graph tells that this product has the potential to save the lives of a statistical number of lung transplant patients. The NDA does not meet the usual regulatory requirements for approval. Should it be approved?

Well, there are advantages and disadvantages to approval in this case. The results indicate that if approved, widespread use of this product would probably save the lives of around 300 to 350 lung transplant patients a year. Now, I should just comment that my comments here are really aimed at the non-statisticians on this panel. The statisticians know how to interpret relative risk and those kinds of things. I thought

it would be useful to translate this into lives saved after a period of time when the product was in widespread use. It appears to improve the survival probability by about 30 or 35 percentage points. You see the numbers there, somewhere around 50-90 percent, and there are about 1000 or 1100 transplant patients so if you do the arithmetic it comes out to around 300 to 350 lung transplant lives saved a year.

Another advantage is--and this is a practical advantage--if this product were approved FDA could require Chiron to conduct the sufficiently large follow-up study that Chiron has proposed. If the study were negative the approval could be withdrawn and, as a practical matter, without approval the follow-up study will never be done. Off-label use of the product would ultimately become a standard of care and failure to use it would be considered unethical and subject to lawsuits and those sorts of things. And it is an interesting aside that we have a very closely related case. Cyclosporine, which is used

universally in the treatment of lung transplants, is not approved for that indication; it is all off-label use. The studies have never been done.

There are some obvious obstacles to approval. We have the results of only one small unconfirmed study. This is a serious problem. It is a serious problem. This one study has a number of flaws that have been noted by both Chiron and FDA. Here are some opinions, one of these is very important; some are potentially important; and some really are inconsequential in my opinion.

The very important flaw in this clinical trial from a statistical perspective is that the stated primary outcome was acute rejection, not mortality or survival. The statistical methods that we routinely use for Phase III confirmatory studies aren't very helpful with this problem, the problem of switching the primary endpoint from what was stated in the protocol to a secondary endpoint. But good, old-fashioned common sense can be helpful. When you see that big an effect on survival you very likely made an important

discovery.

Now, we could use, as statisticians, a branch of statistics called decision theory for formal risk-benefit analyses here but the fact is that if we did that the analyses would be based on a number of assumptions and if you are strongly opposed to approval here you challenge the assumptions, and rightly so. The result is so big, the difference in survival is so big here that we can tell what the outcome would be anyway, that it would lead to a decision in favor of the product.

Some potentially important flaws--let me address those. My time is brief and I won't go into statistical details but there is an important side note here. At least as of a few weeks ago, the FDA and Chiron biostatisticians had confirmed each other's statistical calculations. The point is that there is no issue about correctness of populations. Now, you are going to hear different perspectives obviously from Chiron and FDA. In my opinion, the issues here are about how to use and interpret the statistics, not the actual results,

and I think that is good to know.

There are some potentially important flaws that have already been mentioned and you will hear some more about that in the FDA presentation. The randomization, if done improperly, could be an important flaw; the lack of balance with respect to important baseline characteristics; unmasking or unblinding--we used to call it unblinding but then I worked with some ophthalmologists and they taught me to use the word "unmasking." The study was conducted in such a manner that the investigators could have been unmasked essentially, and the study was conducted at a single clinical center, not multiple centers.

I want to cut to the chase because my time is limited. The bottom line is I reviewed each of the potentially important flaws and my conclusions for each one were that each was either not a flaw at all or was relatively unimportant. For example, the randomization failed to balance with respect to all the baseline factors. It rarely does in clinical trials, even large clinical trials. It

has been my experience over the last 15 years since I began looking at this that only one out of hundreds of clinical trials was balanced with respect to all important baseline factors. So, it is not a case of failure. On request, on somebody else's time, I will be happy to talk about some of these issues.

There are some unimportant flaws in the clinical trial, and they are listed there. We don't have to spend time on that.

Let me raise an important ethical point for the members of the panel. Suppose the data from this study were the results of an interim analysis half way through the study, and suppose the members of this advisory panel were instead sitting as the study's data and safety monitoring board, would we be ethically bound to terminate the study to protect future patients who might be assigned to placebo? I suspect that many of you have sat as members of data and safety monitoring boards and faced precisely this question in the middle of a study. I have. And I believe that

everyone on the DSMBs in which I participated would have stopped this study to protect placebo patients, the results of the study are that compelling.

I think there is another important ethical point. I think the people in this room--again, the FDA staff, the advisory panel, the Chiron staff--are ethically bound to find a way to make this product available on-label to U.S. lung transplant patients. It will be used off-label. It already is being used off-label but without approval for some years this product will only be available to people who can afford to pay for it from their own funds because it won't be covered by insurance. So, we have a product that would be made available to wealthy people and not others.

We also, I think, are ethically bound to find a way to make it necessary for Chiron to conduct the proposed postapproval follow-up study. If we don't, it won't be done. Realistically, it can only be done as a postapproval study for financial reasons that Chiron can talk to you

about.

What an interesting project! Thank you for the opportunity to talk to you.

Safety and Benefit-Risk

DR. DILLY: Thank you, Prof. Helms and thank you, everyone, for your patience in following through our presentation. I am going to conclude with about five minutes of remarks to end the Chiron presentation.

What I would like to do is consider some of the issues relevant to the potential approval of Pulminiq. Clearly, we believe the best way to help lung transplant patients now is to make CyIS available. Lung transplant, as you heard, is in many ways the poster child of the orphan drug indication. Despite the incentive provided by the orphan drug designation, no drugs have been developed for lung transplantation, probably because the economics simply don't work for a conventional development program. So, if we are looking for new drugs, it is going to come from sources like this.

Now, we are not suggesting for a moment that the burden of evidence is any different for an orphan indication. Rather, what we are suggesting is that we must consider the evidence that exists on its merit and, in fact, the case for approval of this drug is very strong.

The scientific premise for inhaled cyclosporine is extremely straightforward. We are giving an effective drug, with systemic toxicity, by inhalation to achieve higher lung levels. This has been done, of course, successfully in asthma, in COPD, in cystic fibrosis. It is a well precedented approach. In fact, as you heard, the idea is so straightforward that many lung transplant centers were already using inhaled cyclosporine empirically before the clinical data of ACS001 were known.

Of course, these are the essential clinical data. Patients who received inhaled cyclosporine in the pivotal trial lived significantly longer than those who did not. You have heard compelling arguments that the difference

in survival was due to inhaled cyclosporine and that the benefit is highly likely to be generalizable to other patients in other treatment centers. Publication of these data will rightly have a major impact on the treatment of lung transplantation with or without approval of Pulminiq. The case for benefit is very strong. Also as you have heard, there is very little risk of harm. This is a known drug. Local toxicity in the lung is minor and systemic exposure is not clinically important. Finally, this is a very small population with an entirely clear-cut diagnosis, lung transplantation. So, the chances of a major public health problem from broad usage is very, very small. In other words, the demonstrated benefit far outweighs the potential for harm. The bottom line is patients will live longer if inhaled cyclosporine is made available to them.

Of course, some questions remain open because of the nature of the clinical program conducted to date. So, the right thing to do for

patients is to approve inhaled cyclosporine now and conduct the appropriate postapproval study to address those outstanding questions. So, I would like to finish the Chiron comments by considering what that postapproval study should look like.

The central question really is how to give inhaled cyclosporine. We have seen benefits from therapy lasting for up to two years. All logic dictates that for a chronic rejection endpoint chronic therapy should be better. We need to study that. We need to study dosing beyond two years. We need to work on making the first few doses as tolerable as possible so we can get as many patients as possible onto an effective dosing regimen.

We would also love to know more about the interplay of the key clinical endpoints, survival, rejection, lung function. You can only interpret so far based on a single, relatively small study with such a bright line survival effect. We believe that 300 mg of inhaled cyclosporine by nebulizer three times a week is a perfectly

appropriate inhaled regimen and the right thing to put in the label, but there are some questions we need a bigger study to answer.

How do patients do if they actually tolerate a dose below 300 mg--100 mg or 200 mg? Is the need for systemic dose intensification reduced with effective long-term inhaled therapy? What is the best way to deal with treatment interruptions, for instance during concomitant illnesses? Of course, it will be informative to have a much bigger safety experience.

So, here is our proposal, essentially this is a very large single-arm study with external controls. We believe that we could draw the control arm now from the UNOS database. From the comments you heard from Dr. Golden and others, we know what happens to lung transplant patients treated with current standard of care. So, 250 patients will be treated with a labeled regimen of inhaled cyclosporine for 5 years. A placebo group is not appropriate and not necessary given the robust survival advantage already demonstrated with

inhaled cyclosporine. There will be 2 external controls, firstly, about a thousand matched patients with long-term follow-on data drawn from the UNOS database. Secondly, a group of contemporaneous controls who will not receive inhaled cyclosporine. The exact size of this group, of course, will be somewhat dependent on the rapidity of uptake of inhaled cyclosporine therapy. So, we would expect that the availability of those patients would go down over time.

What I am attempting to describe to you here is a study that is entirely doable in the postapproval context. The primary endpoint will be chronic rejection-free survival, with all-cause mortality and lung function as secondary endpoints. We see three safety endpoints as particularly interesting: Firstly, infections requiring hospitalization because we believe that that signal in favor of the lower incidence of pneumonia on the inhaled cyclosporine group in ACS001 is probably real and due to decreased lung damage from chronic rejection, making the lungs less susceptible to

infection. Secondly, we want to look at renal dysfunction and malignancy as readouts of systemic immunosuppressive status, as well as diligent follow-up for the other safety events. In fact, this will be the largest study ever done and the longest study ever done in the lung transplant setting.

In conclusion, based on what we know now lung transplant patients will clearly live longer with inhaled cyclosporine. The outstanding questions can be addressed in a postapproval study and so we believe that inhaled cyclosporine should be approved now.

Now I would like to invite Dr. Scaife to the podium as well and we can take your questions.

DR. SCAIFE: Thank you very much, Dr. Dilly. We can open to the FDA and the panel for questions.

Questions from the Panel

DR. SWENSON: Go ahead.

DR. SCHOENFELD: I just had a few questions on acute rejection since that endpoint

wasn't exactly described. How is that diagnosed?

DR. SCAIFE: Dr. Sarah Noonberg?

DR. NOONBERG: It is diagnosed by transbronchial biopsy and it is graded 0-4. So, it is the same transbronchial biopsy that can be used to make the diagnosis of bronchiolitis obliterans.

DR. SCHOENFELD: So, was there sort of a program of periodic transbronchial biopsies in these patients during the study?

DR. NOONBERG: Yes, approximately the first month and then three to four months afterward for a period of two years and then as clinically relevant. It should be noted that the mean greatly exceeded that. All patients had the minimum and the mean was far higher.

DR. SCHOENFELD: Another question about acute rejection, once a patient has bronchiolitis obliterans can they have acute rejection also?

DR. NOONBERG: Yes.

DR. SCHOENFELD: I see. So, it can happen after the chronic rejection has begun.

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: I would like to ask Dr. Golden if he would be willing to comment on this. Let me give perhaps a little bit of a setting for my concerns here. We have a study in which the primary outcome was not met and the secondary outcome is met that at the time the study was conceived didn't correspond to biology that was understood. The understanding of biology has changed but--I would like to say I am not a pulmonary person but I am a transplanter--is still not very well understood. So, I think I need to have somebody who really understands the pulmonary rejection business to tell me a little bit about the preclinical information on the impact of local immunosuppression for chronic rejection in the lungs. Right now the general assumption is that most of the effects of immunosuppression are central. I grant you that there is some very real interest in the possibility of local immunocytes being locally immunosuppressed but this is not what I would call a robustly well understood part of science. So, since we can't look at this really in

most of the forms of transplantation, it may be that we have some better understanding of this from the pulmonary point of view and I would like to get the best understanding I can have of what is currently understood about the impact of local immunosuppression for pulmonary rejection.

DR. GOLDEN: First of all, nobody knows with precision exactly where you are treating locally along the airway. I would infer, given that there is a difference in chronic rejection, that that is generally a more peripheral airway portion.

DR. HUNSICKER: Let me clarify that. I wasn't talking where along the airway, I was talking about central immunological events as opposed to peripheral immunological events. Most of us have assumed that the primary effects of immunosuppression are central rather than in the peripheral organs, particularly of the calcineurin inhibitors. So, what I want to know is, is it known what the effects of local immunosuppression in lung rejection are in experimental models for

instance?

DR. GOLDEN: Let me make sure I understand the question. You want to know when you give systemic immunosuppression centrally how that might affect the airway.

DR. HUNSICKER: Actually, it is the other way around. Let's assume that when cyclosporine gets into the body where it really is doing its thing is in the lymph nodes and the spleen, and stuff like that where the cells are being developed. Then it doesn't make a whole lot of sense that local application should be effective. If, in fact, there is local effect on the lymphatic cells that are in the bronchi, then it might make sense. Right now this is something that is not understood in other forms of rejection because we can't get at the local tissues quite so well. What is known about this?

DR. GOLDEN: I think this is a new area. To answer it the best I can, one would have to infer that systemic therapy does not reach a level of mucosal benefit, that applying the medicine

locally, as you say, must have some local immune benefit. The slide I showed of the mucosa with lymphocytes moving into the submucosa--I can only infer that systemic therapy or having a central effect on lymph nodes, etc., as you say, is not reaching a level of immunosuppression along the airway that is benefitted by a direct local application to the epithelium of an immunosuppressant.

I must say that there are ongoing studies now with other agents, like inhaled rapomyacin, to also try and treat this. That is an animal study, very preliminary. So, the best answer is I really don't know. I infer that there is a benefit locally to applying, as you can uniquely do in the lung as you said, to a mucosal process.

DR. PRUSSIN: Calman Prussin, NIAID. Just to follow-up, in all immunologic and allergic lung diseases I know T-cells are being activated in the lung locally and expressing cytokines locally. So, if you are applying that drug locally you would expect that it would have an effect there as

opposed to cells that are in the spleen which are mostly resting and not producing cytokines. So, it does make sense immunologically.

DR. SWENSON: Dr. Gay?

DR. GAY: Steve Gay, University of Michigan. I had a question concerning the early stoppage of the trial. Pittsburgh is a fairly aggressive transplant institution and it seems as if the study was initially powered for 120 patients. The study was stopped at 56 patients. I was wondering what factors led to the early stoppage with the fact that the primary endpoint was clearly not achieved at that point.

DR. DILLY: The original sample size estimate was based on the availability of patients during the predefined study duration, and the study ended on the day that the study was intended to end. That was not influenced by the primary endpoint. It was simply that there were approximately 120-odd patients during that period who were transplanted at Pittsburgh and around half of those patients went on to the study. So, in

fact, this was a pretty good enrollment of eligible patients at the site.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: I also have a question about that because you say it was not influenced by the results. Does that mean the results were not known at that time?

DR. DILLY: The study was done blinded at that time so the results were not known and the blind was well preserved. We really became aware of those results after the unblinding.

Another thing that we have looked at in some detail--and perhaps Dr. Noonberg or Dr. Capra would like to talk about this--is whether there was something special about the patients that went into the study. Was there something about the placebo group and whether these were a selected group of patients? All the evidence says is that these were the same kind of patients as were not enrolled in the study.

DR. NOONBERG: When we compared the placebo and ACS001 to UPMC unenrolled controls we

found that the survival curves were comparable, with a p value of 0.99, so these didn't represent a select group of patients. One of the reasons for the poor enrollment is that there just simply weren't enough transplants performed during that period of time. During those three years there was a far lower time for--I am just going to stop and show this slide quickly that demonstrate the survival of screen failures, so patients who were not enrolled in ACS001 and those that were enrolled into the placebo group.

But to go back to my previous thought, I mean, they couldn't have enrolled 136 patients. There were 105 transplants performed during the enrollment period. The enrollment period didn't stop early; the enrollment period had a three-year duration and it stopped at that three-year duration. It just didn't enroll the requisite number of patients that it anticipated.

DR. SWENSON: I believe Dr. Proschan has another question, but for the members of the panel here, if you will just simply hit your "talk"

button we will be able to see the light on and you needn't raise your hand. That will probably be easier for us. Dr. Proschan?

DR. PROSCHAN: I guess I was just following up on that because, you know, usually even if it is the primary endpoint to stop early there are boundaries that you use and, you know, the commonly used boundary is called the O'Brien-Flemming type of boundary, and this trial would not have met that level of evidence. But that is a concern, mainly motivated by my thinking that the results were known at the time you stopped and, therefore, the possibility on a random high.

DR. SWENSON: Dr. Moss?

DR. MOSS: I have a question I guess for Dr. Noonberg but you, guys, might answer it too. It has to do with the generalizability of your results and I think you showed it on that slide. Normally when you have figures on a study you say we screened this many people; these many were excluded and we were left with 10 percent of the population. That wasn't included in any documents

but I think you brought it out a little bit there so could you just go over that and say, you know, these many people were screened and these many were excluded and you were left with what percentage of the patients that were actually enrolled in the study, so we can get an idea about the generalizability of your data?

DR. SCAIFE: Dr. Noonberg?

DR. NOONBERG: You want to go back to that last slide?

DR. MOSS: I think the data was there but you never mentioned it before. You don't need the slide, just how many people were screened and how many were excluded and you were left with this many people so we can see how generalizable your data are.

DR. NOONBERG: Right. There were 105 transplants performed during the roughly 3-year enrollment period and there were 68 patients--actually, 58 patients enrolled during that 3-year period; 10 were enrolled the year previous. So, approximately half and, as I say,

the survival in the enrolled and the placebo survival in the unenrolled group is comparable, with a p value of 0.99.

DR. SWENSON: Dr. Venitz?

DR. VENITZ: I want to follow-up on Dr. Hunsicker's question in a different way. He was questioning the biology supporting localized administration versus systemic administration. You obviously looked at exposure to cyclosporine after inhalation relative to oral or systemic administration. Did you look at exposure to the lung in either clinical or preclinical models and compare systemic administration to inhalation?

DR. DILLY: We actually have access to data on a scintigraphy study looking at labeled inhaled cyclosporine, conducted by Dr. Corcoran at the University of Pittsburgh, and I think it would be extremely relevant to show you those data. I will give you the editorial comment while Sarah retrieves the slide.

But with the 300 mg dose put into a nebulizer, what we have seen is that about 25 mg is

the applied dose to the lung. That is achieving dose levels in the lung that would require approximately doubling of the systemic immunosuppressive dose, and that is our central premise, which is that that is not something that you could routinely do in clinical practice because of the toxicities.

DR. NOONBERG: Again, just going back to the first animal experiments in 1988 where they just gave single doses of inhaled cyclosporine, they found that pulmonary concentrations were 10- to 100-fold higher than concentrations in other tissues. In the rat model that I described pulmonary concentrations were at least 3-fold higher than systemic concentrations. So, that is the data that we have for preclinical.

DR. VENITZ: Again just to follow-up, how does that compare if you give cyclosporine systemically? You are talking about what happens after inhalation. Right? The levels in the lung are higher than in other tissues, higher than in plasma?

DR. NOONBERG: Right.

DR. VENITZ: And I am wondering how would that compare if a dose of cyclosporine was given intravenously to those animals. What lung concentrations would you be able to achieve?

DR. DILLY: What we showed was a 25 mg dose applied to the lung through inhalation. You have to remember that when you put 300 mg into a nebulizer an awful lot goes into the atmosphere and an awful lot doesn't get into the lung. That 25 mg applied dose, in terms of mg/g lung weight, equates to approximately an 8-fold higher systemic dose. If you assume 100 percent bioavailability of the systemic dose you have given parenterally, that would mean that you are looking at something like a 200 mg dose given orally to get to the same lung levels. That is based on AUC calculations. If you are thinking about peak levels, then the difference is far greater because, of course, you get the early distribution phenomenon into the lung.

DR. VENITZ: And that is in humans? Any preclinical data to back that up?

DR. DILLY: Actually, that is in the briefing book. The best data we got is in humans. It is actually in the briefing book.

DR. SWENSON: Dr. Burdick?

DR. BARRETT: In Dr. Golden's presentation he showed some data looking at BOS as a disease progression marker. However, in the documentation provided both BOS and FEV1 were not determined to be significantly different between the two groups. So, assuming chronic rejection as the indication here for this product, can you give some reasons why you think that occurred?

DR. SCAIFE: Dr. Bill Capra is the lead statistician for Chiron.

DR. CAPRA: Actually, CyIS did show an effect on BOS, specifically BOS-free survival. The reason why our results are different than the FDA's is that the FDA censors BOS in their analysis and this is informative censoring. Because the reasons for death are disease related, it is invalid to censor deaths in a disease progression endpoint.

The FDA has recently issued a guidance on

this type of endpoint for oncology studies where they recommend using a progression-free survival endpoint in such an analysis rather than time to progression analysis. If you do such an analysis with this BOS what you see is an effect of cyclosporine on improving BOS-free survival with a p value of 0.99.

DR. BARRETT: Could you comment on the FEV1 though?

DR. CAPRA: Sure. We looked at FEV1 in a number of ways. We looked at change from baseline to the final value; change from post-transplant to the final value. We looked at time adjusted area under the curves and we looked at slopes. In none of these analyses did we see a statistical significance. However, in each and every analysis the point estimate favored the active group. As an example, up here I have the results of the change from baseline to the final value and we see that the placebo group increased by 0.15 L and the active group increased by 0.40 L. So, there seemed to be a trend, however it was not statistically

significant.

We think there are some limitations to the FEV1 analysis and we think one of the major limitations is the informed censoring. Because there is such a large number of deaths and because the FEV1 values cannot be obtained from subjects after they die it goes against censoring. Also, FEV1 itself is highly variable. Any single subject might have short-term fluctuations and what BOS does is it basically ignores those short-term fluctuations and looks for a sustained 20 percent decrease. So, when you look at BOS, removing some of that variability, and when you address the informed censoring by use of progression-free survival endpoint rather than time to progression endpoint, we see an effect of cyclosporine on lung function, namely, BOS-free survival with a p value of 0.019.

DR. DILLY: Can I just add one supplementary comment? This is exactly the kind of question that we need to nail down in the next study because what we want to do is take a large

group of patients, enroll them, nail down what their lung function is and follow them over time because, remember, the objective of this treatment is to preserve the lungs in a good condition. So, actually a no-effect on FEV1 in that context in a large group of patients would be a great outcome, and that is what we want to show next.

DR. SWENSON: Dr. Gay?

DR. GAY: My question is to follow Dr. Moss' question from a while ago. I am still not clear on the number of patients, why the number is so small, the number of patients that were included in the study. It is essentially a single-site study in which every therapy is an off-label one for the treatment of rejection in transplantation. I am trying to get a grasp of why there were so many screening failures, essentially 50 percent screening failures in the study over the course of the three years. Why weren't more patients included or made available to be included in the study, and what were the reasons for that?

DR. DILLY: In fact, what we would

consider the 50 percent enrollment of eligible patients as quite good in a clinical study. Our experience has been typically when we are trying to enroll clinical trials, which is what we do for a living, that we see something like 25-40 percent enrollment into the study. So, when we went into Pittsburgh and we looked at this whole body of data we were quite reassured that the patients had gone to the study in an elegant way; that about half of them got into the study; and there was nothing particularly strange about the patients that did and the patients that didn't. So, we did not see that as an issue and we came back to the fact that we saw the data as robust.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: I was impressed by the heterogeneity in terms of the cyclosporine group in terms of the dose that they received. You know, some of the subjects received all the doses for the full length of the study, and various documents suggest that something like 9/36 received 1 month or less. So, my question is did you ever stratify

the analysis for survival based on how much drug they received? It is pretty impressive that 9 of these patients received only a month of drug and yet presumably had a fairly good survival.

DR. SCAIFE: Dr. Noonberg?

DR. NOONBERG: There are several responses to that question. The first is that ACS001 wasn't a dose-response study and we don't have formal dose-response data. However, in one of our sensitivity analyses we did exclude patients, 14, who didn't receive at least 80 percent of the protocol maximum dosing and they are excluded from analysis. As would be expected, the p value is going to go up due to loss of power, however, the treatment effect is essentially unchanged.

DR. PRUSSIN: But on the flip side, why did the patients who essentially didn't receive drug respond to a drug they didn't get? That is what I am more concerned about, not the ones that did receive the drug. Yes, they responded even if the p value is going to be higher, but the ones that essentially were on the active side of the

protocol but who effectively did not receive drug still had an effect in their survival. Correct?

DR. NOONBERG: I mean, we used an intent-to-treat analysis so we include those patients, but there are placebo patients that have long-term survival too. This isn't a uniformly fatal diagnosis so you would expect to see variability in survival. But we include the intent-to-treat analysis in accordance with guidelines.

DR. SWENSON: Dr. Noonberg, I have a question that somewhat follows up on that very same one but is occasioned by one of your graphs here, and that is you continue to see and, in fact, you even highlighted that more patients seemed to be prevented in their chronic rejection appearance following the cessation of their two-year therapy, if I read this graph correctly. Can you explain why this drug may, in fact, have benefits beyond its cessation?

DR. NOONBERG: The CR that is in green on this graph doesn't represent new diagnoses of

chronic rejection but, rather, deaths associated with chronic rejection. So, they are not necessarily new rejection episodes. So, this just highlights the strong association of chronic rejection with death and the fact that you don't see that in the inhaled cyclosporine group. But the chronic rejection episodes are actually occurring throughout the process.

DR. SWENSON: Okay. Dr. Hunsicker?

DR. HUNSICKER: On that same graph, it was not clear to me when you put that up--you don't have to put it back up again, I think we have all seen it--how you made the diagnosis of chronic rejection in those cases. Was that either well defined BOS or a biopsy, or was that a clinical definition of chronic rejection based on the fact the patient had died with lung disease?

DR. NOONBERG: It is either by transbronchial biopsy with histologic proof of the lesion of bronchiolitis obliterans or clinical BOS--

DR. HUNSICKER: So, all of those patients

that had the CR in green there either had one or the other?

DR. NOONBERG: Correct.

DR. HUNSICKER: I have a couple of other questions just to be sure I am correct on this, you referred to the analysis plan. First of all, there was a prospective analysis plan that specified that the total survival at the end of the study was to be used as the primary outcome rather than the data at the end of two years of treatment? I wasn't quite sure. There were three or more different types of analysis that were discussed in the briefing books. What did the original prospective analysis plan say was to be used as the primary evaluation? Was it total survival at March 31, or whatever it was, or was it supposed to be at the end of the two years of treatment?

DR. NOONBERG: It should have been at the end of the study. Dr. Aldo Iacona, the principal investigator is nodding his head so, yes.

DR. PROSCHAN: But it was not survival; it was acute rejection.

DR. HUNSICKER: Well, I understand--

DR. NOONBERG: Right, but the survival is the secondary endpoint--

DR. PROSCHAN: We have so many secondary endpoints to look at, we have to figure out which endpoint we are looking at.

DR. HUNSICKER: And the second question I have is that I thought I found in the briefing book that of the ten patients who were put into the so-called pilot thing, five of them had eventually died. Is this correct?

DR. NOONBERG: That is correct.

DR. HUNSICKER: So, five out or ten patients, and they received treatment for the full two years or at least as much of the two full years as one would have expected them to get?

DR. NOONBERG: Correct. When those patients are included in the statistical analysis, and that was one of the sensitivity analyses that we performed, the results were still statistically significant. They died but the timing of death is very important, as well as the fact that they

died--

DR. HUNSICKER: Sure.

DR. NOONBERG: Here is a Kaplan-Meier of survival from time of transplantation to study end date including the randomized and the pilot, with a p value of 0.018.

DR. SWENSON: At this time we should break. I know there are more questions and they can be taken up in our other discussion sessions later today. We will reconvene at 10:15.

[Brief recess.]

DR. SWENSON: We should make a start on the next session, and Dr. Hernandez, of the FDA, will lead the discussion.

FDA Presentation

Overview of Clinical Trial Efficacy

and Safety Evaluation

Discussion of Analysis

DR. HERNANDEZ: Thank you. Good morning. During this presentation I will describe the Division's perspective on the application for cyclosporine inhalation solution. I will start by

saying that this is not a regular NDA application. The study, submitted to support the proposed indication, is a small Phase II study that failed to meet its primary endpoint for the prevention of acute rejection. However, the potential for the prevention of chronic rejection and improved survival are very important aspects for the lung transplant population for which long-term survival is mostly limited by chronic rejection.

The agency considered that the potential survival benefit in this specific transplant population was reason enough to accept this new drug application for review. The proposed indication for cyclosporine inhalation solution requested by Chiron is for increase in survival and prevention of chronic rejection in patients who receive allogeneic lung transplantation, in combination with standard immunosuppression.

In my presentation I will give an overview of the data submitted in this NDA. Then I will summarize study ACS001 objectives, outcomes and limitations. I will describe the FDA review which

will address the following subjects: Acute rejection, obliterative bronchiolitis, bronchiolitis obliterans syndrome and FEV1 data, and survival. Then I will discuss the recipient and baseline characteristics, donor baseline characteristics, the primary causes of death, available autopsy results, dosing information and related outcomes and, finally, Dr. Cavaille-Coll will give you a summary of the safety considerations and our summary conclusions.

The data submitted to support this application was derived from two reports generated by Chiron Corp. That report was referred to as ACS001 and ACS002. The study ACS001 is actually the name given by Chiron to the study report that summarizes the findings from the University of Pittsburgh Medical Center, protocol 003. In this protocol a total of 68 patients were studied in two phases. First, 10 patients were enrolled in an open phase and treated with cyclosporine inhalation solution. Then the total of 58 patients were randomized to cyclosporine inhalation solution

which contains propylene glycol as a vehicle or propylene glycol vehicle alone.

From here I will refer to these groups as cyclosporine inhalation solution as CyIS or propylene glycol group as PG. Twenty-six patients received CyIS and 30 patients received propylene glycol vehicle. This was administered by inhalation with a nebulizer. It should be noted that all patients received concurrent tacrolimus-based systemic immunosuppressive therapy.

Study ACS002 was the name that Chiron Corp. gave to the study report that summarizes the findings on adverse events in 70 patients selected from seven open-label studies conducted at UPMC. I will refer to these study reports later. Also, I will refer to the ACS001 study and study ACS002 to avoid confusion.

The rest of my discussion will focus on study ACS001, and the primary objective of this study was to determine if cyclosporine delivered to the lung allograft by inhalation prevents the

development of acute cellular rejection.

As you can see from this slide, the study failed to show superiority of cyclosporine inhalation solution over PG vehicle. The mean number of acute rejections of grade 2 or higher per patient was 1.3 in the cyclosporine arm and 1.2 in the PG arm. The median number of acute rejections grade 2 or higher was 1 in both arms. Therefore, the study failed the primary endpoint.

However, we noted that the sponsor reported a difference in mortality and obliterative bronchiolitis between the two arms. In the study report and database OB was reported as 1 for its presence or 0 for its absence. No additional histopathology information was provided. The specimens for diagnosis of OB were obtained by transbronchial biopsies.

The reporting mortality was 12 percent in the CyIS arm and 40 percent in the PG arm. The applicant noted that this represents a 79 percent decrease in risk for mortality in this specific population. The reported rate of bronchiolitis

obliterans or death was 19 percent in the CyIS arm and 60 percent in the PG arm, with a reported p value of 0.003. It should be noted that this difference is mostly driven by the difference in mortality.

In study ACS001 all patients were followed up for three years after enrollment, and thereafter were followed up to document mortality. At the time of the study end when the last patient completed two years of aerosolized treatment in August, 2003, the mortality was 12 percent in the cyclosporine arm and 40 percent in the PG arm. Follow-up data obtained through July, 2004 was submitted in the NDA and it showed mortality of 19 percent in the cyclosporine arm and 50 percent in the PG arm. Additional information submitted in the safety update in May, 2005 showed a mortality rate of 31 percent in the CyIS arm and 50 percent in the PG arm.

At the time the NDA was submitted to the agency, the limitations of the study were known to us. These included the following: This was a

single-center Phase II study. There was a small sample size. The study intended to enroll 136 patients. The case report forms were created retrospectively. Therefore, some important recipient and donor implementation was not captured. Some data were not systematically collected, for example, prospective routine transbronchial biopsies. Some data were not available, for example, some donor characteristics or information on management on acute rejection episodes grade 2 or higher that appeared prior to enrollment.

FDA concerns included the lack of effect on the primary endpoint. We also shared the sponsor's concerns that the study may have become unblinded. For example, patients at UPMC with identification numbers ending in letters B or C received cyclosporine inhalation solution, while those patients with numbers ending in A or D received PG. This may have allowed the investigators to identify if a given patient was receiving propylene glycol or cyclosporine

inhalation solution.

Protocol documentation was limited. Chronic rejection or survival were not designed as the primary endpoints. Furthermore, the protocol for this study did not specify how secondary endpoints would be analyzed, and there was no pre-specified statistical analysis plan.

There were nine protocol amendments. The study was stopped before completing enrollment. There were various protocol violations and there was no stratification by risk factors important for chronic rejection or mortality. We can give an example such as double lung versus single lung. Despite randomization, there were imbalances in baseline characteristics.

Now I would like to describe our approach to the analysis of chronic rejection and mortality in study ACS001. Acute rejection is considered a major risk factor for the development of chronic rejection or obliterative bronchiolitis, and a number of acute rejection episodes experienced early after transplantation are considered to have

a significant impact on the subsequent development of OB.

Even though acute and chronic rejection represent different histopathology and pathophysiology, there is general consensus that the frequency, intensity and duration of acute rejection episodes are correlated with subsequent development of obliterative bronchiolitis.

Strong evidence suggests that acute rejection is the principal cause of chronic allograft dysfunction. However, the role of other immunologic and non-immunological factors have to be considered. Therefore, we examined the following data on acute rejection, obliterative bronchiolitis histological findings, FEV1 and BOS clinical manifestations of the disease, and mortality as a clinical outcome.

Obliterative bronchiolitis is an important cause of mortality after the first year from transplantation, accounting approximately for 30 percent of deaths. FEV1 is the best surrogate marker available for OB, and has been proven

successful in describing--very important--the pattern of lung function decline, described as acute or chronic BOS onset; the identification of the main risk factors for BOS; and the extent and the rate of progression of OB.

The International Society of Heart and Lung Transplantation subcommittee has recommended that the slope of serial FEV1 measurements over time, before and after a therapeutic intervention, should be used to compare treatment responses.

Therefore, if chronic rejection is effectively prevented, we should expect to observe an evident therapeutic effect on FEV1 and BOS. Obliterative bronchiolitis, as defined in the study report, was documented by transbronchial biopsies and was found in 12 percent of the CyIS patients and 30 percent of the propylene glycol patients.

Now there are three points that I would like to make regarding FEV1. First, as you can see, FEV1 values pre-enrollment, that is, after the transplantation but before randomization to the cyclosporine or PG arms, were not available in 40

percent if the patients. This data is shown in the first row. Second, by 3 months there is FEV1 data on essentially all patients, all 26 patients in the CyIS arm and 26/30 in the PG patients. Third, you will notice that there is a difference in mean FEV1 values between the 2 groups. At all point times the mean FEV1 values are higher for the CyIS group as compared to the PG group. Even before treatment assignment higher mean FEV1 values were observed in the cyclosporine inhalation group. This difference may be attributable to the greater number of double lung transplants that were performed in this group, which we will discuss later in greater detail.

Here is a graphical presentation of the data shown in the previous slide. You can see that even though the FEV1 values in the cyclosporine inhalation group are higher than the PG group, the yellow line below, the two curves are essentially parallel. Therefore, it does not appear that cyclosporine inhalation solution has an effect on FEV1.

Complete FEV1 values were not available so

BOS, bronchiolitis obliterans syndrome, as defined by the International Society of Heart and Lung Transplantation could not be calculated using these criteria. Therefore, an alternative definition of BOS, defined by the sponsor and qualified by an independent investigator was used.

As seen in this graph, the time to BOS between the 2 arms is similar, and the log-rank b value is 0.214. This also indicates that the cyclosporine inhalation solution has no effect on BOS. Patients who died without double-blind of BOS, as defined by the applicant, were censored at the time of the last follow-up for BOS.

We observed a difference in OB and mortality at the end of the study in August, 2003. OB was present in 12 percent in the cyclosporine inhalation solution versus 30 percent in the PG group. Mortality was 12 percent in the CyIS arm versus 47 percent in the PG group. No difference was observed in acute rejection, FEV1 or BOS. As a clinician, FEV1 values are really, really important. Questions like "how are you breathing"

are really important questions.

The association between acute rejection and chronic rejection and the effect on patients and graft survival is well documented in registry and published literature. Acute rejection is a major risk factor for the development of chronic rejection or obliterative bronchiolitis. In light of the strong association between acute rejection and chronic rejection, the difference observed in OB was not expected in the absence of differences in acute rejection, FEV1 or BOS, and this warrants further exploration.

Therefore, we asked the question is the mortality difference between cyclosporine inhalation solution and PG in the absence of differences in acute rejection, FEV1 or BOS due to treatment effect or could other factors account for this difference? For example, difference in baseline characteristics of donors and recipients between the study arms, or other factors such as study conduct.

I want to remind you that there was no

difference in acute rejection grade 2 or higher at randomization to the drug or to the placebo arm. In contrast, there is a clinical and meaningful difference in acute rejection grade 2 or higher before treatment assignment. Thirty-one percent in the CyIS arm and 42 percent in the PG patients had grade 2 or higher acute rejection prior to enrollment. Although data were incomplete, approximately 40 percent of the CyIS allografts and 50 percent of the PG allografts were colonized with bacteria or fungi. So, this data is incomplete but I still think it is worth mentioning it. So, if we assume that patients who had acute rejection grade 2 or higher prior to enrollment received some type of steroid treatment or any other treatment augmentation, they could be predisposed to infectious complications such as pneumonia or sepsis.

Now I will discuss other imbalances in patient characteristics. There is well documented association between the type of lung transplant and survival. In this study there is an imbalance in

the number of single lung and double lung transplants between the two arms. Single lung transplants were done in 58 percent in the CyIS arm and 80 percent of the PG patients. Conversely, double lung transplants were done in 42 percent of the CyIS patients and 20 percent of the PG patients. This difference is statistically significant at a level of 10 percent. FEV1 pre-enrollment was lower in the PG arm and may be a reflection of more single lung transplants in this group.

The imbalance between single and double lung transplant is important. The literature and registry data show an advantage for long-term survival and freedom from BOS in double versus single lung transplants. Single lung transplantation is associated with lower exercise tolerance, poorer pulmonary mechanics, and higher infectious complications such as pneumonia.

The International Society of Heart and Lung Transplant registry data show that the there is a difference in survival between single and

double lung transplant patients. The half-life of double lung transplant patients is 5.3 years, as shown in the top line, while the half-life for single lung transplants is 3.9 years. The average survival is shown in green in this graph.

As noted before, the information on donor characteristics was incomplete. Therefore, we examined the data available that was informative about the state of the donor lung, and we noted a difference in donor inotropic support. Fifty percent of the donor lung transplantations to the CyIS patients and 83 percent of the donor lung transplantations to the PG arm came from donors that received inotropic support.

PaO2/FiO2 ratio is an indicator of the severity of acute lung injury and it is useful to indirectly assess the degree of ischemic re-perfusion injury sustained by an allograft. PaO2/FiO2 ratio of greater than 200 percent indicates limited alveolar damage and gas exchange.

Another difference between the two arms was the time in the ICU. While most of the

patients stayed in the ICU for less than 10 days, 4 percent in the cyclosporine arm patients and 20 percent in the PG patients were in the ICU for more than 10 days, and this is kind of important in a single center where the criteria for keeping the patients in the ICU pretty much remained the same The other important thing is that it will reflect how the patients are in terms of degree of severity of the disease. Patients are not allowed to go out of the ICU if there is something that still needs to be taken care of. So, it is a good reflection of the degree of sickness that these patients have.

PaO1/FiO2 ratio is an indicator of the ability of the lung to perform adequate gas exchange, and it is useful to indirectly assess the severity of acute allograft injury. The baseline PaO2/FiO2 ratio on ICU admission was worse in the PG group, suggesting a major degree of ischemic re-perfusion injury in these allografts. Also, perioperative renal dysfunction was in 4 percent in the cyclosporine inhalation solution and 13 percent in the PG patients. Prolonged ICU stay, inadequate

gas exchange and perioperative renal dysfunction are factors that reflect a more severe condition after surgery.

We also looked at the time to the first pneumonia. As noted, there were more cases of pneumonia in the PG arm and this was within the first one to two months of the study. The outcome in patients with these pneumonias is summarized in the next slide.

A large number of patients in the PG arm had early pneumonias and there was a strong relationship between pneumonia and death. The relationship is not surprising given what we know about the causes of death after lung transplantation. The occurrence of these early pneumonias is not likely to be related to any treatment effect but may be related to baseline donor and recipient characteristics or other events which occurred prior to enrollment. These events include but are not limited to episodes of acute rejection requiring additional immunosuppressive therapy or microbial colonization of the graft.

I would like to underline that early pneumonia may lead to histopathological findings compatible with obliterative bronchiolitis. This has been documented to be a risk factor for the development of obliterative bronchiolitis. There were five patients in cyclosporine inhalation solution arm and two patients in the PG arm who developed pneumonia in the first month. By two months there were an additional three PG patients with pneumonia. Of these patients that developed pneumonia, 2/5 died in the cyclosporine arm and 7/13 in the PG arm; 1/5 developed OB in the cyclosporine inhalation solution and 7/13 in the PG group; and BOS was observed in 3/5 in the CyIS arm and 3/13 in the PG arm.

I want to make two observations. There is a strong association between early pneumonia and risk of death. Second, early pulmonary infections and early acute rejection episodes are well recognized risk factors for the subsequent development of chronic rejection.

This table show the primary causes of

death by July, 2004. Three patients in the cyclosporine inhalation solution arm and seven patients in the PG group died of infections, pneumonia or sepsis. In the CyIS arm one patient died of graft failure and in one patient the cause was unknown. In the PG group two patients died of OB; one patient died of pulmonary embolism and another from congestive heart failure, and one from lung cancer. There were three patients in which the cause of death was unknown. The distribution of causes of death is consistent with registry data where infections remain the major cause of death during the first year after transplantation while chronic rejection begins to become an important cause of death after one year, as seen in table 3, reference 1 in your background package.

Autopsy results--from the available data in the application CRFs, narratives and data sets we learned that some patients who died had autopsy performed. In the cyclosporine inhalation solution arm one patient had autopsy and OB was not reported. In the propylene glycol arm 15 patients

died and there were six autopsies. In two of these OB was reported and four of them died of infection, and there was no OB reported out of the six reports.

The protocol specified that patients should receive treatment for two years. The dose should be titrated from 100 mg to 300 mg for the first three days of treatment, then daily dosing up to three consecutive days with the maximum tolerated dose, and thereafter three times weekly dosing for two years. There was a lot of variability in individual patient dosing in this trial.

This table shows the number of doses received by patients. The protocol dosing schedule was not followed in many patients. In fact, six CyIS and five PG patients received less than 25 doses, as you can see circled in this slide. The large variation in the number of doses received makes it difficult to establish a relationship between the specific treatment regimen and the improvement in survival.

Six cyclosporine inhalation solution patients who received less than 25 doses are shown on this table. Two patients received a single dose; others received 3, 12, 13 and 24 doses respectively. The doses show that not all patients succeeded in titrating up to 300 mg. Five out of these six patients experienced adverse events directly related to the administration of the cyclosporine inhalation solution, and three patients discontinued due to adverse events, and three additional patients withdrew consent. We noted, however, that all six patients survived and all are included in the mortality calculations as cyclosporine inhalation solution successes.

There were five patients in the PG arm who received less than 25 doses and, as can be seen, four/five died. Could these be attributable to the lack of cyclosporine inhalation solution? All these deaths are included in the mortality calculation as PG failures.

In addition to the 3 cyclosporine inhalation solution who withdrew consent after

receiving 1, 3 and 13 doses, 3 additional patients withdrew consent--these are the last 3 rows in this slide--1 at 4 months and 2 others at 20 months. The right-hand column shows that 2 of these 3 additional patients survived.

At this point I would like to turn the podium over to Dr. Cavaille-Coll to discuss our safety considerations and give our conclusions.

Safety Considerations and Conclusions

DR. CAVAILLE-COLL: Good morning. We are in general agreement with the applicant that the systemic safety profile of cyclosporine after oral or intravenous administration is well characterized and that the amount of systemic exposure to cyclosporine, meaning what was deposited in the lung and entered in the bloodstream before being eliminated, was not associated with detectable increases in systemic toxicity. There is more limited information on the safety of cyclosporine when administered by inhalation in a propylene glycol solution.

As you have heard, propylene glycol is

classified as an additive that is generally recognized as safe for use in food, mainly through studies using oral and dermal exposure. It is used to absorb extra water and maintain moisture in certain medicines, cosmetics or food products. It is a solvent for food colors and flavors. However, information on the inhalation toxicity of propylene glycol is more limited. There is no approved product for inhalation containing nearly 100 percent propylene glycol such as this product.

The applicant has submitted some preclinical safety data, including a 28-day study in dogs and a 28-day inhalation study in rats. The 28-day inhalation study in dogs demonstrated lung irritation, alveolar and interstitial inflammation in all cyclosporine dose groups and the vehicle control. Laryngeal inflammation with ulceration was seen in the mid-dose group males. Inflammatory cell infiltrates, lymphocytes, plasma cells, monocytes were seen in the control and treated group as well. The dog studies did not contain a sham control. Thus, this confounded the separation

of the extent of pulmonary toxicity due to cyclosporine versus that of the propylene glycol vehicle. No additional cyclosporine inhalation toxicity was observed in the animals. Dose levels in the dogs were limited, however, by the maximum feasible dose. However, serum cyclosporine levels in the high dose group exceeded the human exposure by 2.5-fold.

Again, there were also studies that were done in rats which showed similar findings, except that the doses in rats did exceed about 80-fold the human exposure and there was evidence of increasing toxicity with increasing doses of cyclosporine. The rat studies did include an air control and did show that even in the propylene glycol group there were findings that were not present in the sham control animals.

I would like to address now the clinical safety. In the usual safety review we would look at the rates of adverse events, the grade of severity, the duration of the events and their reversibility, as well as the temporal relationship

to dosing with the study drug. Collection of such information is facilitated by the use of prospectively designed case report forms. The latter often provide another very useful source of safety information in the form of handwritten comments by the investigators on the margins of the pages of the case report forms. Such forms and comments were not available and it is in the context of these limitations that we must evaluate the safety of this product. Evaluation of safety in this fragile population receiving systemic immunosuppression and numerous medications is admittedly complicated.

There are no prospectively designed case report forms to guide the systematic collection of safety data throughout the conduct of the study including but not limited to the use of concomitant medications used to prevent or treat the complications associated with the administration of study drug. Clinical safety data was collected retrospectively from source materials from one double-blind, controlled study and a number of

small open-label, uncontrolled studies at the University of Pittsburgh Medical Center. Comparative safety data is available on only 26 randomized subjects in study ACS001, or 36 subjects that include the first 10 non-randomized subjects from the study. Additional non-comparative safety data was obtained in report ACS002 by pooling data from seven open-label, uncontrolled studies that enrolled 70 lung transplant recipients who were receiving similar tacrolimus-based systemic immunosuppression.

Subjects in study ACS001 were titrated in a double-blind fashion to a maximum tolerated dose not to exceed 300 mg or the propylene glycol control equivalent. That dose was then to be administered three times a week for up to two years. As mentioned earlier, there was a great variation in dose, 100 mg to 300 mg per day, the number of doses administered and, consequently, duration of exposure. I think we have seen those slides before. Subjects also received per protocol premedication with aerosolized lidocaine and

bronchodilators to improve tolerance.

This slide comes from the integrated summary of safety and lists basically the adverse events that occurred with a statistical significance of greater than 10 percent. I think we are in general agreement with the applicant's description of the safety data they were able to collect. We do note that there seemed to have been more respiratory, and thoracic adverse events in the cyclosporine group compared to the propylene glycol group. In all these categories, of course, as I mentioned before, the significance was greater than 10 percent. As in the 28-day preclinical animal studies, there was a sham treatment group to help discern the potential contribution of inhaled propylene glycol to the respiratory tolerability in both treatment groups. Here we do see that more events occurred in the cyclosporine group. These findings in general are consistent with the respiratory safety findings that were found in the 28-day preclinical animal studies.

Another thing we look at when we are

evaluating safety is the discontinuations and withdrawal of consent. Although a greater proportion of subjects in the propylene glycol group, 33 percent, were reported to discontinue study drug due to an adverse event, other than death, than in the cyclosporine group, 15 percent, this comparison must be interpreted with caution.

Six patients in the cyclosporine group, or 23 percent, were reported to have discontinued due to withdrawal consent compared to none in the propylene glycol group. Further examination of the individual case report forms revealed a number of respiratory adverse events associated with the study drug administration which could have influenced their continued willingness to participate in the study. Taken together, a similar proportion of subjects discontinued study drug due to adverse events or tolerability in the propylene glycol group and the cyclosporine group.

We also have some non-comparative data that was presented in report ACS002 from a pool of 70 lung transplant recipients. Again, these

represent a variety of lung transplant types, mostly patients with refractory acute rejection and/or OB who were treated with cyclosporine inhalation solution in seven open-label, uncontrolled studies at UPMC. They were also receiving systemic tacrolimus-based immunosuppression. These, again, represent an experience of a wide range of dosing and duration of treatment, which is really very difficult to interpret. Patients were generally administered the maximum tolerated dose which was individualized and depended on the characteristics of the patients and their response to medication.

In summary, the overall safety database is smaller than usually expected in a commercial application. Respiratory adverse events were common despite premedication and limited the maximum doses used and the durations of the treatment. Data available in the study report and case report forms did not allow us to fully evaluate a temporal relationship between study drug administration and particular adverse events.

Ultimately the acceptability of the safety information in this NDA must be weighed against the degree of certainty of the potential clinical benefit.

These are briefly our conclusions: We have a single small study. There is no effect on the primary endpoint of acute rejection or on measurements of pulmonary function of FEV1 or bronchiolitis obliterans syndrome. There are differences observed in mortality and bronchiolitis obliterans. There also important imbalances in the donor/recipient baseline characteristics. There are also variable causes of death, most with no evidence of bronchiolitis obliterans syndrome. There is variable dosing in both groups, and we have limited safety information.

At this point, I would like to turn the podium over to Dr. Jyoti Zalkikar who will present the statistical perspective of this review. Thank you.

Statistical Evaluation

DR. ZALKIKAR: Hello. My name is Jyoti

Zalkikar. I am the statistical reviewer for the application for Pulminiq, which is the trade name for cyclosporine inhalation solution.

I will be focusing on the efficacy of the product during this presentation. As you know, the efficacy of this product is based on just one small Phase II, single-center study conducted at the University of Pittsburgh Medical Center. This was not designed as a confirmatory study. The planned sample size was 136 patients as per the applicant's study report. The investigators did not use case report forms during the conduct of the study. These were generated retrospectively by the applicant. Also, there was no prospective statistical data analysis plan and no formal stopping rules.

The study began in 1997. The first 10 patients were who were enrolled received cyclosporine as part of the open-label pilot phase. The next 58 patients were randomized to either cyclosporine with propylene glycol as vehicle or propylene glycol alone. Two of these patients did

not receive any dose of the study medication and were excluded from all analyses. The applicant says that the enrollment was stopped in August, 2001 at 68 patients. The study was vehicle controlled. As you know, all subjects received systemic immunosuppression.

Now I will briefly go over some aspects of the study design. As per the initial design, the patients were to be enrolled from 7-21 days after the transplant. But later a 22-42 days window was added to speed up the enrollment. Three patients out of the total of 56 were enrolled past 42 days after their transplant. Randomization was stratified by the enrollment window and CMV mismatch. Donor positive/recipient negative was defined as a mismatch and all other combinations of donor and recipient CMV status were called a match. Two out of 56 patients were incorrectly stratified. Patients were to be on treatment daily for the first 10 days and 3 times a week thereafter for a total of 2 years. Thirty out of the 56 patients discontinued treatment early. All 56 patients were

followed for at least 33 months in the data submitted with the NDA. That is the database I will be using in this presentation.

Evaluation of survival and chronic rejection were not the primary objectives in the study. The prespecified primary objective was superiority over propylene glycol in terms of the rate of acute rejection. The study failed to achieve that objective. In fact, the mean number of acute rejections was slightly higher in the cyclosporine group.

Here is the graph for survival distributions in the two arms. This graph is based on all the data submitted with the NDA and, therefore, is slightly different from the one based on the study end date that was previously presented. The 24-month line indicates the end of protocol specified treatment period. When we saw this dramatic survival difference at the pre-NDA meeting we were excited and encouraged the applicant to submit the application.

When the NDA was submitted, given that the

trial had failed on the primary endpoint, the challenge for the review team was to determine if the observed survival difference was due to cyclosporine inhalation solution.

One of the first things we found was the baseline imbalance between the two treatment groups. Although randomized, due to a small sample size, the study failed to benefit from randomization. Several baseline factors that clinicians consider to influence patient survival are not balanced between the two groups. This means that the two groups are not comparable for evaluating survival or chronic rejection.

Here are the factors that show imbalance. All of these are statistically significant at the 10 percent level, with the exception of grade 2-plus acute rejection prior to dosing. Dr. Hernandez has discussed the clinical importance of the influence of these factors on patient survival. All patients in the study had at least one of these risk factors.

Here is the nature of the imbalance. The

yellow bars represent patients in the propylene glycol group and the red bars represent patients in the cyclosporine group. As you can see, the majority of the cyclosporine patients are on the left, with two or less risk factors, whereas the majority of the propylene glycol patients are on the right side, with three or more risk factors. This can occur in randomized trials, and more so in the trials with small sample sizes such as this one. That is why it is important to prespecify the primary endpoint so that appropriate stratification may variables can be used at randomization to control for at least some factors known to influence that primary endpoint. The study could not accomplish that since the primary endpoint was not survival or chronic rejection.

In this situation statistical methods can be used to adjust for these imbalances, but using these methods to adjust for factors individually one at a time is not appropriate as the groups are still not comparable due to imbalances with respect to the other factors. For simultaneous adjustment

for all the factors the sample size is too small in the study.

We also considered methods that in some situations allow us to handle a large number of factors such as propensity scores, but these have limitations and there are underlying assumptions that need to be validated.

So, given that the trial failed to show a difference in terms of the primary endpoint of acute rejection, given the absence of prospectively defined analysis plan including statistical details such as multiplicity adjustments and stopping rules, and given the baseline imbalances with respect to many factors, the validity of any further inferential statistical analyses on the data from this trial is questionable and lends to caution.

Now I would like to draw your attention to another problem the review team faced. The study was designed as a double-blind study but, as you have heard, a code A, B, C, D was added to the patient number to aid pharmacy in preparing study

medication. Patients with A and D in their patient number received propylene glycol and patients with B and C received cyclosporine. The applicant stated in their study report that this may have revealed a treatment assignment to the investigators. This fact, together with the retrospective nature of the study, makes it vulnerable to the introduction of bias, as inadvertent as it may be. For example, if the investigators knew that patients were getting propylene glycol they may have adjusted systemic immunosuppression to compensate for the lack of cyclosporine, inadvertently predisposing the patients to infections like pneumonia and sepsis which were among the leading causes of death in the study, as discussed by Dr. Hernandez. Detection of the presence and magnitude of bias is difficult, but its possibility certainly lends to caution when interpreting the study results.

Now I would like to illustrate how small perturbations in the assignment of the subjects in a small study such as this one can change the

picture dramatically. Here is a graph of survival distributions again. Please notice that there were three early deaths in the control arm due to pneumonia and sepsis. These patients received very few doses of the study medication. The review team felt that these deaths were not expected to be influenced by the treatment assignment. There are eight different possible ways to assign these three patients to the two groups. The current assignment is the only assignment that results in statistical significance in terms of the p value. For assignments in which one of these patients gets assigned to the cyclosporine arm the p value is over five percent. For assignments in which two of these patients get assigned to the cyclosporine arm, the p value is over 12 percent. And one possible assignment in which all 3 patients get assigned to the cyclosporine arm uses this picture. This is completely different and no longer shows a survival difference. This illustration shows that due to small sample size the results of the study are extremely sensitive to very small perturbations

in the assignment of the patients.

Now let's look at the discontinuations. More than 50 percent of the patients in the study discontinued for various reasons. Please note that there were six patients who withdrew consent. They all were in the cyclosporine arm. One of them was crossed over to the open-label cyclosporine study. All of these patients were followed for survival even after the withdrawal of consent.

This table shows the number of doses received by the patients in the study. As you can see, there is large variation in the amount of treatment received. Please note that there are 11 subjects who received less than 25 doses, which is less than 10 percent of their protocol specified treatment. Four of these 11 subjects received only one or two doses. As discussed by Dr. Hernandez, the review team felt that this short duration of treatment would not be expected to result in significant benefit to the patients.

Therefore, we conducted sensitivity analyses to assess the impact of the data from

these patients. In the first analysis we would exclude all 11 patients. Here are the results. The survival difference is no longer statistically significant.

In the second analysis we will treat the six cyclosporine patients as a control patients. So, we will have 20 patients in the cyclosporine arm and 36 patients in the control arm. And here are the results. Once again the survival difference is no longer statistically significant.

In the third sensitivity analysis we define treatment failure as death or discontinuation within 25 doses due to either adverse events or withdrawal of consent, and we analyzed time to treatment failure. Here are the results. These results do not show a difference between the two arms in terms of time to treatment failure.

I recognize that all these sensitivity analyses are subject to criticism, but the point is that the data from subjects who discontinued very early and received very little treatment has a big

impact on the study results, as shown by these sensitivity analyses. This certainly lends to caution when interpreting the study results.

Now moving away from survival, I will briefly go over some results related to lung function. Here is the descriptive data on FEV1 previously discussed by Dr. Hernandez. Please recall that data on pre-enrollment is missing for 43 percent of the patients in the study. But the available data shows lower FEV1 values on average for the propylene glycol arm at pre-enrollment compared to the cyclosporine arm. This may very well be the effect of observed baseline imbalance with respect to the type of lung transplant among other factors.

Here is the graph of these numbers. The lines for the cyclosporine and the control arm are parallel over the length of the study, showing that treatment with cyclosporine had no effect on lung function in terms of FEV1. This, together with the observed survival difference, raises an interesting question. Is it plausible that the patients in the

PG arm were predisposed at pre-enrollment due to compromised lung function to a higher probability of getting serious infections such as pneumonia and sepsis and then dying from them? If so, how can one adjust for this phenomenon to get an unbiased estimate of the treatment effect in terms of survival in this small data set, where nearly 43 percent of the pre-enrollment FEV1 values were missing?

Here is a graph of time to BOS as defined by the applicant when patients who died without diagnosis of BOS were censored at the time of last follow-up for BOS. This analysis is subject to criticism of informative censoring but it helps to assess the effect of cyclosporine on BOS in the absence of a survival difference. Again, consistent with the analysis of FEV1, the difference between the two arms is not significant.

Please recall that there were 10 patients who received cyclosporine as part of the open-label phase of the study. There was very limited information on these patients but here is some that

was available. Please note that these 10 patients showed remarkable similarity with the propylene glycol group in terms of 2 important factors, the type of lung transplant and emphysema as the underlying condition requiring lung transplant.

So, we overlaid the survival curves from these 10 patients. Please keep in mind that the patients were not randomized to this group so direct statistical comparison is not possible. But given that, this group does not seem to support the survival difference between the randomized cyclosporine group and the propylene glycol group.

In summary, the study failed to demonstrate effect in terms of the prespecified primary endpoint of acute rejection. Several baseline factors considered to affect patient survival were not balanced between the two arms. There were concerns that blinding may not have been adequately preserved in the conduct of the study. The study is also highly sensitive to small perturbations in the assignment of patients. Patients who discontinued early and received very

little treatment had a big impact on the study results. The study failed to demonstrate a treatment effect in terms of FEV1 and BOS, and additional data were not supportive.

So, the question still remains is the observed survival difference between the two arms in the randomized portion of the trial due to cyclosporine inhalation solution or due to other factors? This concludes the FDA presentations.

Questions from the Panel (Continued)

DR. SWENSON: We are ahead of time here and there were a number of questions that were left from the previous session. I believe we could probably open it up to both the applicant and the FDA. So, let me begin with Dr. Sampson.

DR. SAMPSON: I had a number of questions, this one to both the applicant and the FDA. It is still not clear to me about the actual data that was collected in the original UPMC study and the data that was collected retrospectively. I understand the safety data was primarily retrospective but, for example, was the designation

of BOS at a specific time point designated in the charts as occurring at that time point, or was that made by reviewing the charts and saying yes/no there was BOS at that time point? I think I have asked that question appropriately.

The other thing is when the charts were reviewed, were these reviewed blinded to treatment or did the reviewer know the treatment the patient was on? I have several other questions in addition but just give me some information on that, please.

DR. CAPRA: You are correct that the safety data was collected retrospectively. The efficacy data consisted of survival, the results of the histology, the FEV1 data which was used to calculate BOS. The survival data was obtained on CRFs but retrospectively but it was confirmed through the source data with the autopsy reports. The results of the transbronchial biopsies were sent electronically from the University of Pittsburgh to Chiron. So, we didn't collect that information on case report forms. They basically maintained the database throughout the study and

they sent that database electronically to Chiron. Similarly, the FEV1 data and their lab data as well were collected on a central database at the University of Pittsburgh Medical Center. Those data were sent electronically to Chiron as well. So, none of the efficacy data, with the exception of the actual survival days, were collected on retrospective case report forms.

DR. SAMPSON: There is something there that says 20 percent reduction in FEV1 in the presence of no other clinical symptoms. How would that be determined just purely from FEV1? Is it just such an automatic algorithm that you don't look at other clinical symptoms, or was there a judgment made on that?

DR. NOONBERG: Well, it is a definition that was determined by a consensus group from the International Society of Heart and Lung Transplantation and the definition of BOS grade 1 or higher--and there is successive grading--is 20 percent decline in FEV1 from a post-transplant maximum. Now, post-transplant maximum generally

doesn't occur for three to six months due to postoperative factors. So, the missing early FEV1's are not expected to influence at all the designation of BOS because all patients, unless they die early, increase their FEV1 up to a period of time, generally an average of about three to four or five months. Then that post-transplant maximum, a rolling average, is used as their baseline from which you determine a 20 percent decline. So, that is how the definition is and that is not set by us; that was a definition proposed by the International Society for Heart, Lung Transplantation. The 20 percent was just programmatically defined and then we reviewed the cases to determine that there were no other clinical causes which were defined as acute rejection, concurrent pneumonias or other clinical causes that would impair lung function.

DR. SAMPSON: Again, were all the retrospective chart reviews done by people--was it possible to blind them to the treatment assignment, or did they know the treatment assignment when they

did the chart reviews?

DR. NOONBERG: Treatment assignment was known at the time of chart review.

DR. SAMPSON: I would like to switch gears and ask a different question that I have been puzzling a little bit over, and that is the study design stratified by two variables, the CMV match/mismatch and the start date. I don't recall seeing survival data--there is possibly something for the CMV mismatch, but does the sponsor have survival data done by strata? In particular, one of the standard questions when you have a stratification factor in any clinical trial is the question of whether or not there is strata by treatment interaction; whether or not the survival is comparable across strata; is it something that is poolable? And I have not seen any demonstration of that, I don't think, for this data either for CMV match/mismatch or the start post day 21. I was hoping you might have slides on that some place as backup.

DR. CAPRA: Can we see slide CE-18,

please? Unfortunately, I don't have the analysis here just limited to two stratification factors but the results are consistent. But here, in the last row of this slide, we show the survival analysis where the 2 stratification factors, as well as the other known risk factors that were imbalanced and were agreed to by both Chiron and the FDA, were included, namely, single versus double lung transplant, prior acute rejection, and primary diagnosis. The results show a significant value of 0.032 with a consistent p value. The results aren't shown here but the results are very similar when you just limit it to CMV mismatch and the primary diagnosis.

DR. SAMPSON: I did some sketching of my own. I don't have it with me for the CMV match/mismatch. I think you have some of that data, don't you, in the document? It is page 17 in the document.

DR. CAPRA: Can we put slide BD-5 up, please? You are correct, in the briefing document there is a table showing the number of deaths by

the CMV match and mismatch. For those who had a CMV match, 51 percent of those--I am sorry, this is on chronic rejection-free survival. Can we have BD-3? For survival data, 39 percent of the placebo subjects who had a CMV match died versus 14 percent of the cyclosporine. Among the mismatches, 71 percent of placebo, 0 percent for cyclosporine. The numbers are small but what we are not seeing is we are not seeing the survival effect limited to just one of the two subgroups.

DR. SAMPSON: Again, I agree that the sample sizes are small, but it looks like there is quite a bit of difference in the effect of CyIS depending on whether you are a match or mismatch. I realize that is the log-rank but I am trying to figure out if it is comparable across both arms. Would you have just a log-rank statistic on the matched group alone for the folks that had the CMV match? Is there really a significant difference in survival based on 9 and 23 and 3 and 21?

DR. CAPRA: I don't have that log-rank limited to that subgroup.

DR. SAMPSON: And then you don't have anything on the other stratification variable?

DR. CAPRA: We looked at that similarly where you see that in the case of the breakdown is limited to 1 into 2 subgroups. But, you know, the numbers are small and what we did was we did a stratified log-rank rather than do a log-rank by subgroups because the numbers are limited.

DR. SAMPSON: There wouldn't be an interaction here though. I mean, that is clear at least for the CMV mismatch, but you don't have that data for the other--

DR. CAPRA: We looked at the interactions between the major risk factors and we didn't see any significant interactions, nor interactions with those major risk factors with the treatment effect.

DR. SCHOENFELD: I am curious about one other thing. You know, I looked at the AR data. There is a real difficulty even analyzing that data. For instance, the three patients who died early, they may have been the bad actors and they may have been the ones that would have had a lot of

acute rejections. So, I don't know if either you or the FDA made any attempt at trying to analyze--you know, it is a strange situations when the primary endpoint is essentially an endpoint which is un-analyzable. It comes from the fact that I assume you assumed there would be no survival difference so you chose an endpoint that is very hard to analyze in the face of a survival difference. So, was any attempt made to model that? I don't see the study as negative in terms of the AR difference.

DR. CAPRA: We looked at AR-free survival but what happens is the ARs are occurring very quickly and I didn't feel that that was necessarily as meaningful on average because the effect seems to be limited quite early in the first couple of months.

DR. SWENSON: Dr. Mannon?

DR. MANNON: I had a couple of questions and a continuation so let me just pose one to both the applicant and FDA. There was a comment made about drug levels between the two groups. That

information isn't always clinically obtained. Do you have a sense of mean levels over time between the two groups both for tacrolimus and/or cyclosporine between the two groups?

DR. NOONBERG: We looked at mean blood levels of tacrolimus. It is really dosed by levels rather than by actual doses, and at the three-month time points the results were always comparable between the two groups. We also looked at prednisone doses between the two groups and they were comparable as well. We looked at immunosuppressive intensifications between the two groups and that was also comparable.

DR. MANNON: But these are three-month levels that you were measuring. So, then looking at the comparability later of intensification, that is based on dose again or based on level?

DR. NOONBERG: I am sorry, can you repeat that?

DR. MANNON: So, the levels that you had at three months where you saw no difference between the two groups--

DR. NOONBERG: Three months, six months, nine months, all the way up through final.

DR. MANNON: My second question deals with nephrology insofar as there appeared to be a significant increase in perioperative renal failure between the propylene glycol versus the CyIS. What was the sense of serum creatinine or calculated creatinine clearances between the two groups, say, at six months and 12 months? Also as a second part of that question, was there a difference in the possibility of dialysis or intervention of dialysis between the two groups?

DR. NOONBERG: We looked at creatinine levels because we had all the laboratory values transferred electronically to Chiron, and we didn't see any difference in creatinine levels at the same specified time periods. moxifloxacin

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: Yes, I would like to address a question both to Drs. Zalkikar and also, if he is still willing to talk about things, Dr. Helms. I am interested in what I might call study

ascertainment bias. This is a small study. Let me again start out by saying that the reason that we are here is that there was a striking p value for the difference in survival. So, that p value is reasonable if it is a true p value that is not a selected p value. The company has described how they became involved in this as having been told by a rep. that there was a study that was remarkably positive. So, we have here now a selected study. This is a classic issue in selection bias of studies, or what is called publication bias, and I would like to have both Dr. Zalkikar and also Dr. Helms discuss how seriously we should take this primary p value given that it was a study that was selected on the basis that the p value was highly significant, without knowing how many studies it might have been selected from. What I am basically doing is challenging whether the primary p value is a real p value. Did you understand my question, Dr. Zalkikar?

DR. ZALKIKAR: The primary p value was actually the p value associated with acute

rejection because that was the primary endpoint.

DR. HUNSICKER: No, I am sorry, I am not talking about the designed study's primary p value. I am saying that we are looking at this study because it has a p value of 0.007, as I recall. Is that something that we can rely on, that this is truly an unexpected result based on chance given that the study was selected based on the fact that there was a very highly significant primary p value?

DR. ZALKIKAR: From the only analysis that I have seen in the data, I would be very concerned that the study was selected in terms of the p value.

DR. HELMS: You remind me of a couple of students in my linear models class who always ask the tough questions. I think the short answer is that the p value that is reported with the Kaplan-Meier curve is not a real p value. I have warned you in one of my slides that the opinions I express are not those of Chiron or FDA, or anybody else perhaps. There is some obvious selection

going on here.

But if you will let me be informal for a moment, the difference is so big it passes the intraocular trauma test--it hits you between the eyes. So, if there were a good statistical procedure--I also made the point in my slides that this is the primary problem here. This is the real problem that we are facing because we don't have a real p value. As I said, we could do the decision theory analysis. But, again, if you didn't want to approve it you could question the assumptions, and so on. But the difference is so huge that we cannot ignore it. So, the short answer to your question is no, the p value--I mean, you could put in as many decimal places as you wanted; it is computed, but it is not a real p value in that sense.

Let me make a point that might help, and my statistical colleagues can correct me. Basically, this is high stakes gambling, and the best people at gambling in the world are the casinos and there are certain bets in a casino

where you get partial data and then you can place an additional bet. Black Jack is one of those. I am not an expert at that. We are in that kind of a situation. We now have the results. How striking are these values? And it is very difficult for statisticians to come up with real answers to that question. We have to bounce back to common sense.

DR. HUNSICKER: If I might, I do have one other question. There seems to be a difference between the survival curves that we have been shown by the company and by the FDA based on time to either BOS or death, depending upon exactly how the BOS has been defined. I am not sure I understand whose graph is the one that I should be looking at. As I understand it--and I am putting this question to both groups--as I am understanding it, the company has shown us that if you look at time to BOS, when you include death when it is presumed to be due to BOS there is a significant difference. I think you showed 0.01, or something like that. When the FDA showed this based on censoring all of the patients whose death was not proved to be due

to BOS, when that BOS was defined according to a specific thing, it was no longer significant. I do not understand what the discrepancy is here. Can this be clarified for me by the company and by the FDA?

DR. CAVAILLE-COLL: Well, I think that all the BOS-free survival is largely driven by the difference that is observed in mortality, and we tried to look at it differently. Is there a possible way of seeing an effect on BOS? Looking at the FEV1 plots, we don't believe that there really is a treatment effect on BOS. Certainly, we were not able to use the definition of the International Society of Heart, Lung Transplantation because the baseline would require the average of two maximum values more than three weeks apart. We didn't have that type of database. So, we were able to look at it basically based on the applicant's definition, but we are really very concerned about the completeness of the collection of that data.

I also want to go back to another issue

having to do with the background immunosuppression. That information was not available in the original application. We had to request some of that information from the company, and they even said there was a lot of difficulty in collecting that. Therefore, we asked them to provide us at least with some summary statistics of what would be the mean exposure at certain time points to at least give ourselves a qualitative impression of whether there was similar treatment between the two groups. But this is certainly a very unconventional application and we did not have the level of detail that we normally get in an application.

DR. HUNSICKER: Could I get the company to clarify for me then? If you use your definition of BOS, which we understand cannot be ISHLT's definition because you don't have the baselines--if you use yours and do time to BOS, whether it was ascertained at death or otherwise, do you or do you not find a significant difference?

DR. CAPRA: We find a significant difference and there are two differences between

our analysis and FDA's. Number one reason is the informative censoring because we are including deaths as an endpoint, as occurs by FDA's own guidelines for oncology studies. I also want to make the point that we did get all the FEV1 values electronically from the Pittsburgh database. There were no values that were missing from our data.

The second difference is that we are including in a definition of chronic rejection both BOS, as determined by a sustained decrease in FEV1, and OB, defined by presence of OB or change on bronchial biopsy.

If we could show slide CE-30, please. Combined in that chronic rejection analysis we are including as chronic rejection either OB or BOS. When we censor those patients and, granted, informative censoring is going to bias against the treatment groups, we still get a significant value of 0.015 in favor of the treatment group.

This is an analysis of chronic rejection-free survival with deaths censored, and it demonstrates that inhaled cyclosporine prevented

chronic rejection. So, the effect of cyclosporine on chronic rejection was not determined solely by mortality.

DR. HUNSICKER: If I could be clear on this because I think it is a fairly important thing, Dr. Cavaille-Coll, do you agree that this is an accurate survival curve, assuming that you are now looking at time to chronic rejection as evidenced either by BOS in accordance with the applicant's definition or biopsy documented OB? Is that fair?

DR, CAVAILLE-COLL: This is one of the retrospective analyses. This was not from prospectively designed data analysis plan, and it is combining two things, OB as diagnosed by transbronchial biopsy, for which we know the sensitivity is fairly poor--the specificity is great but the sensitivity is very poor, and also bronchiolitis obliterans syndrome, which is the clinical description of that. As we have seen before in the FEV1 plots, there really is no treatment effect. If you want to look at it this

way I am not sure how we would interpret that p value when you are combining two different types of things.

DR. HUNSICKER: But I am taking a clinician's judgment here that if there is anything that you can say, it is that when you have a biopsy documented OB, that is OB, for God's sake. So, if you add biopsy documented OB into your analysis, do you then get this graph?

DR. CAVAILLE-COLL: We didn't do this particular analysis and we didn't mix OB with BOS because BOS tells you something about the rate and the extent of progression. The transbronchial biopsy doesn't tell you anything about the extent or the rate of progression so we didn't mix the two.

DR. SWENSON: Dr. Hernandez, do you have a quick question here relevant to this?

DR. HERNANDEZ: Yes. I just want to make a comment from a clinical perspective. When you are analyzing chronic rejection and you combine OB and BOS there are several things that you have to

take into consideration. The first is the natural history of the disease of chronic rejection. It is something that can be rapidly progressing; it could be slowly progressing. So, the diagnosis of OB by transbronchial biopsy in a patient that has a very slow progression is not of the same significance as the patient that has, you know, OB biopsy diagnosed that is rapidly progressive. That is why the best surrogate marker is FEV1.

So, when we are trying to analyze by putting together two of these definitions for chronic rejection we come to that problem. So, the problem of this natural history of the disease that we still do not understand is not only due to immunological causes. There are other non-immunological causes that contribute to how this disease behaves. So, basing our diagnosis and taking that as an endpoint as OB by biopsy becomes clinically not really meaningful because the bottom line is how well the patient is breathing, and FEV1 as a diagnosis of BOS is really relevant.

DR. NOONBERG: I just want to make the

point that Dr. Golden made initially, which is that OB and BOS are not two different entities. They are clinical and histologic manifestations of the same process. The problem with BOS is that you have to use an unexplained decline in FEV1 and we already know that BOS is intricately related with pneumonias so patients will often have pneumonia and, by definition, you have to say, "okay, not yet BOS," wait for the pneumonia to be treated and see whether the decline in FEV1 is still there and the patient gets another episode of pneumonia.

So, the diagnosis of BOS, exactly when you get BOS, is very hard to make, unlike transbronchial biopsy where you have that diagnosis. Really it is a spectrum of disease and, therefore, we feel that both have their strengths and limitations in the diagnosis and the specificity and sensitivity, but they are the same clinical process.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: Yes, I think that was a really good question Dr. Hunsicker asked and I just

wanted to clarify. In your analysis--you may want to pull up a chair--

[Laughter]

--in the analysis that you did, are you saying you effectively used the composite endpoint, death or BOS, or did you only count deaths for which you could confirm there was BOS?

DR. CAPRA: It was death or BOS. In the analysis of chronic rejection-free survival we include all-cause mortality. So, it is death or chronic rejection or both.

DR. HUNSICKER: But is it not the case that the non-prospective--all of that stuff--analysis that showed time to either death with documented BOS or OB with death is not due to those documented, censored?

DR. CAPRA: Yes, 0.015. So, we looked at a sensitivity analysis where we censored deaths. So, we included just time to first case of chronic rejection, either OB or BOS, and we basically ignored death and that was significant.

DR. BRANTLY: I still have one concern.

The definition that the sponsor is using for BOS is 20 percent drop. Is that correct?

DR. CAPRA: It is the 20 percent drop from the previous peak FEV1 that is unexplained by other clinical manifestations.

DR. BRANTLY: My concern in using that is basically the difference between a double lung transplant and a single lung transplant because, obviously, if you use that 20 percent it is going to take a lot longer to drop to 20 percent on double lung than it is on single lung.

DR. CAPRA: Not necessarily. Dr. Zalkikar, in fact, showed that the double lungs had higher FEV1s and we agree with that. But we are looking at a change, a decrease in 20 percent. So, a double lung transplant subject who is starting with an FEV1 higher has more room to drop. Basically, what happens is you are controlling for that in the analysis because you are looking for a change from the previous values.

DR. SAMPSON: Excuse me, we have seen OB or BOS censored by death. We have seen BOS

censored by death. Does somebody have OB censored by death?

DR. CAPRA: We have that.

DR. SAMPSON: Did you show it to us? Did I miss that?

DR. CAPRA: No, we haven't presented any of that. It is one of our backups. Can we look at SA-35? Again, this is censoring deaths. It includes informative censoring so it is going to be biased against the treatment group. But when we look at this analysis we get a p value of 0.06 on time to first case of OB.

DR. SAMPSON: And this is the deaths that resulted from OB that are included as an OB event? Correct?

DR. CAPRA: No, but they would have had OB before. It is only cases of OB documented through the histology. We are ignoring deaths in the analysis. We are censoring those subjects. So, those subjects who died for other causes are basically censored in the analysis. Subjects who had an OB and later died are included on the

Kaplan-Meier curves at the time of first case of OB, first diagnosis of OB.

DR. SAMPSON: I am not asking the right question but I am going to try, were there subjects that did not show OB before death but on autopsy were diagnosed as dead primarily from OB?

DR. NOONBERG: In our autopsy reports all patients that were said to have had OB were called OB, and none of the patients that we didn't say had OB have OB on autopsy.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: I would like to think about the biology of what happens in the lung a little bit. We have this huge difference between the two groups and you would have thought that if the huge difference is due to the only thing we think cyclosporine can be doing you would have a huge effect on what you think cyclosporine is supposed to be doing. We have just had a long argument about OB and, leaving that aside, I am also concerned about the absence of effect on acute rejection. If the tests we are looking at for both

OB or chronic rejection and acute rejection are meaningful, it is of some concern.

In particular, we have talked about systemic versus local effects and the biology of that, and I think that is a bit speculative at this point, as people have said, but one thing that is very clear is that cyclosporine is chemically very lipophilic and it ought to move rather quickly through the small distances between the bronchioles and the small vasculature. I am concerned about the interpretation that somehow this is only affecting what is going on in the respiratory space and not in the vasculature nearby where it ought to have a big effect on acute rejection if it is an immunological effect that the cyclosporine is having. So, I just wonder if there is anything more to be said about that.

DR. DILLY: Because of the very phenomenon you describe, the lipophilicity, we know that when cyclosporine is given directly into the lung the plasma half-life is actually 40 hours as opposed to when it is given systemically where the plasma

half-life is six hours. So, it is clearly sticking around in that compartment for a long time.

Now, one admittedly simplistic way of looking at this whole picture is that everyone was getting full dose of systemic immunosuppression. If you accept that acute rejection is largely driven from the vascular compartment you would expect it to be treated similarly in both groups because we believe, for the reasons you say about the short diffusion distances, there is really little difference between getting immunosuppression into the vascular compartment and diffusing out on both sides in terms of the vascular compartment.

In fact, we think the very lack of an effect on acute rejection makes the chronic rejection difference more meaningful because we don't have the confounding variable. Imagine if were trying to interpret this study and there was a huge signal that cyclosporine had suppressed acute rejection, then we would all be standing here, saying, well, you can't then surmise it did anything to chronic rejection. So, our hypothesis,

put really simply, is acute rejection was treated systemically; we are treating chronic rejection. The fact that there was no difference in acute rejection actually makes the effect on chronic rejection and survival more interpretable rather than less interpretable. We are deliberately keeping it simple right now because that is the extent of our biological knowledge if we are really truthful about it.

DR. SWENSON: Dr. Tisdale?

DR. TISDALE: I am having trouble here. There are two pieces of data--I didn't mention when I introduced myself that I am a hematologist so I don't know anything about the way that you grade BOS in this clinical context, but there are two pieces of objective data that I find very striking. One is the survival curves that you presented and the other is the analysis of FEV1, which are parallel. So, to me these seem almost irreconcilable. On the one hand, we have mortality decrease presumably due to decrease in chronic rejection, which should be shown by change in the

slope of the FEV1, much like you would see for creatinine in chronic allograft nephropathy.

So, I am wondering, number one, did you do the analysis for the FEV1 with all patients, or was that censored in some way? If so, maybe somebody could comment to me on what is the proposed mechanism of action of inhaled cyclosporine if it doesn't prevent a decline in FEV1?

DR. CAPRA: We did look at FEV1 in a number of ways. We looked at changes from baseline. Could we have slide SA-27 up, please? We saw a trend in favor of the active group. This is a representative example, a 0.15 increase in the placebo group versus a 0.40 increase in the cyclosporine group. It was not significant, as were all the analyses, but all the analyses did trend towards a favor of the active group.

Could we have the next slide, please? We think the reason why is because of two reasons. Number one is informative censoring. We are not able to get FEV1s on subjects after they are deceased. Secondly, FEV1 is highly variable and it

is subject to short-term variations. The BOS analysis basically ignores short-term variations and looks at a sustained 20 percent decrease in FEV1. By sustained, it has to be for a period of at least 3 weeks.

So, ignoring the short-term variations and addressing the informative censoring what you have is an analysis of BOS-free survival and that was significant, with a p value of 0.019. We are not claiming a direct effect on FEV1 because we did not hit that statistically in the analysis, but we do think that these data support that there seems to be some improvement in lung function, namely, through BOS-free survival.

DR. HUNSICKER: Could I address that specific issue very quickly? You said that you can't get the data after the people have died, and that is true, but you can do a mixed model and still get an accurate and relatively unbiased assessment of whether there is a difference in slope and I am surprised that that wasn't presented by either of you.

DR. CAPRA: We did look at slopes through a mixed model in the NDA and, again, that was not significant but the point estimate favored the active group.

DR. HUNSICKER: That should eliminate some of the problems of missing data.

DR. NOONBERG: One of the pieces that we looked at, since it is the heart of your question, is biological plausibility and, to simplify it, chronic rejection is mediated in the airway epithelium. Dr. Golden has described that the epithelium is key to this process and we are delivering an immunosuppressant directly to the airway epithelium. Chronic rejection is a progressive problem and so it is decline in FEV1 but it is also recurrent pneumonias and all sorts of other complications. Graft failure as you see in the chronic rejection process is really a setup for all sorts of mortality and, therefore, the key point that we want to make, and what is so important about the analysis where we censored the deaths with our chronic rejection, is that

treatment with inhaled cyclosporine prevented chronic rejection, and by preventing chronic rejection we improve mortality. I mean, it is clearly more complicated than that but that is the simplified story and to me, as a clinician, it makes good sense.

DR. SWENSON: Dr. Barrett?

DR. BARRETT: I was really struck by Dr. Zalkikar's simulations or the analyses looking at the assignment, in particular one looking at partitioning out subjects who got little drug. I know there was no a priori statistical analysis planned, but I guess I was curious from the standpoint of the sponsor, would you declare evaluable subjects based on the limited number of doses received with inhaled cyclosporine based on this data? And what is your take on that?

DR. DILLY: Our take on that is that when we go from 26 patients treated with active and long-term follow-on to 10 times that number we will be able to draw a much more accurate confidence interval around the trajectory of the patient. We

think that is really the bottom line of what needs to be done now because I think Prof. Helms' statement about is the p value real--who can say? We want to put a real p value on what happens to respiratory function; what happens to survival; what happens to chronic rejection. At the moment, we need to include in the prospective study that we want to do an intent-to-treat analysis because we want to describe what happens when patients are prescribed 300 mg three times a week of inhaled cyclosporine. So, yes, we would evaluate those patients. Does that answer your question?

DR. BARRETT: No, I guess I was looking at if you were going to define criteria on evaluable subjects based--I mean, in this situation you had difficulties. Again, it was a study that was done already at the University of Pittsburgh, but very heterogeneous dosing exposures.

DR. DILLY: So, one of the things that we have clearly not done, we have clearly not got a formal dose-response study sitting in front of us. Right? One of the analyses that we want to do is

an achieved dose duration analysis versus benefit. Absolutely, that is one of the critical parameters in the study.

DR. ZALKIKAR: Can I just put in a couple of words regarding FEV1? We looked at the FEV1 data as much as we could. The pre-enrollment data was missing on a large number of patients, as I mentioned. We tried to impute the pre-enrollment data by the type of lung transplant that the patients received and see the difference between the final FEV1 and the pre-enrollment FEV1, and none of those analyses has shown any difference between the two arms.

We also looked at the three-month data and treated that as some sort of baseline because it was available, and saw a difference from that to the final FEV1 that was indicated in the database and, again, there was no difference between the two arms in terms of that.

DR. PROSCHAN: Yes, I thought it was very interesting to see the sensitivity analyses, and it seems like both parties did something

reasonable--you know, not that you haven't been doing other reasonable things. You basically threw out those early deaths and did a sensitivity analysis and showed that the results were still significant. On the other hand, you switched the treatment labels and showed that things become not significant once you do that.

You know, I want to go back to their analysis. You would think that if you threw out those three placebo patients with the early deaths, you are throwing out sick patients and, therefore, the remaining placebo patients should be healthier than the patients left in the CyIS arm. So, it seems like that is somewhat reassuring, that even when you throw those out it retains the significance. I guess it is not really a question but a comment.

DR. SWENSON: At this stage we are close to the end of the morning session--oh, Dr. Reiss?

DR. REISS: I just have one question. It might have been discussed and I might have missed it, but the bronchial biopsies for the diagnosis,

were they done in a routine, standard manner or were they done for cause?

DR. NOONBERG: The short answer is both. There was a protocol specified minimum and then also for clinical cause.

DR. WATKINS: At this point, I just have a brief statement before we adjourn for lunch. I would like to remind the committee that, in the spirit of the Federal Advisory Committee Act and the Sunshine Amendment, discussion about today's topic should take place in the form of this meeting only and not occur during lunch or in private discussions. We ask that the press honor the obligations of the committee members as well.

Additionally, any open public hearing speakers who have not yet checked in, please do so at the registration desk. And, if everyone could return just prior to one o'clock we will reconvene.

[Whereupon, at 12:00 p.m., the proceedings adjourned for lunch, to reconvene at 1:00 p.m. this same day.]

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

DR. SWENSON: Welcome back to the afternoon session. This session will have initially an open public hearing to hear from interested parties outside the company and the FDA. Then we will move back to general discussions of concerns and problems and issues, and then ultimately we will vote on the particular questions that are posed to us by the FDA.

Before starting the open public hearing, I would like to read this particular message: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you

may have with the sponsor, its products and, if known, its direct competitors. For example, this financial information may include a sponsor's payment for your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So, with that said, I would like to introduce Miss Esther Suss. She will be our first presenter. Miss Suss, are you here? You can use that microphone over there.

Open Public Hearing

MS. SUSS: Before I start my statement I would like to point out to the board members that I was one of five persons on Team Pittsburgh who agreed to be filmed and interviewed by Chiron during the 2004 Transplant Games as part of an internal campaign by Chiron to...[microphone

off]...

As a follow-up to that interview that I gave at the games, Chiron asked me to demonstrate the use of inhaled cyclosporine as part of a demonstration DVD to be given to new users of this therapy. Thus, in March of 2005 Chiron paid my travel and other expenses to Orange County, California for the taping of my portion of the DVD.

Now, ladies and gentlemen, I appreciate the opportunity to tell my story in this public forum because I feel that the FDA approval of inhaled cyclosporine is extremely important to persons like me. For over 30 years I worked for the International Monetary Fund and traveled extensively to Latin America, Europe, the Soviet Union and Africa. In fact, in 1992 I opened the IMF's rep. office in Latvia and was essentially the ambassador there and I lived there for two years. After working in Latvia, I then was based in headquarters but traveled to Uzbekistan where I worked for two and a half years, and then to Armenia where I worked for two years, and then I

returned to work in Latin America.

During this time I often had trouble with some bronchitis, some asthma but I was away from Washington for over half of the year. In January, 2000, after a vacation to Florida and a visit to Pittsburgh to see my family over the holidays I came down with what I thought was the flu and had trouble breathing and my inhalers weren't working. At that point, I finally went to the doctor. I went to the hospital and I was admitted to the hospital where my doctor told me we think it is just an exacerbation of your asthma by the flu; your x-rays look fine. But the next day I had a classic asthma attack in the hospital and went into total respiratory failure. After not improving for the next two weeks, they brought in a pulmanologist. The pulmanologist told me "you're in end-stage emphysema and you will never go off oxygen again." And I was devastated. I was 52 years old. I couldn't believe that this could happen so quickly and I asked him, "how could this happen?" And he said, "first of all, your x-rays

were terrible. Secondly, some people push themselves so that they use up every margin that they have and when they fall, they fall completely off the cliff." And, that was the situation that I was in.

At 52 I faced the possibility of never being able to travel again, quite honestly. I spent about a month in the hospital and was able to improve significantly more than they had anticipated. In the end, by the time I was out in a month, I was on oxygen only when I was doing any real physical activity. But I returned to work full-time and during the day I didn't really need to use my oxygen. But if I needed to walk--today, for example, to walk from this building across the street to the cafeteria would have just about killed me even using my oxygen.

In June I asked my doctor to check, to do PFTs again to see if anything had really improved and the answer was no, it hadn't. That was as good as I was going to be. I was told then the only other thing to do was to have a transplant. So, I

asked my doctor to write the necessary letters of introduction and I was evaluated both at the University of Pittsburgh and at NOVA Fairfax. I am originally from Pittsburgh. I have my Ph.D. from the University of Pittsburgh. My younger brother is a physician from the University of Pittsburgh Medical School. So, I was pretty familiar with the programs in the hospital there and I felt quite comfortable with the people there.

Well, 22 months and five calls later I got my transplant in August, 2002. It was just incredible. On August 13, 2002 I had a new beginning. I had a new lung. I no longer had blue lips, and for one week my progress was impressive. Then I had a major acute rejection, was in the intensive care unit on a ventilator for several weeks, and I just kept taking one rejection after another. I had an agreement with the doctors and Dr. Iacona was wonderful--"if you don't give up on me I'll keep fighting" and that model has worked very well. They haven't given up on me. I kept fighting and here I am today.

I returned to Washington in November of 2002 to have Thanksgiving with friends but then had to be rushed back to Pittsburgh again at the beginning of December with a major infection which resulted in another rejection episode, and came back to work full-time in March, 2003 and I started traveling again. I went to South Africa to visit a very dear friend in October but, unfortunately, in December, 2003 I came down with a viral infection which got my immune system roughed up again and gave me another acute rejection. At that point the doctors decided, once they got the acute rejection under control, to put me on the inhaled cyclosporine therapy.

Since then I have spent the whole year of 2004 out of the hospital and, with the exception of an intestinal flu on New Year's Day of 2005, I have been out of the hospital and I have not had a rejection episode for over a year. I have been able to resume my life that I had before I got sick. In October, 2003, as I said, I went to South Africa to visit a dear friend and in June, 2004 I

took my nephew to Paris and Madrid for his 13th birthday. I participated in the 2004 Transplant Games where I ran an 800 meter, women's 800 meter and got a silver medal, and I did a 5K in about one hour. Pre-transplant I would never have been able to do that even with oxygen in two weeks, the 5K.

The inhaled cyclosporine is the first, and at this time the only drug which is aimed at preventing or at least postponing the onset of chronic rejection. I am a classic profile for someone who will get chronic rejection because of my multiple acute rejections. For those of us who have been given a second chance for having a good life it is so important to have this treatment available. I am eternally grateful to my donor for the gift that I received and I feel that wherever I go I am taking my donor with me, and I hope that he enjoys traveling because he is doing a lot of it.

I am aiming at setting the record of being the longest survivor as a lung transplant recipient, not withstanding the survival statistics that you all know quite well. As we know,

statistics are for large numbers of people and for any individual they don't necessarily apply, and I intend to be on the plus side of those statistics. And, I believe that by using the inhaled cyclosporine I am doing everything possible that I can to preserve and protect this wonderful gift that has been given to me and that it will help me accomplish my goals.

I have had no adverse reactions or problems using the inhaled cyclosporine, and my hope is that your approval of this drug for the general population will allow many other people to have the same long-term goals for themselves. Thank you.

DR. SWENSON: Thank you Miss Suss. Our next speaker is Mr. John Sullivan.

MR. SULLIVAN: My name is John Sullivan. I appreciate the opportunity to address you today. I have not had any financial rewards from UPMC or Chiron to come here and speak.

I would like to tell you a little bit about myself. I had alpha-1 anti-trypsin

deficiency when I was 35 years old. That was in 1981. In 1991 I had a single right lung transplant. I did fairly well for about six months when I came down with pancreatitis which they for some reason thought immune suppression caused. So, they had to reduce my immune suppression and I am still alive but after three weeks my lung capacity had greatly been reduced and I was rejecting. I had a couple of bouts of acute rejection then I had chronic rejection.

In 1994 I came down with aspergillus and I ended up there at the UPMC for three months on a ventilator. Then I went home for three years on a ventilator and I was put back on the list again. I was lucky enough in February, 1997 to receive a double lung transplant. I had to have a double because of the aspergillus. I was in a coma for two weeks after that and I also lost my kidney during that operation. As soon as I came out of the coma, Dr. Iacona and also Dr. Griffith put me on inhaled cyclosporine because I already had shown that I was a chronic rejector. I have been on

inhaled cyclosporine to the current time. I have been reduced to once a week.

The only time I have had any chronic rejection or any type of rejection was in June of 1997. I had fallen and broke my left hip. So then, when they put the pins in I came home and I was doing fine for about 10 days. All of a sudden I had a grand mal seizure and I drove my femur straight through my pelvis on my right side but and on the other side bent the ball right over. But because of the grand mal seizure they put me on dilantin which reduces or dilutes your immune suppression. So I went into acute rejection. I was actually in Michigan and then Pittsburgh had me switched over to Norantin. That is the only rejection I have had since 1997.

In January of this year I had the flu and my immune system kicked in. My temperature went up to 102, which isn't very good. And, I was on it once a week. They jumped it up to twice a week, hoping to stop any kind of rejection. I have had my PFTs done as well as biopsies and I show no

signs of rejection at all.

I feel that the main reason I have done so well is because of the inhaled cyclosporine. I think that has helped me. I don't show any rejection and there hasn't been any adverse effect on me at all. Thank you very much.

DR. SWENSON: Thank you, Mr. Sullivan. Our next presenter is Mr. Bill Stein.

MR. STEIN: I want to address the committee today and tell them that I appreciate you allowing me to take the time to tell a little bit about my past disease history and what the transplant has done for me to date.

I am a 32 years old and I had a double lung transplant in August of 2002, after suffering devastating effects of cystic fibrosis. I was diagnosed at the age of eight and I lived a fairly healthy childhood in adolescent years until I was approximately 20 years old. That was my first hospitalization with the complications arising from cystic fibrosis. I thought after the initial hospitalization that things would get better and I

would just go on my merry way with my life, but it didn't turn out that way. That first year I was hospitalized over five times and progressing over the next eight years my lung function went from approximately 95 percent to 18 percent at the time of the transplant.

In January of 1999 I was listed for transplant at the University of Pittsburgh Medical Center and in the years leading up to my surgery I faced the reality that my own lungs may not sustain my body until new lungs became available. In 2002 my health declined to a point so bad that I was on oxygen 24 hours a day until August of 2002 when I received my double lung transplant. I was called four times for transplant. I had three false alarms until I got the actual call in August of 2002. It was a very emotional ride, as well as a very physical one, you know, dealing with the trips to the hospital and all the prep procedures where you would have your surgeon come in and tell you that, you know, the operation wasn't a go.

It has been almost three years now since

my transplant and in that time I have managed to reclaim my life and venture forward with my goals. Less than three months after my transplant I returned to the ice hockey rink. I was an avid ice hockey player and I also played golf and, sort of against a lot of people's wishes, I wanted to go back and enjoy the sport I loved. I took the necessary precautions; I wanted to know that I could do it again.

Less than six months after my transplant I decided, well, it is time for a career change so I decided to go back to school and take preparatory classes to pursue my ultimate goal of being a physician assistant. The long hours have paid off and after all the long and hard work that I have spent for the past two and a half years, I will be accepted to the class of 2007 physician assistant studies program this August.

Words cannot express the gratitude and appreciation I have for the support that was given throughout my journey by my friends, my family and my medical team and, most importantly, the gift of

life given to me by my donor and the decision by her family.

I realize that my disease did not allow me the convenience of making an easy decision regarding my transplant but in the years that followed my transplant I have been able to overcome the hurdles associated with the complexities of the surgery, and even the care that followed. I knew going into transplant that infection and rejection would be issues that I would have to address in future care. The statistic that was provided to me prior to transplant was not very impressive, given that the five-year survival rate was approximately 50 percent, but what was the alternative? I chose the transplant and took my chances at that point.

I have been very fortunate and have only had to deal with a few cases of acute rejection that were resolved with conventional steroids and adjustments to my immune suppression medication. I was able to battle through these minor hurdles; I always worry about what happens in the future, what happens the next time I get rejection. Is it going

to be treatable? Or, what happens if it just turns into chronic rejection? Do I have something to look forward to, to help me treat it? Just given what I have heard with the inhaled cyclosporine, it just seems like it is a tremendous asset to the transplant community to have it available for patients like myself that might run into problems and conventional therapy might not carry you. I have seen a lot of my friends be in a situation where they are in intensive care for months on end. A few of them have passed away. It is very heart-breaking knowing that I am well and that they are gone because there wasn't a drug available to combat the effects of rejection.

A new drug such as inhaled cyclosporine will help benefit transplant patients such as myself and prevent or reduce the probability of rejection occurring in transplanted lungs. The drug can also help eliminate some of the traditional side effects that patients like myself deal with. My creatinine level is currently 1.5, 1.6 so I am teetering on the sea-saw as to which

way I am going to go. So, will inhaled cyclosporine give me that opportunity to lower my current immune suppression in the future and maybe have dual medications to help alleviate some of the toxicities on the other organs? Those are questions on our minds and, you know, I am sure there are a lot of transplant patients who feel the same way, and I believe the long-term benefits of the inhaled cyclosporine will provide new hope and opportunities for many patients allowing them to live long and prosperous lives without worry of additional complications. Thank you very much.

DR. SWENSON: Thank you, Mr. Stein. Our last speaker is Miss Renee Moeller.

MS. MOELLER: I am a double lung transplant survivor of three years. Although I am doing very well, I am concerned about the long-term risks associated with my current rejection drugs. I feel that taking cyclosporine as a preventative medicine will benefit my long-term survival rate and I will tell you why that is important to me.

I am a 29 year-old young woman who for all

of my life coped with cystic fibrosis and took care of myself for years. I lived a pretty normal life except for the daily routine of taking 50 pills a day. After I finished college my health declined dramatically. I thought my life was over. I was completely devastated knowing that I was so young and I had to deal with death. A transplant was my only hope. My whole life I dealt with an incurable illness. Finally I could breathe like a normal human being after this wonderful gift of a transplant. I don't want to risk losing this new life that I absolutely love and have longed for.

I am afraid of getting rejection. One of my best friends died because she rejected to the point of no return. It affected me a great deal and I don't want this to happen to myself. This is a huge concern of mine and I would love to have the opportunity to take cyclosporine. By taking this drug my other organs can be saved and, hopefully, I can live a longer and prosperous life. Thank you.

DR. SWENSON: Thank you. At this point I will turn the meeting over to Dr. Albrecht to give

us a charge for the rest of the afternoon's considerations.

Charge to the Committee

DR. ALBRECHT: Thank you. Before I read the questions let me just spend a couple of minutes summarizing some of the salient points and some of the questions that we still have remaining that we would like the committee to talk about.

Let me just reiterate, as we have heard, that a single Phase II study was performed and Chiron submitted this, and we accepted it, knowing the size of the study, given the dramatic difference in mortality that was seen. As you have heard before, the reason for this is that the incidence of lung transplants is fairly low. The current mortality is higher than with other transplants. There is no approved FDA therapy and, clearly, there is a need for safe and effective therapy in this population, as we have heard so eloquently stated.

In the Chiron presentations you heard quite a bit of information presented about this

study and you heard Chiron's assessment that they felt that these results were really quite robust and supported the survival difference and warranted a positive regulatory action.

During the FDA presentation you heard a somewhat different perspective or interpretation of the very same data in the following way: We acknowledge that there was a difference seen in OB and mortality. But OB is a histologic finding and a histologic finding without some clinical signs and symptoms causing mortality doesn't quite follow. So, when we looked at some clinical signs and symptoms, for example characterized by FEV1 or BOS, and did not see that difference we were puzzled and continued to do additional analyses. Again, just to remind everyone, the primary endpoint of acute rejection also was not demonstrated to be significantly affected by the aerosolized cyclosporine.

So, we looked for other explanations that could possibly say why was there a difference in mortality without seeing differences in FEV1 or BOS

and found a number of characteristics that were imbalanced in the two populations which, as we heard, of course, had been randomized but sometimes the risk of a small study is that randomization may still not lead to an adequate balance in characteristics.

One of the main ones was double lung versus single lung imbalance. Then you heard a difference in the incidence of early pneumonias that happened in the single lung in patients to a greater proportion than the double lung patients. Dr. Hernandez then admitted that we do not have a lot of information on the donors but used the available information that we had to try to get a sense of the donors, as well as the early courses in the recipients, and pointed out that the inotropic to support to donors was longer; the PaO2/FiO2 was less than 300 in the PG arm whereas it was greater than 300 in the double lung arm. Then the recipients also had a longer stay in the ICU which correlates with their clinical course post-transplant.

So, seeing these imbalances, we thought could this be part of the explanation because the mechanism of action of cyclosporine and the incidence of pneumonia did not seem to be directly correlated. Then we see from the literature that there is a strong association between acute rejection and chronic rejection. The assumption is that acute rejection episodes through various cycles do lead to BOS and chronic rejection and mortality.

We also heard that non-immune causes may be responsible for this and again, as I mentioned, we did see that there were differences in some of the donor and recipient characteristics, as well as differences in pneumonia, so perhaps this was in part accounting for the differences we were seeing.

In my reading I actually came across a statement by the pathology group from Pittsburgh that occasionally organizing pneumonia-like reactions in airways and air spaces may induce bronchiolitis obliterans. So, perhaps these are some of the known immunologic features that may

predispose to bronchiolitis obliterans.

Then you heard about the risks of a small study, such as the fact that when you have a small study the small sample size results are highly sensitive to small perturbations in assignment of patients, and you heard some of the results of the sensitivity analyses and their impact on changing the significance of the detected mortality and, finally, you also saw that if we looked at patients who received less than 25 doses, which was less than 10 percent of the intended two-year dosing regimen, the difference in survival was also no longer significant.

So, having said all that, let me now go ahead and turn to the questions that we would like the committee to deliberate. Having read them earlier, I will not read all of them. I will start with question one. I just did want to mention that this is also attached to the agenda for ease of reading and it is now being displayed on the screens.

So, the first question, is there

sufficient information to make the determination whether the observed survival difference in study ACS001 is due to study drug or to some other factors?

In your deliberation we would like you to keep in mind the information that you heard this morning, including the statistical issues that were raised; the differences in baseline donor and recipient characteristics; the effect that was demonstrated or the differences or the lack of differences that were demonstrated on various endpoints, including the survival endpoint, acute rejection, BOS, FEV1 and OB; and whether you think some other endpoint showed a demonstrated benefit or difference.

Let me just mention parts (a) and (b) of question 1 which is that if after you deliberate you believe that the answer to the first question is yes, what we would be interested in is hearing about the generalizability or, more specifically the labeling recommendations or the labeling summaries that would then evolve from the results

of this study.

If, on the other hand, you believe that the answer to the first question is no, we would be very interested in hearing a discussion of what additional clinical studies you would recommend be conducted. Here we would be interested in specific recommendations regarding the patient population, drug dosing and regimens, drug administration and efficacy endpoints. I will stop there and then we can return to the second question.

Committee Discussion and Vote

DR. SWENSON: For ease in going through these discussions, I would ask that you just tap your "talk" button and we will see the red light go on and then we will call people in turn.

I would like to first step back and allow for some potential questions that were possibly not brought up in the morning session and maybe to spend some 15 minutes or 20 minutes on that because I think that will be part and parcel of your answers to these questions. I know that Dr. Mannon had some unanswered questions and we will start

with her. But anybody else that has new ideas or something unanswered from this morning, please let us know.

DR. MANNON: This is a question sort of involved in Dr. Proschan's question earlier this morning on page 84 of the Chiron binder. I was struck by the number of patients that completed therapy. Maybe I am misinterpreting it but only about half of the patients, maybe less than half in the placebo group but about half of the patients in the CyIS group were able to complete therapy. So, I question both the sponsor and the FDA about what were the reasons for the lack of completion of therapy. Also, from a clinical perspective, how do you interpret the outcome when half the patients in your treatment group did not complete full therapy?

DR. NOONBERG: To address the first part of your question, the reasons for early drug discontinuation are shown in the table below. The primary reasons for the placebo group are due to a variety of adverse events. We have already discussed the withdrawal of consent. Again, there

were some problems with early tolerability that could be fed into the adverse event group of the inhaled cyclosporine group. The unsatisfactory therapeutic response, those are patients that were taken off study drug in order to cross over into the open-label protocol. Protocol deviations and violations were largely due to medical non-compliance and smoking. So, those are the range of reasons. There were no patients that discontinued because they died. They discontinued for other reasons prior to death.

DR. MANNON: I guess my second question is when only half of your patients complete the proposed therapy, what is your interpretation of the outcome of those patients when only half completed really the full therapeutic part of the trial?

DR. NOONBERG: Well, my sense is that inhaled cyclosporine helps patients early on and continuously because chronic rejection--it is not like acute rejection where one day you have it and the day before you didn't and two weeks later you

don't. It is a gradual process that probably starts very early on and only after a year it is able to be detected by transbronchial biopsy and certainly by a decline in 20 percent of FEV1. Again, there is nothing magical about the 20 percent decline and, therefore, it is not an episodic process and, therefore, patients who appear to get more drug did better. How we justify this really is using an intent-to-treat analysis.

DR. ZALKIKAR: Can I respond to that question? We agree with the reasons for discontinuation that were displayed here a while ago. As for the sensitivity, I have shown you some sensitivity analyses where we treated the patients who received very little therapy in three different manners, one, excluding all 11 patients who received less than 25 doses; secondly, treating the cyclosporine patients who received very little treatment as the control patients; and, thirdly, defining treatment failure as discontinuation or very early discontinuation due to adverse event or withdrawal of consent. All of those sensitivity

analyses show that the survival benefit is no longer significant. So, the interpretation is really hard.

DR. NOONBERG: Well, I would comment that one of the reasons that patients didn't get 25 doses is that a couple of them died and, therefore, couldn't have gotten 25 doses. When we did a sensitivity analysis and only looked at patients who had 80 percent of protocol maximum dosing adjusted for death we found the results were statistically significant. I don't know if you want to bring that slide up again just to show the results of our sensitivity analysis.

DR. SWENSON: I think you have made the point well and I think we remember it.

DR. ZALKIKAR: Can I counter that? Again, the few early deaths--is it really possible to attribute those deaths to lack of cyclosporine? That is also a question we had a hard time dealing with.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: Just for the record, I would

like to know just a little bit more about how the randomization actually occurred to the extent that that is reconstructible. About half of the patients done during that interval actually were in the study. Were all approached? If not, what were the criteria? Who made the decisions, and when? And was it blocked by two, by four or six? So, what was that process like?

DR. IACONA: I am the principal investigator of the study. About 120 transplants were done at the University of Pittsburgh at the time of the three-year limited enrollment period. Out of those patients, about half enrolled. Unfortunately, we had about 20 percent death rate during that interval which excluded a large number of patients, which we could do nothing about. We did screen through other patients and, to be quite frank, there were a lot of things going on. We didn't want to push the drug because we had it for other studies and it was an open-label protocol. That was one issue. The other issue was that the patients didn't like the idea of receiving a

placebo. So, when you pushed them, their gut reaction was why should I go into the study when I can get the drug if I should reject? So, that is how it was done. That is how I approached patients and my colleagues did.

As far as randomization is concerned, I had no part in randomization. It was done by the University of Pittsburgh statisticians and I had no idea as to how blocks were assigned. I never received the coding for randomization and there was no way any investigator in the program had any idea as to who was receiving drug or placebo.

DR. SWENSON: Dr. Hunsicker? I am still a little bit foggy about exactly how the analysis plan was constructed. We have a study for which the primary outcome was something that is not now really the issue of evaluation. So, the presumption is that you noticed a very substantial difference in the death rate and that is what now powered the rest of the analysis that was going on. So, my question is, and I don't know how I can put this quite precisely, but to what extent was the

analysis plan developed before the data were looked at so that you knew what you were looking to test? Because, clearly, if the analysis plan knew the outcomes it is no longer really an unbiased analysis. So, I have to ask at what stage in the development of this thing was the analysis plan finally formalized by which the analysis specified that we were going to look at these things? Was it after you knew the frequency of BOS and so forth, or was it simply when you recognized that there was a difference in the rate of death?

DR. CAPRA: As we have heard earlier in discussion, the enrollment was for three years in the randomization portion of the trial, up to August of 2001. The last subject was followed for an additional two years for treatment. At that point the study was unblinded and at that point the analysis took place, and there was no prospective analysis plan because it was an investigator-sponsored trial done at Pittsburgh.

What they had in their protocol was they had a primary endpoint of acute rejection. The

prospective endpoints were chronic rejection and overall survival duration. There was no prospective analysis as to what kind of covariates to include in the survival duration endpoint. So, the trial was over; the results were this; treatment assignments were unblinded so we looked at survival duration from the time of transplant to when the study was closed in August of 2003 and the results were unblinded. And, that is why we looked at a number of analyses. The first thing is straightforward log-rank test. It was significant. Then we went from there and started looking at other sensitivity analyses which basically confirmed the overall result.

DR. HUNSICKER: The specific issue that I am getting at is what you chose to use as your endpoint beyond simply survival. I am going to assume that that is well defined, and everybody knows whether you are alive or dead. But when you create an analysis like this you can have any number of things that you put into a composite. You know, you are looking at a whole series of

composites and if you know what the outcomes are before you build your composites, then you are not blinded as you create your test and it means that you can't really test it that way. So, I am trying to get a sense of how you developed what you were going to do--you understand what I am talking about.

DR. CAPRA: Sure. The secondary endpoint was chronic rejection. So, in discussion with the doctors both at Chiron and then with Dr. Iacona at Pittsburgh I understood that chronic rejection is measured both histologically through OB that is on the biopsies, as well as the BOS which is the sustained 20 percent decrease. From there, we looked at time to first occurrence of chronic rejection, again, first doing it in an unadjusted analysis, looking by log-rank test, and then forward from there.

DR. HUNSICKER: But were there analyses done so that the people at Pittsburgh--and if I had been there I am sure that I would have done these things so that as you did this you would have known

what the rate was of OB and BOS before you began putting together your composites. Is that the case?

DR. CAPRA: I guess I will have to yield to people from Pittsburgh. I haven't seen that so I will let them discuss it.

DR. IACONA: So, the question, as I understand it, is what was prespecified in our NIH grant. We had an NIH grant that supported the study at the time. The primary outcome, as written by Howard Rockette [?] at the University of Pittsburgh who is the head of our biostatistics section, states that we would use acute rejection as our primary endpoint evaluating acute rejection by Poisson analysis.

We also evaluated survival and freedom from rejection as secondary endpoints, as stated in that grant. The freedom from rejection was specified for both acute and chronic rejection as determined by Kaplan-Meier and evaluating by log-rank analysis.

DR. HUNSICKER: So, it was freedom from

both acute and chronic?

DR. IACONA: Freedom from acute rejection was primary--

DR. HUNSICKER: No, no, no, I understand, but your secondary endpoint was--

DR. IACONA: Freedom from chronic rejection. It is stated in the grant, yes.

DR. HUNSICKER: And was the definition of chronic rejection in there? The major issue here is that you are depending a fair amount on BOS.

DR. IACONA: Yes.

DR. HUNSICKER: You know that because of the way you did things--you can't use--what do you call it?--the heart, lung transplant definition because you didn't have the baselines. Did you have your definitions in place before you started building an analysis?

DR. IACONA: Yes, the definitions were in place as specified in that NIH grant, and we can certainly provide you the statistical section of that grant. We evaluated chronic rejection by two means, by BOS and by histology.

DR. HUNSICKER: But those endpoints were defined before you did the analysis?

DR. IACONA: Yes, in the NIH grant.

DR. CAPRA: I think there is also a misunderstanding about the baseline BOS. Baseline is a running average as a function of time so because subjects were enrolled as early as seven days after transplant, sometimes a subject didn't have an FEV1 value available in that first week; they had one maybe on day eight or day nine. We were able to calculate a baseline BOS, which is a running average, and then look at change from that value for calculation of BOS.

DR. IACONA: Could I make a statement about the initial PFT? Before these patients go on aerosolized cyclosporine or placebo they are postoperative patients, some of whom have tracheostomies; they have chest pain; they are not candidates to actually journey to a bronchoscopy laboratory to get a PFT and if they did get a PFT they would be highly inaccurate. So, that initial PFT, in most cases where it was not present, would

be impossible to get under the clinical circumstances of a postoperative transplant patient.

DR. SWENSON: Dr. Moss?

DR. MOSS: I think this is all really interesting. I think Chiron has done a great job in presenting the data and actually the question is not for you but you can stay up there if you want. The data that Pittsburgh and Chiron have presented is extremely interesting and very thought provoking. There was a comment made that if the decision was made by this committee/FDA that further studies needed to be performed, maybe a larger multicenter trial to really determine the potential answers, that Chiron would not be able to do that or was not committed to do that. I just wanted to understand your reasoning behind that because if you are this committed to this and you really, really believe that this really works, then why would you throw in the towel now? I hope the answer is more than, you know, it costs a lot of money. Let me prop this up by saying that there

are other ways of funding studies or co-sponsoring studies like that with the NIH, etc. potentially.

DR. DILLY: The answer is not it costs a lot of money. The answer is we don't think it is an appropriate thing to do. Just think through the practicalities of running another placebo-controlled trial even in a multicenter site. That involves IRB approval. That involves informed consent. Frankly, it would be inconceivable--you have heard from the patients already--that patients would be willing to go on placebo in a randomized, controlled study with this kind of clinical signal. We believe that that question is behind us.

What is important is to really address some of the questions about the relationship of the endpoint. Now, there is no such thing as absolute certainty in science. Therefore, we think that the right thing to do is to run a large group of patients, prospectively defined, follow them for a long period of time so we can really characterize the natural history of patients treated with

inhaled cyclosporine so that we can address those questions once and for all. So, it is just not the right thing to do, to do another controlled trial before approval.

DR. SWENSON: Dr. Sampson?

DR. SAMPSON: It is actually a small point. I just want to follow-up on Larry's question about endpoints because in the Chiron report it says chronic rejection as manifested by OB and BOS, and the variable that you used was OB or BOS in your primary analysis. Is that right, or am I just getting caught up in "and/or's" in this? Again, it is the same issue, you know, about looking for the right variable to produce the answer.

DR. CAPRA: The answer is it is and/or. So, it is OB or BOS or both. I don't know if one of the doctors wants to comment on the clinical relevance of the use of the composite.

DR. NOONBERG: Again, I just want to reiterate that chronic rejection can only be diagnosed in two ways at present, histologically

and clinically. There will be patients that have histologic OB, and they will have it on autopsy, that don't subsequently go on to BOS in the time period of the study. However, like I said, there is nothing magical about 20 percent. They may have 18 percent decline, 19 percent, or 25 percent decline but they have an episode of pneumonia. So, there are also patients that have BOS but, due to the insensitive nature, it is not picked up. So, really chronic rejection encompasses both groups of patients but they are not really distinct groups. They have the same clinical process. It is just a matter of how it is detected. And, the whole BOS criteria became necessary because of the insensitivity of transbronchial biopsy, not because of the poor specificity or the thought that these patients who had it on biopsy didn't really actually have bronchiolitis obliterans. It is just that there was a sense that there were other patients who also had chronic rejection that weren't coming up as OB.

Again, I want to clarify this question

about Chiron's definition of BOS because it is really not Chiron's. We used the programmatic definition developed in 2001 by a consensus committee, and it uses a post-transplant maximum. As you may remember from the FDA's slides, the initial FEV1 is rarely, if ever, your post-transplant maximum. It usually really doesn't come for several months and, therefore, it doesn't affect the diagnosis of BOS. So, we didn't come up with any special criteria for BOS. We used the same programmatic definition that is used in the transplant community.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: I want to get back to the monitoring issue because that is still bothering me a little bit. It is hard for me to imagine that in this study that was done at the University of Pittsburgh there was no group looking at the results on an ongoing basis. I mean, is that what you are saying, that there was no data and safety monitoring board or no group or individual that was looking to see whether, for example, the mortality

was in the active treatment arm?

DR. DILLY: There are two points, one which I would like Dr. Iacona to comment on, the one about monitoring of endpoints. One of the questions that we have been discussing is just how much did the people that entered the endpoints in the CRs know about the treatment assignment. I think there was some confusion in the way this was communicated this morning. The endpoints that appeared in the case record forms, that appeared in the data that constituted the analyses you have seen, were taken from source patient records, source documents. The people managing the patients were blind to treatment assignment, as you have heard from Dr. Iacona. The people transcribing the data from the source document into the database could theoretically have known what the treatment assignment was. There is no evidence that is the case. However, both we and the FDA went in an audited the data in the database against the original source documentation and it is a matter of common understanding that the data in the database

reflect the source documentation. So, we believe that the data that you see have very, very little liability to be biased.

DR. PROSCHAN: No, I am not worried about that. What I am worried about is that the study was stopped on a possibly random high. That is, someone is looking at the data, seeing the results and then saying, "gee, if we stop now, look, it's going to be a p value of 0.007."

DR. DILLY: Remember, the study was stopped on the date that was prospectively defined for the study stop. There was a completion enrollment date in August, 2001 and completion of the study in August, 2003.

DR. IACONA: Correct. So, Dr. Proschan, the enrollment period went on for a duration of three years. There was a safety and monitoring committee during those three-year intervals that met at yearly intervals, to the best of my recollection, and they looked at safety and the primary endpoint, and they reported that safety events were no different between the groups looking

at renal function and infectious processes between the groups, which is of concern, and they looked at acute rejection. At the end of the three-year block the safety and monitoring committee ceased to meet. The patients who were enrolled at that three-year interval went on to receive their two-year course of therapy, and all the patients in the study were continued to be monitored. At some point, right before the end of the study in June, Dr. Corcoran had done lung function analysis and he was unblinded. At that point Dr. Corcoran also looked at survival and it became apparent that there was a difference in survival. Up to that point we had no idea that survival was different. I knew that survival was significantly better in the aerosol group and I wasn't unblinded yet. I was told of this information. I contacted the members of the FDA, Dr. Albrecht and Dr. Cavaille-Coll, and we had a conversation. I also contacted our IRB. And, the decision was made to proceed to finalization of the trial in August of 2003 until the last person received two years of

therapy as prespecified in our NIH grant.

I would like to make one more comment in reference to the differences in AA gradient between the donors, between the immediate post-transplant patients. Since more of the cyclosporine patients had double lungs you would expect that their PaO2/FiO2 ratios to be higher. It may not reflect anything of the donor per se, just the fact that they had double the lung surface volume.

DR. SWENSON: Dr. Hernandez?

DR. HERNANDEZ: I am going to make several comments. The first is regarding the study termination. I have the impression that the study was terminated early and what I see is that an amendment was implemented to terminate the study earlier, before reaching the 126 patients that were initially planned. Because of reasons that were not in the hands of the investigators, the study needed to be terminated earlier, before 126 patients.

DR. IACONA: Yes, Dr. Hernandez, I appreciate the point. Logistically, we were not

able to proceed with the enrollment. We had requested additional funds from the NIH and the funding supply was exhausted at that point. We recognize that we were not able to enroll the number of patients as prespecified and extend the study. I made a specific request to the NIH to extend the funds and they were not allocated. So, we were forced to make do with what we had.

DR. HERNANDEZ: This is a very difficult thing to me, but I think because I am a clinician I would like to insist on this, when I changed to the area of transplantation I became a transplant surgeon and very committed to my patients, and I believe that most transplant patients are very educated about what the transplant is. I think they are getting explained perfectly what is going on and they understand clearly. The thing is that I don't want to raise false expectations in my transplant patients. First, I don't want them to get the impression that this treatment is a calcineurin-sparing drug because there is no data to imply that. This drug has not demonstrated an

effect on recurring acute rejection. So, I think that we need to clarify that with patients where they can understand exactly what we are looking at.

What matters to me is the function of these lungs. Histology has several limitations. Transbronchial biopsy doesn't tell you anything about how extensive the disease is; FEV1 does. Transbronchial biopsy doesn't tell you anything about the clinical course of the disease and, as we know, chronic rejection can go very, very slowly over time and just maintain like that and not give too much disturbances. Other clinical courses are really, really dramatic that go from a very fast onset. What is indicated in all this is that there are several factors that are not only immunological but are also non-immunological factors, namely, infections that can, you know, go through this vicious cycle where the patient has rejection, gets immunosuppression, gets infection, more rejection and finally all these stimuli and calcineurin damage may lead to chronic rejection. But what is really, really important is the effect on the

function of the graft--FEV1 and BOS, and this has been addressed by the International Society of Heart, Lung Transplantation that has, you know, clearly specified. And, when we are looking at the treatment we have to look at the effect over time of serial measurements of FEV1 before and after the treatment in order to assess an effect of this drug.

DR. DILLY: If I may comment, our perspective is we endorse--we want to know the effect of inhaled cyclosporine on lung function, but we would suggest that the cardinal endpoint is whether the patient is alive or dead and, frankly, you know, whether they are breathing easily is secondary compared to whether they are alive or dead. And, we have a very strong signal in favor of mortality here which makes interpretation of some of the other endpoints rather difficult. That is why we are suggesting that the right thing to do is to benefit from that finding, take this drug forward and study it in a much larger group of patients where we can really nail what the

trajectory of FEV1 is in patients who have their rejection controlled by inhaled cyclosporine.

DR. ZALKIKAR: I want to make just one point regarding monitoring the study. The study report that was submitted to us mentioned an interim analysis that was conducted by UPMC during the conduct of the study. However, we did not receive any report. There was no adjustment. There was no information about the boundary used or anything like that. So, we requested that information. In response, what we received was that the interim analysis that was mentioned in the study report was really the so-called final analysis from UPMC. But prior to that during the course of the study there was another interim analysis that was also conducted. The data was blinded at that point. University investigators were blinded at that point and that data did suggest a difference in survival, although not significant at that point. Again, there were no formal statistics done on these interim analyses.

DR. CAPRA: Let me comment on that.

Again, Chiron came into the study at the end of the trial basically when the results were already over. When we had the discussion with Dr. Iacona he talked about this analysis, and what he was referring to late and which we learned later was that this was the analysis looked at by their data monitoring committee. There was a misunderstanding between Chiron and Dr. Iacona over terminology between basically the data monitoring committee versus formal interim analyses. You know, in the analysis that was done by the data monitoring committee no adjustments were made as far as we could tell or Dr. Iacona communicated to us, and the study continued as planned.

DR. ZALKIKAR: Also, I want to address an issue that came up about the definition of the endpoints. Although the endpoints may have been defined, on reading of the document, it suggested that the definition was simply survival, chronic rejection and lung function in terms of FEV1. Also, the data analysis plan was created retrospectively after unblinding of the data as to

how to analyze those endpoints.

DR. CAVAILLE-COLL: I want to address some of the comments or some of the questions by Dr. Hunsicker. I think that we share with you concerns about when this data was really looked at, and we do know that the study was presented at the International Society of Heart, Lung Transplantation at an open session. So, there were some analyses done at least before that presentation. I don't recall the exact date of that and I don't recall when that took place with respect to the involvement of Chiron and this application.

We do not have a prospectively defined data analysis plan and, certainly, we were willing to look at survival because that is certainly an unequivocal endpoint. But when it came to the secondary endpoints, such as those used to define chronic rejection, there really wasn't anything that was prospectively discussed with us and that was defined before the information on survival had become public.

DR. PRUSSIN: I have a question as far as the charge to the committee. Do we go over that now? Is this a reasonable time to do that?

DR. SWENSON: Let me hold your question. I have several and we may have one other but we will get to that. My question is to both sides here, and that is that in all of this we haven't discussed any issues around the potential toxicity over a longer period of time of these very high concentrations of drug on the airway. The animal data rest largely on one-, two- and three-month data. As I look at those data, I see that transiently at peak there are 100-fold greater concentrations of drug applied to the airway epithelium. It does tail off but it still remains high. And, the risk, as I see it in this field, is the issue of malignancy developing and the problem of post-transplant lymphoprolific disorder. So, I wonder if both sides might touch on this issue about this dosing and down the road possible adverse consequences.

DR. JOHNSON: Dale Johnson, from Chiron.

One of the things that we did, of course, was to do toxicology studies in normal animals at high doses and look at those particular findings. What you actually saw on the listing, for instance, doesn't actually describe the severity effects which are barely detectable. So, from an acute standpoint it is fairly clear it is not an issue. Chronically, there have been studies and they have been done with monkeys, and what I would like to do is to refer you to Dr. Allan Singer, who is from Battelle Institute, who actually has knowledge of those studies.

DR. SINGER: I am Al Singer and I am from Battelle, which is a not-for-profit organization. We actually do very little work for Chiron so I don't really have a whole lot to gain one way or the other here. They are not paying my salary, Battelle is. They are reimbursing Battelle for my time for today.

The monkey studies were actually run with propylene glycol. Those were run over a period of 13 months at a saturated solution. They caused no

effect. But your question really relates to cyclosporine. The main contribution I can make here--I was not the pathologist, veterinary pathologist, toxicologic pathologist; I was not the pathologist in either of those studies but I did peer review both of those studies, the rat and the dog study. The lesions which were diagnosed--and there were lesions--there were minimal inflammations, sometimes mild inflammations in the alveoli and in the interstitial areas of the lungs and, frankly, it is within the realm of normal. We did not run an air control on the dog study, and that is simply because we have run so darned many air control dogs through the years that it is just a waste of dogs. At some point you have to decide why you are just putting more animals on a study; it is just a waste of animals.

The lesions that were seen in the propylene glycol controls are typical of what you would see in an air control in that study. The pathologist reviewed those dog slides and we cut 35, 40 slides. He spent most of his time on 40X

looking for a few cells.

The only thing that we actually had any trouble with was the pinpoint ulcers in the larynx of some of the dogs, and we typically find those in controls as well. It is my belief that it is the function of the way the mouthpiece works in the dog. The rats are put into a tube and they have to breathe through the nose. But in the case of the dog it is actually a tube that goes in the mouth and they have to breathe through the mouth, and I think that is somewhat drying. But they are all within normal limits. There are no acute findings within 28 days to speak of.

DR. SWENSON: Well, I can imagine that they are typical. What we are talking about is a concern raised in the literature that cancer and malignancies will be a problem with long-term chronic immunosuppression, and cyclosporine has been pin-pointed as a possible risk factor for that. So, I don't think the animal studies are going to answer that. Cancer just takes too much longer to evolve. So, it is going to be an issue

only in the humans because what you are proposing is to take this out for more than two years, maybe five years or the life of the patients.

DR. DILLY: Exactly right, and it may be worth showing slide PK-26. First of all, there are few safety endpoints that trump survival and patients have to survive long enough to see the toxicity. Second of all, what you are talking about are going to be low incidence signals. If it was a high incidence signal it was likely to have been picked up by now. Those will only be found with a significant sized study for a long time, and that is why we say that actually to nail questions exactly like the one that you are posing, the right way to do that is a five-year study following a large cohort of patients through treatment so we can look at the incidence.

We also have the very nice reference point of, for instance, the UNOS database, where we can look at the incidence in people not receiving inhaled cyclosporine. So, that is why we see in this context that a postapproval study, running for

a long time to gather this kind of data, is entirely the right way to go.

DR. SWENSON: Before you step down, let me raise just one issue. If, in fact, this committee votes positively to proceed here, what assurance do we have that this study will be done? The track record, as was highlighted recently in an article in the LA Times last week pertaining to fast track approval, and in essence this is something similar to fast track approval, and many of these promissory notes have not been delivered and, therefore, if this does go to approval it is really a contingent approval.

DR. DILLY: I will give you three answers to that. The first one is that it is entirely within the FDA's regulations, FDA's own regulations to hold us to a postapproval commitment, not withstanding whether it is accelerated approval or not.

Second of all, this is part of a much broader commitment of Chiron to lung disease, and we have referred to our treatment of cystic

fibrosis with TOBI. We followed that population. One of the reasons we got here in the first place was patients with cystic fibrosis receiving TOBI for pseudomonal infections. We have been very diligent in furthering that treatment, for instance with our drug powder inhaler program where we followed through with a program to optimize that therapy.

Third of all, and probably the most important, is think about how you commercialize a drug like this. Trying to get broad adoption of a treatment based on a single-site study in 26 active patients versus 30 control patients is an uphill proposition. This is exactly the study that we want to do to generate publications, to generate more data to talk about, and to underwrite the widespread adoption because if we can do the study, then we can optimize the dosing regimen. We have the option to optimize the formulation. We have the option to just get it right in the long-term for patients with lung transplantation.

In the absence of this kind of study this

could be the sum total of the clinical experience with inhaled cyclosporine that is interpretable, for some of the reasons that we talked about before. So, it is in our mutual interest to do this study.

DR. HUNSICKER: Just an extension of that, you argued before that one of the major reasons for requesting approval now, rather than doing a definitive study that you just talked about, would be that it would be both unethical and impossible to recruit patients to a study if there was this publication, which is undoubtedly going to be out. But you just said now that you don't think you can commercialize this unless, in fact, there is better data. That would imply that there would be patients who might be available and that it wouldn't be unethical. So, is there a contradiction here?

DR. DILLY: Not really. We are talking about 250 patients over five years compared to about approximately 2000 patients treated worldwide every year. So, during the conduct of this study,

say, we take a year to enroll 250 patients and then five years to follow them up, that is six years worth of treatment and that is 12,000 people worldwide getting transplanted. It is a relatively small subset of the overall population that we would be putting in this study. We do see that having a robust, ongoing program of research to optimize the drug is the right thing to do because, as we said from the get-go, not all the questions have been nailed down by the single study right now.

DR. ZALKIKAR: If I may just say something that came to my mind as I looked at this slide, PK-26 that the applicant put up, we saw this slide and an effort was made to match the placebo patients to the UNOS data, but we didn't see any effort to match the cyclosporine patients to the UNOS data in terms of baseline factors.

DR. DILLY: In fact, you did see that slide during the presentation this morning, and the p value and the point estimate were almost entirely the same as in the original analysis.

DR. ZALKIKAR: That was a comparison of the cyclosporine arm in the study to the UNOS matched controls.

DR. CAPRA: As Dr. Zalkikar was mentioning, we did compare the cyclosporine subjects to the UNOS matched controls and we used the same matching criteria. We matched by transplant type, CMV match or mismatch, early acute rejection, age where we took the ages in brackets, and sex and, not surprising--I mean, this result is positive given that the comparison from the placebo to the UNOS was nearly identical. So, here the p value is 0.19 and the relative risk estimate of 0.252 is nearly identical to what we saw in the primary analysis of 0.213.

DR. SWENSON: Dr. Tisdale?

DR. TISDALE: I had a question that was percolating some time ago. We seem to be inferring from the analysis of this study that it is all post hoc and the primary endpoint was not met. But I imagine the primary endpoint was decided upon because it was felt that it was more likely to be

impacted by this.

But I want to be sure that I understand that in the original study that was written for three years--it wasn't re-funded, probably because the primary endpoint wasn't met and there was no difference--survival was in fact one of the endpoints, one of the secondary endpoints, and in the analysis of one of the secondary endpoints that was a planned part of this study there was a highly statistically significant difference, and that is the reason why we are all here.

DR. IACONA: Unfortunately, I don't have the statistical section of the NIH grant with me to show the audience. It is written as an endpoint of survival as a secondary endpoint, as is chronic rejection and bronchiolitis obliterans syndrome. One of the analyses that I did independently was to actually look at change in FEV1 from peak, as is conventionally done, and calculate individual slopes. I calculated individual slopes between the cyclosporine and the placebo patients and, at least by my independent analyses, I am showing a

difference between the rate of decline in the cyclosporine versus the placebo. Now, I don't have the background that Chiron does, but that was also mentioned as part of the analysis. I am not sure why that is not being presented or accepted, and I can show you how I did it independently. But the chronic rejection is a secondary endpoint and we looked at chronic rejection in our study by bronchiolitis obliterans syndrome and by histological rejection. If one should read through the transplant literature, our pathology department is probably the best in the world in diagnosing chronic rejection by histology and we really emphasize that in our grant, that we are going to look at histological OB.

The second point that you made was what we should pick as a primary endpoint. Well, when you look at transplant drugs it is believable and acceptable by the NIH, if one should mention acute rejection as a primary endpoint and that was our thinking, Dr. Griffith's and my own thinking, that acute rejection is a conventional endpoint for a

transplant drug. It is taken as an endpoint because it is a surrogate marker of chronic rejection. If I went and I suggested that aerosolized cyclosporine would be the first drug ever to prevent chronic rejection my grant would not get funded.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: I would like to just explore the alternative to the proposed study, which would be perhaps a smaller number of patients, a randomized trial. I think a lot is being hung on the perception that around the country it would not be possible to do that. I am not totally convinced. I think there is obviously a great deal of interest around the country in this potentially radical advantage. But I think that a lot of patients don't complete the course; don't get very far in the course. It is a huge expense--there are a lot of things about it I think. I would like to hear perhaps more of the argument that a randomized trial, much smaller in scale but powered to provide capacity to see the difference that we are hearing

is believed this trial gave us from the data we have now, why that wouldn't be a viable alternative.

DR. DILLY: There are several points. First of all, our analysis of the data, as we have said from the very start of our session today, is that there is a robust survival advantage for inhaled cyclosporine. Therefore, we think the right thing to do is to make this treatment available to patients with lung transplantation. Therefore, we actually do not see withholding therapy, even in the context of the clinical trial, as a desirable way to go if there is an alternative.

We believe the very strength of the available data on the natural history of survival after lung transplantation means that we don't have to randomize patients to placebo. So, we took what we saw as a much more sound approach of saying let's do a big study rather than a small study which will allow us to also look at some of the secondary phenomena like the effect on pulmonary

function, like the effect on chronic rejection, as well as survival. So, we felt it was a more elegant way forward than another placebo-controlled study and a more appropriate way forward.

We also had advice from our advisers that it would, in fact, be rather problematic, and we did our own internal soul searching around how would you write an informed consent form with that Kaplan-Meier shape. And, drawing on my own personal experience in oncology where, in the face of this kind of survival endpoint, you do everything you can to get patients onto active therapy.

DR. BURDICK: So, in essence, what the proposal is--the point that it is effective is proven and we are going on from there to look at the details. I think that that happens a lot, especially in transplantation where the numbers are small and there are a variety of sort of opinions around the country about exactly how to best treat patients and you end up with a series of papers written showing exactly how this or that effect is

optimized by this or that approach, and a lot of good things, and ultimately truth comes out of that. But that would happen anyway if the FDA just said, okay, approve it.

The trial you propose with an OPTN control, which is going to have some problems--I am not sure exactly what is in the OPTN database that would provide you with what you need for your control group. Maybe it is good. Maybe you could address that. But I am concerned that we will have a series of opinions about details around the treatment but it is not going to extend how convincing the big picture is, which is does it make a difference or not since you are hearing some concerns about whether that really has been proven.

DR. DILLY: Our take on that is that currently the five-year survival for lung transplantation is quite well nailed down at around 50 percent, and that has not been a point of major contention. The control group in the ACS001 study behaved very like a control group in external controls. It has all been about the remarkable

trajectory of the patients who received inhaled cyclosporine, and what we want to do in the confirmatory study is confirm that remarkable trajectory. Therefore, we can draw statistical plans around the point estimate and the confidence intervals of one year, two years, five, and so forth, and we see that as the most powerful way of generating the data that are necessary to address this question.

DR. BURDICK: I don't mean to argue this extensively, but you are caught in the same situation as we are in transplantation otherwise. By the time you are calculating your endpoints you are going to have patients on MMF being moved back and forth on rapomyacin and you are going to end up with a series of observations that characterize certain subsets or certain areas and seem convincing, and it is not again going to provide you further strength against the critics who might say this is very interesting but we haven't seen that it is really making a difference that is proven.

DR. DILLY: If in seven years time we are looking at data that says that the point estimate on five-year survival with inhaled cyclosporine really is 85 percent, it will be absolutely clear that that is different from the current practice. And, we are confident enough in these data having, as you have seen stress tested them every way, that we could think of that as appropriate, that we are going to see an effect that is clearly different from past practice and that is what we are interested in pursuing.

DR. GOLDBERGER: Dr. Swenson, I was wondering whether it would be helpful--the company has Dr. Golden here and another expert, if maybe it would be helpful to the committee to hear their views on the types of trials that could be done with and without prior approval because they are the kind of people who actually have to do those trials practically.

DR. SWENSON: Fair enough. Dr. Golden, do you want to take that?

DR. GOLDEN: I got most of your question.

Do you mind just summarizing it?

DR. GOLDBERGER: Yes, there has been a lot of talk about what kind of trial could be done. In particular, whether a placebo-controlled trial could be done at this point in time with this information already public and and probably will be more public when an article comes out about it, and what your take is about that and about the situation for further studying this therapy.

DR. GOLDEN: I have to believe that given the change in survival in this study that that is, (a), going to be sustained in another study and (b), it will be very hard to look at my patients and ask them to be in a placebo arm. This is always the problem with any study. But I happen to think that in my institution my IRB will likely say, especially after a publication, that this information is already out there in abstract form and otherwise. I have to explain to a patient that this inhaled therapy, a novel approach, has been the first absolute study to show a change in our dismal outcome at five years.

I must say to the point of rapomyacin trials, now at 24 months, it hasn't shown any difference in obliterative bronchiolitis. I think, as a physician, that I am not going to be able to entice patients to go in a placebo group in the context of this inhaled therapy.

I would very much actually like to ask Bert Trulock his opinion on that question as well.

DR. TRULOCK: Thanks, Jeff. Bert Trulock, from Washington University. I don't have very much to add to what Jeff has already said. But presented with this evidence, I am not sure that there is an IRB in the country that would approve a randomized, placebo-controlled trial. Certainly, at our university when presented with this kind of information these days, it is very difficult for the IRB to approve a placebo-controlled trial.

Aside from that, there are the emotions that Jeff described in convincing patients to go into a placebo-controlled trial when this information is already in the public domain. So, I don't believe that it is practical to do a

placebo-controlled study.

DR. SWENSON: Instead of a placebo arm, what about the possibility of some lower dose that might achieve at the airway level essentially the same levels that are obtained with oral dosing? This would then offer patients at least something active, and it is still a question that is relevant because we don't know what the dose-response relationship is.

DR. TRULOCK: I can't speak for Chiron, but I think those kind of dose-ranging studies are obviously important, and there are many things like that that can and need to be done in a postapproval study.

DR. SWENSON: And it doesn't seem as if you would need 250. If this is really as robust as it is, simply another trial of 50-75 patients, if it showed exactly the same--I think the question would be moot about survival advantage. Dr. Proschan?

DR. PROSCHAN: If I had anything to say, I have forgotten it now.

[Laughter]

DR. SWENSON: Dr. Barrett?

DR. BARRETT: As I was listening, particularly as the sponsor pointed out what their plans were next, I am not so sure that an additional confirmatory trial, ethical reasons aside, is going to be necessarily informative here. There are so many other questions with regard to how often this agent should be given; what dose; and the disconnect between acute response and the chronic response data that you see here. There is some disconnect as far as disease progression. The FDA pointed out that these two maybe should be closer linked and the overwhelming evidence that you have a signal here, although unanticipated, is very large in magnitude. Those seem to be more relevant questions that would be addressed not from repeating this with a bigger N but with a study design that is perhaps more exploratory in nature.

Maybe just to ask the FDA, you know, you put in your slides the expectation of the correlation between acute rejection and chronic

rejection but I didn't see any references there. Could you comment a little bit more about what you would expect to see there?

DR. HERNANDEZ: Yes, this is well documented about the relationship between acute and chronic rejection. This has been documented in literature and registry data. As a matter of fact, the sponsor agreed that one of the factors that is important to take into consideration is to take into consideration acute rejection. Basically, I would say the natural history of these patients will be developing acute rejection; getting treatment for this acute rejection and infections. So, this meets the category of the multifactorial nature of chronic rejection.

If we are looking at a drug that is supposed to prevent or decrease the degree of chronic rejection, which is one of the leading causes after the second year of transplantation, it is completely reasonable to look at long-term outcomes and look at correlation with the degree of disease progression which would be reflected in the

histology of the lung. As I pointed out before, the limitations of defining chronic rejection only by biopsy and giving it weight similar to BOS, from my clinical perspective, is not adequate because, as I said before, it doesn't have the ability to predict the extent of the disease, the rate of this disease progression, and those are things that are very relevant questions. When we don't see this correlation between acute and chronic rejection, and if chronic rejection is really prevented, we would expect to see at least some evidence on the preservation of lung function and we don't see that. And that is one of the disturbing things that put a question mark in this difference in mortality.

It is not that we are questioning that these patients are not dying. There is no difference in the graft. The problem is are the patients in the placebo group dying because of other causes, because of the baseline characteristics of these patients, or are these patients surviving because they have better

starting points and not because of the cyclosporine? I mean these kind of questions when you don't see these correlations, when you don't see that everything is going in the right direction, then make you think about what is going on over here.

DR. TRULOCK: There has been an association between acute rejection and chronic rejection in most of the multivariate analyses that have been done. However, many patients develop chronic rejection without ever having a single episode of acute rejection. Furthermore, just because there is a statistical association in multivariate studies, that doesn't mean there is a cause and effect relationship between acute rejection and chronic rejection. That is, it is not a requirement that acute rejection occurs before chronic rejection can develop. All of these things are probably in the continuum of allo-reactivity that is not well controlled by the current immunosuppressive medications.

DR. HERNANDEZ: Yes, I agree with that

fact. Acute rejection could be not clinically evident and could be subclinical, and I agree that chronic rejection could be developed without acute rejection but that is not the rule. I mean, I understand that, for example, there are other factors that could be taken into account for the development of chronic rejection and acute rejection is only one but the rule, what you would like to see, is the patient who had acute rejection correlating with chronic rejection, not the other way. It is not the rule that the patient doesn't have acute rejection and develops chronic rejection. That is my point.

DR. SWENSON: At this juncture I think we probably need to get to the questions at hand. Dr. Prussin, you had a question about the charge and maybe we could have you ask your question and then Dr. Albrecht will proceed with the discussion to those questions.

DR. PRUSSIN: Dr. Albrecht, the charge as written has a fairly binary yes or no answer to the question and I think what we have seen here is that

this is a fairly unusual application. There is a lot of grey area. We were talking about p values and the fact that while these p values give you an indication they really shouldn't be thought of in a quantitative sense. So, I guess my question for you is if you could elaborate a bit and clarify--and I know from statute that approval of a drug such as this has the same requirements as drugs for larger patient populations that are not orphan drugs, but how should we manage that? Clearly, this is not the typical binary situation where we have Ns of thousands, and this is a population of patients that clearly has a huge mortality. Can you give us a little more instruction on how to factor that into our thinking? Thanks.

DR. ALBRECHT: You raise good points and you have very well summarized the challenge before us. The truth is our decision does have to be binary. As I mentioned in the introduction, we did have difficulty reaching the conclusion that would allow us to make that decision. So we did, in

fact, want to bring this to the committee to hear your perspectives on this with all the challenges that you have identified.

In the event that it is difficult to come to sort of a yes or no recommendation, it would be very important for us to understand both where you believe the data are convincing and where you still, in your own assessment of these data, have questions and where you believe the unanswered questions are.

I don't know if that helps but I think we all acknowledge that this is a very difficult scenario. I think we heard earlier during the day about there being promising potential here, something to that effect, and I think we certainly concur with that. I think we heard some analogies to gambling and I think, being regulators, we are not willing to gamble with patients' health and, therefore, we take these questions very seriously and are very seriously looking into your perspectives and how much has been demonstrated; how confident are we that the questions have been

answered about the efficacy of the product, mainly the safety, or how confident are we that there is still further information that needs to be gathered.

Parenthetically, I know we talked about the pharmacology/toxicology information. I didn't know if we needed more information on that, but our pharm/tox review is available. Just to repeat, the FDA only received those one-month toxicology studies. I could parenthetically say that for products that are administered chronically the FDA actually does request carcinogenicity studies. Those can be done preapproval or those can also be done as postmarketing commitments after approval. But we do not at this point have an aerosolized cyclosporine carcinogenicity study. There were carcinogenicity studies done with the systemic formulation.

DR. SWENSON: Dr. Venitz?

DR. VENITZ: I have a follow-up question, not regarding the process as much as the consequences. Let's assume that the committee

votes in favor of approving the product and let's assume you follow our recommendation, what are your tools to enforce a follow-up study as suggested by Chiron?

DR. ALBRECHT: As you have heard allusion to accelerated approval, that is a regulation that allows us to approve a product on a surrogate endpoint and then request confirmatory studies. At this moment, I do not believe that is the question on the table. So, in a setting of approving a product in the conventional fashion what we can do is request that a company commit to conducting a postmarketing study and we put that in the action letter. We put that in the action letter after receiving a letter of commitment from the company. I don't have the data as far as postmarketing studies for what the record of completion of those is but, again, our expectation would be that the postmarketing study would be done as committed to by the company.

DR. VENITZ: The reason why I bring that up is that somebody mentioned the survey that was

published, I think it was in "The Los Angeles Times," and only 50 percent of those promises are kept. I think that is obviously something we have to consider as we discuss the responses to the question. You are basically saying a letter is going to be written that is going to be agreed upon by both parties, but from that point on there is nothing that you can do.

DR. ALBRECHT: I am not aware that, other than having that commitment, there are other sort of regulatory steps that the agency has available.

DR. SCAIFE: May I just comment on that? I obviously defer to the FDA regarding legal requirements but I think it is true, what you say, that the commitment that the FDA issues to a sponsor is a legal commitment. This is not "would you like to do this?" This is not an option. Whether the Office of the Inspector General, in other words the chief counsel of the FDA decides to enforce, that is really a decision of the general counsel. If you actually look at the trends over the last few years and if you actually look at some

of the congressional activity, there are very strong signals that they are going to tighten this up. If you look, for example, at warning letters, a warning letter is issued by the FDA that is sanctioned by the OIG which is basically telling the company you have got to do something; if you don't there will be a legal consequence. If you look at the trending over the last few years, those letters have changed in tenor. So, those letters now almost invariably are actually issued and go through the OIG. That is basically saying an attorney is underwriting this. So, I think if you actually want to look at the statistics, when those letters are issued those postapproval commitments would be enforced. It has a legal meaning. It is legally binding. Up to now the question has been whether the FDA has been prepared to enforce it or not. But if you look at the statistics, OIG is getting a lot more blunt about it.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: Are we at a point now where people can begin making their comments on the

data, or are we not yet at that point?

DR. SWENSON: We are fast approaching it. Do you wish to start that? We could go ahead and focus on question one. You are first.

DR. SCHOENFELD: First I want to talk only about the mortality endpoint and the discussion that we have had about various covariate adjustments of that endpoint and various subgroup analyses.

First, people should realize that if you do a randomized study a p value is valid if you close your eyes entirely to the patient characteristics. You don't need to look at patient characteristics to justify a p value. What ends up happening is that if there is no difference you can be wrong five percent of the time, and rolled up into that five percent are all the times that you get a bad break or a good break with covariates. So, that is the first thing to realize. Covariates don't count. You don't have to look at them.

The second thing is if you do look at them, if you decide to split your data by one

covariate and to analyze within each covariate group and pool the results, in a randomized study the randomization carries over to each subgroup. That is very nice. That means that when you split there is no presumption--let's say you do a study and you do have imbalance in one group and you decide, well, I am going to split, you are now saying I am not going to use the original p value. I am going to do another p value, and that p value is also valid which, of course, is a big contradiction in people's minds. How can two different p values be valid? But they are. The fact is that there should be no presumption that because they are unbalanced in one covariate they will be unbalanced in other covariates because they were randomized within whatever subgroup you view, and this is something else.

Now, people often expect that imbalances will propagate down subgroups because they are used to observational studies, and in observational studies this isn't true. In observational studies you don't have that factor that randomization

protects balance through subgroups, and when you see imbalance in one subgroup you presume it is going to be imbalanced in other subgroups and you presume it is going to be imbalanced in things that you didn't measure. But a randomized study is not that kind of study. A randomized study is a study that if you didn't measure something you should assume it is balanced in it and not that it is unbalanced in it.

These are just sort of factors that people should try to understand. So, I thought that the survival analysis was robust and the reason is that, first, all of these subgroup analyses or these stratified analyses are somewhat post hoc and you can search for good p values or bad p values. You can make just as much of a mistake trying to kill a p value as you can to sort of create a p value. So, when you have a lot of them they are all suspect. So, you end up having to use your reason, watching them and watching them, and it is clear that the FDA did admit that they were driven to look for imbalances by another problem, which is

the problem that the rationale didn't fit. Okay? Then they were looking for something that would throw away the p value, and I think that that is kind of not a good idea. So, I think that survival benefit can't be thrown away because of all these various analyses. I think that you have to see it as standing. So, I wanted to say that first.

Now let's deal with the other analyses because I think the thing that the agency was sort of concerned about was sort of mechanism of action issues. That is, they said, well, so there is a survival difference and the mechanism of action doesn't seem to work because there wasn't an acute rejection difference. This is probably a harder problem.

First, one of the things is that I am used to survival being the primary endpoint and one of the reasons that survival is often the primary endpoint in studies is that when there is a survival difference you never can analyze for anything else because what happens is that the deaths cause biases. So, it is important to

understand this phenomenon. For instance, if there were three people who were quite sick and died right away even if it had nothing to do with the treatment, those are three people who are bad actors who have been pulled out of the placebo group. Okay? That automatically means that if you just remove those people and look subsequent to those three deaths every analysis is biased by the fact that the patients aren't balanced in the two groups.

In fact, this is a problem in general, that any analysis that is based on subsets that are defined after treatment began is biased. Those are problems that you have in really even analyzing FEV1, acute rejection, chronic rejection, all of those things where you try to remove survival. For instance, I was sort of scratching my head about the FEV1 because I couldn't really know whether it was due to the different amounts of follow-up time in the two treatments. This is also acute rejection. I mean, the FEV1 is particularly strange because actually the treated group had much

better FEV1 during the whole course of treatment, but this could actually be a benefit of treatment but we don't know because we don't have a baseline. Actually, it is not clear that baseline is even that meaningful. So, it is difficult to analyze.

So, when you look at these secondary endpoints, if the deaths that occurred without these secondary endpoints had nothing to do with the secondary endpoints, then those analyses would become unbiased but nobody really believes that is true. So, we have a bunch of biased analyses, and most of them actually would be biased towards placebo basically because I think it is reasonable to assume that the people who died would tend to be the bad actors and that would bias FEV. It would bias acute rejection, and so on.

Anyway, when I sort of count those up, FEV1 was negative. Acute rejection was negative. Chronic rejection was positive including both endpoints. So, I think the situation really is that we have a fairly robust survival benefit and our problem really simply is that we don't really

understand this acute rejection well enough to really use it.

DR. HERNANDEZ: Well, my main concern is acute rejection, of course, but my main concern is this, if I am following a patient with FEV1's and I have a drug that is going to graft rejection I would like to see that this FEV1, which is the physiology of the lung, to be preserved regardless of at what level they start, whatever the baseline. And, what I would like to see is that if the group that has not preserved that function, I would like to see the natural history of decline of these FEV1 declines over time. But if I see these two graphs to be parallel and the slope analysis doesn't show any significance and the slope is similar, then I don't see any preservation of the function.

DR. SCHOENFELD: Those graphs are biased anyway because in one group people are being culled out by death and in the other group people aren't being culled out so fast. So, a longitudinal graph over time where you are just looking at the marginal comparison isn't actually valid. It isn't

a valid statistic. That is, in other words, if you look at the FEV for all patients at, let's say, two and a half years you have six or seven people who are not in one group and who are in the other group. That is, the only valid analysis would be somehow to subset the analysis by the people who would have been alive on both treatments if they had had both treatments. You can create models to estimate that but they are all models and nothing is perfect. But just looking at the graph isn't really a fair comparison.

DR. HERNANDEZ: The only thing is not only looking at the graph but also to look at the incidence of BOS as defined by the sponsor. Really this is something that is bothering me. If you look at a drug that is preserving the lung function, that is preventing chronic rejection, you need to see a benefit in the function of the lung. That is something that you would like to see. I mean, you can't say to the patient I am going to give you this drug that is going to prevent chronic rejection but I am not sure the lung function is

going to be improved or is going to be maintained. That is my main concern.

DR. ZALKIKAR: I want to address a couple of things. There was pre-enrollment FEV1 available in the patients and the final FEV1 available in the patients and we took the difference in each patient between the final and the pre-enrollment FEV1, and even those differences didn't show any significance.

DR. SCHOENFELD: But that was already subsetted. That was only about half the patients who had pre-enrollment FEVs.

DR. ZALKIKAR: That is right. Of course, we had to impute the missing data.

DR. SCHOENFELD: I mean, I think it might be reasonable to say--I mean, I really am supporting this application now but I would think it is reasonable to say that there is something that we don't understand here. Okay? And, that is true but I think that then the question is do we have to understand everything in order to approve drugs? If things were completely the other way, if

there was no difference in survival but you did see a difference in FEV we would be in the same situation in a sense. We would still have the question of, well, how come it produced a difference in FEV and how come it didn't produce a difference in survival? Especially with a small study, we can't understand everything. Even with a big study we tend not to be able to understand everything.

DR. HERNANDEZ: My problem is this, if you are going to give a drug it does need to have a clinical effect. If you are giving this drug to prevent chronic rejection, this drug should have a clinical effect.

DR. SCHOENFELD: You mean a physiological effect.

DR. HERNANDEZ: Exactly.

DR. SWENSON: We should move on to other members. Dr. Hunsicker?

DR. HUNSICKER: First, I would like to suggest, Dr. Swenson--I may be totally out of order, but if we are going to go back and forth

between either the FDA or the other side arguing each point, we are never going to get anywhere, and I would really suggest that we limit the discussion for the time being to the committee members unless we have specific questions of the other people.

DR. SWENSON: I agree. We need to move on to a vote and I would like to at least open this up to the rest of the panel members here for any other questions or observations before we make that vote.

DR. HUNSICKER: I have a technical response to the question from--I don't know what your name is--

DR. SCHOENFELD: David.

DR. HUNSICKER: David. There is, in fact, a way to look at the FEV1 data that hasn't been done so we can't use it today. You can do a mixed model analysis so long as you include the last measurement that was associated with what caused the failure. And it has been shown that that unrelieves the bias of informative censoring.

DR. PROSCHAN: That is not true. I mean, it depends on whether it is missing at random

versus not missing at random.

DR. HUNSICKER: We can discuss this later on but there are additional analyses that could be more informative than what we have.

DR. PROSCHAN: That is true.

DR. HUNSICKER: I would like to give my approach to this which I offer up because it is really opposite to yours, Dr. Schoenfeld. Where we start out in this application is that there was a very well formulated hypothesis that use of this agent would affect acute rejection. We didn't find that. We find now no effect on that. So, we start with the usual presumption that if you have something that turns up in a secondary analysis this is considered hypothesis-generating and needs to be then retested.

I can practically quote Flemming on this who says that if you have a secondary outcome that is significant or if you have a subset analysis that is significant, almost irrespective of the p value for it, if you repeat it only about a third of those are confirmed when they are then repeated

because there is an effect of regression to the mean. You have chosen them because they were further, more deviant from the mean.

So, we start here with why we should not or should look at this as being different from the usual circumstance where the primary outcome was not recognized, was not achieved, but a very striking secondary outcome has been found either in a subset or with a secondary thing.

This really is related to Dr. Helms' comment where he says that this is sufficiently strong that it strikes you between the eyes. That is true. There is a strong thing here. So, how do you evaluate this kind of a thing when it was not the primary question?

There are two ways that you look at this. First of all, does this have a credible underlying hypothesis? Now, I would say that with respect to the hypothesis that local administration of an immunosuppressant agent might be effective in preventing chronic rejection is credible but it is certainly not something for which there is any

experimental data. This is something that is really de novo. It is not impossible. It is a rather attractive hypothesis but it is not based on the same kind of data that we have for the assumption that immunosuppression would affect rejection in a broader sense.

So, that is a weakness in the hypothesis. Then the second question, and this is why I do believe that looking at the relationship between the deaths and all the other stuff is relevant--we have a circumstance where there is no question; it is absolutely clear that there were fewer deaths in the group that was treated. That is not a matter of statistics; it is a matter of fact. So, then we can ask ourselves is this difference in fact something that was the result of the application of the treatment or is this a fluke, if you will. This is a small study so flukes are more possible. We have the problem that I referred to before of having sort of chosen this to bring forward because it was an attractive, unexpected finding. That is why we are here. That is not true for Dr. Iacona.

I don't mean to imply that he is in quite the same situation. He put out the hypothesis that there would be a good outcome. But we are looking at it because this is one of the unusual circumstances where you have a really striking p value in an unexpected circumstance. So, we have to deflate the p value for that.

Then we look at the circumstances that deal with the question of whether, in fact, it is credible that this thing is affecting chronic rejection and, thereby, is preserving people's lives. That the lives were preserved is unequivocal. Then one question that could come up is, well, there was no difference in acute rejection and here I have to say that what I consider to be an appropriate analysis actually favors the company rather than the FDA. There is no reason why acute rejection should be the prerequisite for chronic rejection. As the FDA probably knows from other circumstances, I have argued in the past that what we call chronic rejection is generally a mixture of immune and

non-immune events. Everybody has agreed upon this, and you don't ever quite know how much of this is immune and how much is non-immune. In fact, even earlier failure, whether it is graft failure in the case of the kidney or death in the case of lung transplantation, could be the result of a process added to something, what I have called in my area which is nephrology interceptant [?] slope. If you start lower you are going to get to your endpoint sooner than if you started higher and it has nothing to do with the rate at which chronic damage is being done. So, there may be a difference in chronic rejection or fibrosis that has nothing to do with acute rejection.

On the other hand, what we have seen is parallelism with all of the limitations of the methods that we are using--parallelism in the outcomes in terms of the FEV1 and other things like that. So, at the bottom what I wind up with is that this is a very promising therapy but it is not a therapy that is now established. This is in a way very strong hypothesis generating. So, has

this reached the status of substantial evidence from well designed and executed clinical trials, or something like that? But I don't think we have gotten there.

I do want to say one last thing, which is the Helm's comment. I find myself worried about the idea that we would be chased into approval because if we didn't approve nothing would ever happen again. I think that would be a very bad precedent because then all that a company would have to do in coming to this group is to put you in the position where, if you don't approve the drug, nothing is ever going to happen. There are lots of ways in which this drug can be studied further. It is not this group's business to figure out what happens if we don't approve it. The question we have to deal with is whether it has reached an approvable status or not.

DR. SWENSON: Dr. Gay?

DR. GAY: We have been given a challenge that our cardinal task is to consider alive or dead. There are significant things, in my opinion,

that compromise our ability to decide this. We cannot underestimate the potential bias that occurs with the fact that there are more patients who underwent double lung transplantation in the treatment group as opposed to the placebo group. We have different criteria for listing for double lung transplantation than we do for single lung transplantation. The patient population is younger. There can be potential selection bias because the wait list time tends to be longer with the double lung transplant population. Thus, if they can get to transplant they tend to be potentially healthier at the time that they are transplanted with a lack of other potential problems and medical issues that could compromise their survivability.

I am concerned that this puts into this process a profound amount of bias, and my concern is, as optimistic as I would like to be for this to be a therapy that we should consider, that the explanation of the change in survivability can't be easily explained by that and that alone as opposed

to factors that we cannot determine with the lack of change in FEV1, the lack of change in the presence of acute rejection, and with this I do feel that a significant amount of increased investigation is going to be required to make absolutely sure that the difference we are seeing between alive and dead are secondary to the therapy. Because once we move to approve our first therapy for lung transplantation I think we can guarantee that it will be utilized in full force and we must be cautious in doing so.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: You know, this is a very difficult decision for me. One of the things I was struck by is that really small trials go both ways. That is, in this particular trial you would think that because it is a small trial and you are seeing more placebo deaths, then those people who are dying are the sicker patients. Therefore, the remaining patients in the placebo arm should be healthier than the ones in the cyclosporine arm. So, I would expect in a small trial, even if you

see a benefit at first, that the curves would tend to come back together because of that survival of the fittest phenomenon--you know, you have only the fittest surviving in the placebo arm and everyone surviving in the other arm. So, I would expect them to come back together and the fact that they didn't come back together is something that I think influences me when I try to think about is it real or not.

The statement has been made that no IRB would allow another randomized trial. Earlier than that a statement was made that if you were on the DSMB you would definitely vote to declare treatment benefit. I think that is not true at all. I think that a DSMB would be struggling just as we are and that it would not be a slam-dunk. In the cardiac arrhythmia suppression trial there were 19 events in one arm and 3 in the other arm and they didn't even want to be unblinded yet. They said whichever way it went, it is too early to tell. So, that was 19-3 and they didn't even want to become unblinded.

So, I think the idea that this is a

slam-dunk and the question has already been answered is not true. I struggle with this and I do agree that the survival result seems to be robust to various sensitivity analyses and, you know, that makes me feel a little better. I agree with Dr. Schoenfeld. That does make me feel a little better.

Then the question is what degree of evidence is required. If it is like a civil trial where you just need a preponderance of evidence there is no question in my mind that that has been shown. If it is like a criminal trial where you need proof beyond reasonable doubt, I am not sure that that has been shown. So, to me, it is somewhere in between those two and, you know, the question becomes how much evidence do you need.

DR. SWENSON: Miss Drittler?

MS. DRITTLER: I am a lung recipient and this is sort of getting away from the questions presented to the committee but what I wanted to know--the first year and a half after my transplant I went through approximately three rejections, one

very serious one. Of course, nothing was available at that time. After that year and a half I have not had a rejection but, as we all know, rejections can occur at any time. If I were, say, in my fourth year to encounter this problem, would the inhaled cyclosporine be beneficial to me at that time? Because I am assuming that these people who were in the study were put on the inhaled cyclosporine immediately after transplant and followed for the two years. So, I want to know is it beneficial to somebody--Dr. Suss stated that she was put on it a year and a half or two years after transplant. Is this going to be the case, that it will benefit those of us? If I hit my five-year survival rate, which I don't believe in, will I be able to take it to prevent or stop rejection?

DR. SWENSON: Well, I think that is a pretty hard question because it wasn't studied in that fashion. Maybe someone from the company might just spend a minute or two, not any longer, just answering her question if you think you have something to either agree or to put a different

light on it.

DR. DILLY: Our belief is that we are preventing or slowing the trajectory of chronic rejection so our hypothesis, which is worth testing and we have already seen the RAR data being very provocative, is that the drug would benefit patients already some way down the road from their transplant. But that is not the basis of ACS001.

MS. DRITTLER: Thank you.

DR. SWENSON: Dr. Barrett?

DR. BARRETT: I just wanted to again reiterate that this was really not designed as a registration trial. It is a Phase II trial, not even with the benefit of a formalized statistical analysis plan prior to proceeding. So, applying the conventional statistical criteria, as has been done by both the agency and the sponsor, makes it very difficult and I think is the cause of all our unhappiness as we sit here and see the data summarized.

Having said that, I do believe Dr. Schoenfeld's assessment of the forgiveness of the p

value given--maybe short-sighted--but the attempt to randomize patients as was done in this trial. However, I also feel the way the FDA has done their subset analysis was absolutely relevant in order to define which criteria are in fact sensitive to these results. Because of that, it makes it very difficult. I believe that the signal is, in fact, valid and robust but I don't know if I would feel comfortable generalizing the magnitude of this effect from this one trial in a subsequent study.

DR. SWENSON: At this juncture I think we should go ahead and take the vote, unless there are any committee members that feel that they really need to say one more thing.

DR. VENITZ: Yes, one more.

DR. SWENSON: All right.

DR. VENITZ: I am not a statistician but I am trying to use informative decision analysis to approach the problem that we are facing because I think everybody would agree it is a close call. The way I approach things like that that are a close call is that I am going to look at what is

the likelihood that we are right or wrong and what are the stakes. In other words, I do what Helms suggested. I am a rational gambler. And, I think to some extent, whether we admit it or not and that includes the FDA, we are rational gamblers when we review evidence to decide what the significance is both in terms of the statistics as well as the consequences.

So, I think, like most of you, I am obviously not convinced that this is beyond any reasonable doubt for proving that the mortality benefit that was demonstrated was due to the treatment as opposed to something else that we don't know about, no matter how much we try. However, I do think that it is plausible, and I do think that it meets the civil trial standard. It is the preponderance of the evidence; not beyond reasonable doubt but preponderance of the evidence. So, there is some 30 percent likelihood of coming up with the wrong answer, that we find a difference that really doesn't exist.

Counteracting that is the fact that it is

a large difference in terms of the mortality. That is all I am talking about. And, counteracting that is the fact is what is the competition that we are trying to beat right now? There are no drugs approved. It is a dismal disease. Right now we have a 50 percent mortality rate with the current treatments. Maybe there are other ones being investigated. So, I think the stakes are high and I am willing to take a chance on the likelihood that this might be a study that doesn't prove beyond any reasonable doubt that the drug actually works.

So, in my final summary then, I would conclude, even though I have this doubt about the likelihood that this is real, the stakes, to me, favor saying that this is sufficient evidence. That is a word that is in the question here, I think there is sufficient evidence to say that the survival benefit is due to the treatment that patients might benefit from.

DR. SWENSON: We will go ahead and begin the voting. I will ask Miss Schell to give us your

vote.

MS. SCHELL: I am Karen Schell and I am the consumer representative. I would just like to add one comment before I vote. Looking at the question on sufficient evidence, I am a practicing respiratory therapist and I also do perform FEV1 pulmonary functions on a daily basis, and I think those objective measurements are very important in a study. And, because of the limitations of this study I think the study needs to be bigger. I think that whenever there are unanswered questions more research needs to be done. So, I am voting as a no.

DR. SWENSON: Dr. Sampson?

DR. SAMPSON: It is obviously a very, very difficult decision. I have listened to my statistical colleagues and my clinical colleagues and have wrestled with this more than I care to admit, and I think all I can conclude from this single trial is that the observed mortality difference may be due to treatment. There is the other uncontrolled data, the ACS002, that is

supportive but it is certainly uncontrolled.

My basic problem, as has been stated by so many other people, is if it is due to treatment the question is why, and what has been demonstrated to cause the survival difference. I don't see strong enough evidence, certainly not in acute rejection. In fact, at least by the sponsor's own analysis, acute rejection rates are higher in the CyIS group. And, I think there are a lot of other statistical difficulties in the analysis of the chronic rejection data, both in the definition of the endpoints and the analysis.

DR. SWENSON: Your vote then is no. Dr. Schoenfeld?

DR. SCHOENFELD: I guess I will be very brief. My vote is yes.

DR. SWENSON: That was brief. Dr. Proschan?

DR. PROSCHAN: To me, what you want is compelling evidence to offset any potential harm that there might be that is hard to see based only on 100 patients on the safety data. So, my short

answer would be no, that it is not sufficient.

DR. SWENSON: Dr. Barrett?

DR. BARRETT: I am going to key in on two words, "sufficient" and "survival" and because of that I am going to say yes.

DR. SWENSON: And I will reserve mine till the end and move on to Dr. Moss.

DR. MOSS: The thing in making the decision for me is that based on the small study the outcome of five or so patients, if they had gone the other way is going to change the standard of care for a thousand patients each year based on that outcome of just a few. I think there is some precedent with the gamma interferon trial, with the steroid trial for ARDS of two small studies that when the companies were able to go ahead and do larger trials, it showed that those things were not true.

On the flip side, with the ventilator strategy for ARDS the paper in The New England Journal of Medicine it showed that the ventilator strategy worked and work now shows that, in fact,

it was true. So, I think it was possibly due to the studies. But I don't think we should change the practice based on a small study where a few patients can weight the whole outcome so I would say no.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: I sort of approach this question in the setting of the thousand shades of grey that were dealt with by something that others have said, and that is where is the greatest harm? I think the tradeoff we have is believing the survival or believing just about everything else that would make sense about it. I think, in my view, the greatest harm would be to not proceed with approval. So, it is a yes.

DR. SWENSON: Miss Drittler?

MS. DRITTLER: Well, of course, as a patient I have to look at the survival rate and the application that it has on chronic rejection, and my vote will be yes.

DR. VENITZ: I have said my piece. My vote is yes.

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: I have said my piece and my vote is no.

DR. SWENSON: Dr. Gay?

DR. GAY: Considering all the factors involved, understanding that this is a therapy that will be adopted across the board, understanding the limitations of the sample size and the potential for a skew on this, I must vote no.

DR. SWENSON: Dr. Mannon?

DR. MANNON: With due respect to the thoughtful presentations by both Chiron and the FDA, and I also empathize with the patients for coming here, as a solid organ transplanter, you know, facing life and death is a difficult issue but, be that as it may, my vote is against approval. Again, it is because, to me, though the survival effect may seem to be a statistically and a reality-based issue, it is not clear to me what caused that and it is not clear that the drug itself was responsible, particularly when only half of the individuals on that treatment completed the

treatment.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: I usually like to think of things in mechanistic terms, but in this disease we don't really understand the mechanisms enough and I think ultimately the uncertainties are much greater but ultimately it appears relatively safe. We haven't seen evidence of toxicity. There is a potentially huge upside so I will vote yes.

DR. SWENSON: Dr. Tisdale?

DR. TISDALE: Well, I am basing my decision on the fact that this was a secondary endpoint in the study, that it did come out in the original planned analysis of the study. There was a clear survival advantage. I am not saying that I believe that there is a connection between the drug definitively and the survival advantage but, when considering everything on balance, I am going to have to vote yes.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Having been involved in treating individuals with rare diseases for the

last 20 years, I crossed this bridge about 20 years ago actually when I first started. My vote is yes for the reason that I believe this offers probably the best promise at the present time and has sufficient data to support that.

DR. SWENSON: My vote is no, not overwhelmingly no but for reasons that have been stated here, I don't think it is proven and I think that the issue could possibly be resolved faster than what has been stated in a smaller trial. If this is really as strong an effect as it is, it should be borne out very quickly. So, I don't think the evidence is yet there.

What this means is that we have a tie vote. Dr. Albrecht, how do we proceed here with the second portion to this question?

DR. ALBRECHT: I think next time we will invite an odd number of consultants--

[Laughter]

If I may ask you to please move to the second part of the question, I think it would be very helpful for us for those who believe the

evidence is sufficient to please address the yes part of question 1(a). For those who feel that the data are not in, to please give us suggestions about additional studies. So, please discuss either option yes or option no.

DR. SWENSON: What I would ask then--and we will go through the order just as we did--is that those voting yes please answer (a) and those voting no to offer their suggestions. So, Miss Schell?

MS. SCHELL: I voted no and I would like to have more data concerning the donor and also post-operation, some of the other factors that would be sufficient like the FEV1 and less decline. Basically, I would like to know more about the donors' lungs before they were donated.

DR. SWENSON: Dr. Sampson?

DR. SAMPSON: I voted no and, as I started to say before, I think there is a struggle and I think there are certainly very strong arguments as to why CyIS would work. But to do another two-year treatment study with a survival endpoint and

reasonable follow-up would be a lengthy undertaking. I would encourage the agency and the sponsor to work together to design a prospective, randomized, blinded trial but with a more innovative design. I don't know if that means doing something like low dose versus high dose to increase enrollment, as has been suggested, or introducing a reasonable surrogate endpoint for survival that could be measured earlier than waiting for it two or three years post treatment.

I have heard arguments pro and con why FEV1 might be such a surrogate. I think it is really critical to identify and agree upon important baseline variables, and perhaps even employ some sort of stochastic, dynamic balanced randomization scheme that would try to keep all these variables between treatment groups reasonably comparable and maintain the blinding so that we would not have a discussion like this again.

As is usual in regulatory studies, the study protocol and the SCP should spell out the objectives very clearly; the primary variables for

analyzing these; and the primary analytical methods for the primary variables. I also think that this is the kind of study, given the kind of difference that we have seen up to now, that would benefit from some sort of sequential design which would allow for an early stopping if, in fact, the differences persist of the magnitude that we are seeing so that a quick decision could be reached.

DR. SCHOENFELD: I won't be as brief this time. I am going to look--

DR. SWENSON: I should say that is Dr. Schoenfeld. We need to keep that for the record.

DR. SCHOENFELD: I am sorry. I think that in regards to 1(a) it is sort of a difficult situation because this study would indicate that the biggest difference created by this treatment was survival. I mean, this would be the thing you would want to look at as the thing that would be the most likely endpoint to show a difference in a subsequent trial. As I have said before, even analyzing any of these other endpoints that would give you a good idea of the mechanism is very

difficult in the face of a big survival difference. This was the big difference, by the way, in the ARDS. We still don't know why 6 mg/kg works. Because, in fact, all the oxygenation parameters and all the various parameters don't really show a difference between 6 mg/kg and 12 mg/kg--I am referring to the study of low versus high pressure ventilation for ARDS. None of those mechanistic things work because you can't really compare them because of the difference in mortality.

So, I think that this leaves a big problem for someone coming to a future trial because their best shot is mortality and the other things are going to be probably fuzzy, like they are now. I think that is something to realize. So, the big advantage they will get in doing another trial is that mortality won't be a secondary endpoint and there will be now two trials, and maybe a multicenter trial so they will get some of these other things dealt with.

So, I think that in terms of 1(b) you end up having to repeat the trial and it would sound

very funny if you then argued--you know, you wouldn't have any of those secondary endpoint arguments at that point.

I don't know how you could balance it because I am sure that, no matter how carefully you stratified the trial, if people were really trying to knock it down by finding different covariates you could find some. So, I don't think there is any way of perfectly balancing a trial. So, it would be a confirmatory trial and that is probably what should be done if you want to go forward.

Now, in terms of 1(a), this is always a problem, how to generalize clinical trials either from one institution or from--so I just answered 1(b) and I guess the answer to that is you are going to have to do another survival trial, bigger and multicenter.

In terms of generalizability, that is always a problem in clinical trials, generalizing from the few patients you treated to the patients you didn't treat. This trial randomized about five percent of the patients in the United States that

have this disease. That is, you randomized about five percent of the people which is much better than we did in ARDS network. So, I don't know how you can answer these questions. Nobody knows whether you can generalize. Usually what you end up doing with clinical trials is you close your eyes and you generalize.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: For what additional information would be needed, to me, I think you do have to do another randomized trial. I don't think you can get away with a single-arm trial where mortality is the primary outcome. And, I don't agree with a comment made earlier that it could be much smaller. I think that is an invitation for disaster again because then you could get a p value that is 0.10 or something and you might also get the baseline imbalances. So, I do think it has to be a larger trial, perhaps multicenter.

I am not as concerned about the issue of generalizability. To me, the issue of generalizability is, you know, University of

Pittsburgh does a lot of these and maybe they have learned something about how to deliver this aerosolized cyclosporine and maybe other centers that are just starting might not know that. So, to me, that is the issue of generalizability. Is there anything special that Pittsburgh learned and other centers that try to do this might learn the hard way? So, to me, you have to do another trial where survival is the primary outcome, a randomized trial.

DR. SWENSON: Dr. Barrett?

DR. BARRETT: I voted yes. However, as I mentioned before, I think there is very little that you can generalize from the previous study, and for all of the analyses that the FDA showed there are several factors which make the existing data, primarily due to the small sample size, very suspect.

One of the most important things I thought was the idea that the acute rejection doesn't necessarily correlate with the chronic rejection. And, one of the things that I am more suspicious of

is the maintenance of the survival benefit in the face of limited dosing and/or exposure. It simply may be that we don't understand how to dose that particular facet of rejection progression. It is an interesting finding. I don't know if I would walk back into the quicksand and do another survival study though. I think there are better studies to do now with the idea of really figuring out how to dose this agent.

I think there was a rationale for inhaled cyclosporine at the very beginning that prompted this trial, which I think is probably still there. There is, for sure, a regional delivery advantage, however, it is probably not maintained by conventional pharmacokinetic behavior so we simply don't understand what is the local exposure requirement in order to maximize the benefit of this route of administration.

So, as far as studies go, I think a combination of preclinical models as well as different dosing scenarios where you consider low and prophylactic regimens to be more beneficial.

DR. SWENSON: I voted no, and I have mentioned my thoughts here. I think another trial, maybe two to three times larger than this one that might incorporate several centers and, of course, I think with the problems that develop in the design and then ultimately coming here could be corrected from the start. That is, we would have all the preliminary data. There would be no question about loss of data in a prospective study. I think another study of that magnitude would be what would be necessary, and possibly a stopping point could be agreed upon early. If, in fact, this major survival advantage persists the study could be concluded earlier on the basis of that, given what we have seen with this study. Dr. Moss?

DR. MOSS: I really don't have a lot to add to what Erik just said. I think that the results need to be confirmed in a larger multicenter study where the study is performed more rigorously and, of course, add some longer-term outcomes that won't preclude people from voting yes to approve the drug, but that that would be kept in

mind in terms of carcinogenic possibilities.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: The big issue in generalizability is what was observed before, that about two-thirds of the patients in this trial weren't on up-to-date immunosuppression. So, for all programs, including Pittsburgh, I think that is a question that remains in terms of using this regimen today.

I think the other major issue is that if this is effective, if the results of this trial haven't misled us due to happenstance, or whatever, then there needs to be some inventive thought about how to look at it with things other than biopsy, FEV1 and other things which have not correlated with the outcome.

DR. SWENSON: Miss Drittler?

MS. DRITTLER: Again from a patient viewpoint, I feel that what I am reading in the data with the survival rate, the safety problems don't seem to exist. I just think that having been very sick for ten years, hoping something would

come along as many patients are doing, grasping at straws actually, this seems to be something that could be very profitable to the lung transplant population. And, I just feel that it is an important thing at this particular moment not to preclude necessarily further studies. I think that could be necessary but in the meantime there will be patients dying who might profit from this. Thank you.

DR. SWENSON: Dr. Venitz?

DR. VENITZ: Obviously, I voted yes so I am down to "yes-(a)" I guess. Confirm efficacy; establish mechanism of action; expand safety; and optimize the dose. Those would be the outstanding issues in spite of the fact that I did vote yes. Confirm efficacy in a larger, more heterogeneous population. I think mortality is definitely going to continue to be an outcome that is of interest because you have to come up with labeling language that reflects whatever the committee recommendation is and the FDA final judgment on this is going to be, but I think also an assessment of mechanism of

action would look at FEV1's. It would look at the relationship between some of the markers of disease progression relative to survival to understand what actually happened in this study. Expanding safety, I think that is question number two, is to look at long-term safety five-year safety data. It was already mentioned that there is a concern about the incidence of cancer as a result of chronic immunosuppression even though you would think, due to the low systemic exposures, that is minimized but, nevertheless, you would like to have some empiric data.

Lastly, I don't think the dose--and I agree with Dr. Barrett on that, I don't think this is the optimal dose, as it usually is not. I would like to believe that it is a safe and effective dose but I don't think it is an optimal dose. So, I think in addition to efficacy, safety and mechanism of action, additional dose optimization studies are appropriate. In particular, what I would be interested in would be the dosing interval. Right now I don't know whether the drug

has to be given three times a week. It could well be that you could give it once a month. It could well be that you don't have to give 300 mg and expose patients to the hassle and the inconvenience of being bronchodilated, getting lidocaine and then sitting in front of a nebulizer for ten minutes. So, I think there are some dosing questions that should be addressed in clinical as well as possibly some of the preclinical studies as well.

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: I was a no voter. One of the committee members down the line there, whose name I can't see, suggested that we should not exclude the possibility of preclinical studies. I am, for one, not absolutely sure that we have an established mechanism that we are working towards. It may be that it is obvious to some that locally administered immunosuppression should work. It is not so obvious to me. So, I would not forget the possibility of doing preclinical studies that are really properly designed to see whether topical administration of this in the lung transplant

setting--which you can do and it is really unique in the lung transplantation that you can do this--is effective in preventing chronic rejection. I think this is a very interesting question and that shouldn't be forgotten.

With respect to the clinical trial, it seems to me very straightforward, as has already been said, that the next trial should have mortality as its major endpoint. That is where we are, and if the next trial shows an advantage in mortality it doesn't make any difference what else is shown. That confirms it. At this point, this is now starting from "we think that this might work" and that would just nail it down. But I would hope that that trial would have defined in advance very well how to at least look at the issues of fibrosis and function, these being the two major things that are involved in chronic rejection of lung, as well as the other organs. So, I think of things like the endobronchial biopsy that was being discussed--some knowledge of what is actually happening to the lining of the bronchi

which is where the fibrosis is going on would be very helpful in eventually being able to analyze this.

Finally, with respect to the study size, I would just caution you that virtually always when you have a striking effect like this the next time you look at it the effect is much smaller. So, do not assume that you are going to get this size of effect the next go around even if this is a real thing. You have to power the next trial sufficiently to be able to detect a difference that would be convincing to you and important to you irrespective of it is the size that we see in this trial. So, I think it is going to wind up being a fairly large trial.

Then you get into the issues of can you ameliorate the ethical quandaries by having a different randomization scheme, 2:1 rather than 1:1 and things like that. These are well within Chiron's and Pittsburgh's ability to figure out and I don't think it is going to help us any for me to go on about it. So, basically, it needs a new

clinical trial and I would love to see some basic studies.

DR. SWENSON: Dr. Gay?

DR. GAY: I voted no because of the problematic nature of attempting to define mortality in the transplant population and the causes for mortality. Unlike the oncology studies where mortality usually results from progression of the primary malignancy, with factors related to both rejection and infection and side effects from the immunosuppression, I believe mortality becomes very hard to power for. Where a significant impact may be present is the fact that we have no therapy whatsoever that intervenes on chronic rejection, and if we can have a proven theory that affects BOS-free interval, if we can show that you can go longer without developing BOS with a therapy as opposed to without it, I think you will find a therapy that will have significant positive benefit and a reasonably easy course for possible approval. So, I would attempt to put together a randomized, controlled trial that would deal as the primary

endpoint with BOS-free interval in enrolling a patient population post-transplant.

DR. SWENSON: Dr. Mannon?

DR. MANNON: Again, I was a no vote. To reiterate, I think a proper prospective collection of data, so a randomized trial, and also with balance of the two critical components, that is double versus single and acute rejection rates. I think that is a big sticking point for me in the analysis of the initial data.

I also think it would be important to have a spelled out standardization of immunosuppressive strategies whether it is one center or multicenter, as well as standardized strategies for patients with acute rejection so that all patients are receiving similar therapies. Then, if they fail those therapies there are appropriate outcomes.

Obviously, a formal safety data monitoring board, with an appropriate stop point, the endpoint being survival. But I also think, as Dr. Hunsicker pointed out, an opportunity to collect mechanistic data as additional information, including

standardized time points for FEV1 and bronchoscopy, but also maybe localized as well as systemic measurements of allo-immunity because you have a small group on specific therapy and that may actually shed some light even if the study is not huge.

Finally, I think we need some long-term safety data. There was a discussion of potential malignancy from this drug, but cyclosporine also stimulates TGF-beta and whether this local effect may in the long term actually promote fibrosis indirectly, which we don't know, is something else that I think needs to be answered.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: Most of my comments have already been addressed. In terms of generalizability of the study, I think the population that is being looked at could be more ethnically diverse than the small study in Pittsburgh, and that probably would be addressed if it is a multicenter study.

Also, the whole issue of an inhaled

formulation in terms of SOPs for nebulization. I gather that inhaled lidocaine is not approved so that whole usage and how that is delivered should certainly be standardized.

DR. SWENSON: Dr. Tisdale?

DR. TISDALE: I was a yes but, as I said the first time around, my decision was based mostly on a risk-benefit assessment. Here the risk seems to be extraordinarily low and the benefit is possibly extraordinarily high. So, that weighed me. I sat right on the fence the whole way around the table until it came to me, and the whole morning as well.

But when it comes to the question of generalizability, that is the yes-man's question. Certainly the control group correlated well with the experience that is out there, the broad experience for transplant. This represented a very sizeable fraction of the transplant patients over that period of time. So, any new therapy that is tried, for example in bone marrow transplant, is always a very small fraction. A hundred things are

different about each protocol so in this I was actually encouraged by the fact that there was a big percentage of patients that were studied and that the control group looked just like the broad experience of transplant patients. So, I felt like there was at least some generalizability of this information.

We have had a lot of people bring up the issue of the collection of the data being problematic in this study and, certainly, the study wasn't designed as a pivotal study for FDA approval of this drug so there are a lot of problems with the collection of the data but the endpoint that we are looking at, which is survival, was a secondary endpoint and this is not a subtle endpoint. I mean, you are alive or you are dead so that is simple to look at. And, whether you look at it a week after the study closed, a year after the study closed, there is no arguing about whether or not there is a survival advantage. So, to design another randomized study with a survival endpoint is the study that we already have. It was a

randomized study with a survival endpoint, and the survival endpoint was statistically significant.

So, you know, what is necessary for me to move it on--you know, not everyone is going to adopt this. People will look at the study when it comes out and realize that there are problems with the study and not everyone is going to do it. Certainly, it requires further validation in another study I think which doesn't necessarily need to be, in my mind, a randomized, controlled trial. There are many different ways to get at the questions that still remain beyond the survival, and the survival can be compared, I think, to the existing survival data because we have heard over and over again that this survival curve has not changed in more than a decade.

So, I certainly feel comfortable with comparing whatever is seen in a subsequent trial to the existing 50 percent survival rate. I don't think that is likely to change in a big way, and if the next study is a negative study everybody is not going to be giving inhaled cyclosporine. It is a

pain for the patients; it is a pain for the placebos. They have all demonstrated that it is not something that people are going to wildly run to without further information. So, I think a subsequent trial that is not randomized is certainly sufficient to get at the questions that weren't addressed in the original randomized, controlled trial.

So I agree that the things that need to be addressed next is that we need a study that confirms the efficacy on survival. That is easy enough to do in a study that is not randomized. We need to better establish the safety. That is easy to do in a study that is not randomized. And then optimize dosing, which I think would be very difficult to do in another randomized, controlled trial. So, those are what I would see as the ways to move forward on whether or not this is actually generalizable.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I was a yes voter, and I think that, number one, my greatest concern with

the study was the fact that there was an imbalance in the double lung/single lung transplants and that that plays strongly into survival benefit.

As far as generalizability, I have questions about how generalizable these studies are, and I believe that that should be expanded in a good controlled study in the future. I would recommend basically having four arms, which would be double lung, single lung, a low dose versus the standard dose, which would answer some of the questions regarding both the ethics since we really don't know what the dose is in this particular study group. I think it would be acceptable to the patients and probably get to the answer about survival.

DR. SCHOENFELD: I just want to say something because this keeps coming up as double lung and single lung. I think that the stratification by double lung and single lung as was done in the analysis pretty much shows that the benefit occurred in both groups, and when you control for single and double lung the relative

risk stays exactly the same and the estimates stay the same. So, to consider that as a major problem with the study I think is not borne out by the data. I think that the FDA would even agree with that, that that isn't the primary problem with this data. Their stratified analysis on that simple stratification was still highly significant. If that was the problem, it would just go away, the significance.

DR. ZALKIKAR: The model that included just the single versus double lung, yes, the data was significant, just that one factor at a time.

DR. SWENSON: Dr. Albrecht, hopefully, we have satisfied your charge here on this question. It looks like it is a split and I don't think the yes/no are really that far apart. We all have concerns and we all have, obviously, great hopes for something like this to work and hope that a speedy answer could be obtained. Shall we move on to our second question?

DR. ALBRECHT: Yes, please, and I think I will elaborate a little bit on it to see if I can

probe for some more comments and advice. The second question is fundamentally focused on safety, specifically, has the safety of the product been adequately characterized for its intended use?

I know we have heard some of these comments already during the past discussions, but in these deliberations please consider both the amount of preclinical information and the clinical information that is available on the administration of cyclosporine, as well as the vehicle, through this route, and the number of patients that have been exposed to the inhaled cyclosporine in this application at the proposed recommended dose.

Here is where I would like to just elaborate a little bit more, if I can, which is if you answer yes to this, and especially this in addition to question one, here is where I would really like a lot of comments from you, if possible, about what you would envision in the labeling, I think both the positive as well as what kind of cautionary or negative language you might include. So, specifically for what population

would you suggest, if you are advising that the product be approved, that it be labeled for what patients perhaps should receive the product and where the data may in fact be limited or absent as far as patients that perhaps shouldn't at this point be advised or recommended to receive the product.

Also, it would be very beneficial if you could comment on the dosing regimen, the preparation, the administration route, the dosing intervals and the duration, again basing this on the information that we have in the application. How comfortable would you be summarizing the information in labeling and, again, what kind of cautionary information do you believe or would you recommend that we consider putting in the labeling regarding what isn't known about the product.

Also, if you could, because I think as we have heard and has been stated, the difference in mortality that has been presented is fairly dramatic and, at the same time, there are not differences in some of the other endpoints like

acute rejection, BOS, FEV1--how much of this information would be valuable in labeling; how much of the information might not be ready for labeling based on the comments you made about need for corroborative data, and so forth.

So, I would like to hear as much discussion as you can give to the "yes" part of the question. I notice that we were getting recommendations both on "yes" and "no" so on the "no" side it would be really useful--and I know we heard a lot of comments about traditional studies, both efficacy and safety and dosing and preclinical, but if you could just elaborate in any way that you can specifically on study designs. We heard some suggestions for randomized, some non-randomized, but if you could perhaps give some further details about study designs that may be coming to mind as you go around the table.

DR. SWENSON: Well, we could do it in the same fashion as before, a vote, but maybe as much as we have talked already, if the committee would be willing just to go ahead and take both in turn

individually. Do I have any strong dissent for that? Just for fairness, we will start on the other direction and I will ask Dr. Brantly to start off.

DR. BRANTLY: Well, if yes, I would argue based on the study I read--I would say the population is lung transplant. I would make it no more specific than that.

As far as the dosing regime and dosing intervals, I think they have to stick closely to what was done in the original trial. At the present time we have no other information.

Regarding 2(c), I believe that this can only be labeled as having a survival benefit. There is no evidence to suggest that the other things were changed by this drug.

DR. SWENSON: Dr. Tisdale?

DR. TISDALE: I think I would have to echo almost identical statements. If yes, only for prolongation in survival in recipients of single and double lung transplants.

The same dosing regimen should be listed

in the labeling even though it wasn't completely followed by all the patients.

There should be I think no expected benefit with respect to the other endpoints since they weren't shown definitively to be altered by the cyclosporine inhalation.

I think there also should be caution that there is no safety data regarding carcinogenesis effect on lung scarring or that sort of thing. So, I think there should be caution that there is incomplete data on carcinogenesis in laboratory animals and in humans, and that it is too early to know in the recipients that have been treated with this regimen whether that is a concern.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: Along the same lines I guess, you could put for the dosing 300 mg three times a week as tolerated. In terms of duration, obviously the study was for two years and so you would put in some caveat that use of this has not been shown to be of value beyond the two-year point.

There is the whole quandary of the lidocaine use and how do you put that into the labeling since that is an integral part of the drug but is not an approved drug itself. I think, other than that, that is the only unique thing.

DR. SWENSON: I should step in here and say that another party has entered this position about lidocaine and I am not sure that 100 percent of patients had to have lidocaine as pretreatment. It was a large fraction. Could the company just comment on that? Did everyone get lidocaine as part of this or was it only as needed?

DR. NOONBERG: It is my understanding that most, if not all, patients were initiated on inhaled lidocaine without butyryl. However, how long they continued with it was variable. We don't have exact information on duration but certainly it wasn't uniformly continued.

DR. SWENSON: So, this probably should just be a point for further discussion and decisions about how lidocaine might fit in this and whether it needs its own labeling. Dr. Prussin?

DR. PRUSSIN: Obviously, these people have been followed closely but, because this has been used in such small numbers of patients, something about follow-up and close follow-up and long-term safety has not been established.

DR. SWENSON: Dr. Mannon?

DR. MANNON: From the perspective of long-term safety, we do now have a patient population that is available that has been on the therapy for a number of years, and perhaps we will be able to incorporate them insofar as giving us some of the more long-term data rather than relying on a dog model or a rodent model where the dosing is different. You know, the opportunity to keep dogs around for five years may not be feasible.

I am not really sure how to address the tolerability of dosing. It wasn't clear to me what was the cut-off. Were patients having either sufficient bronchoconstriction that they had to stop, or coughing or wheezing, whatever? But I think that we need to have a better understanding of the tolerability of dosing and what is

appropriate pre-medication. As we alluded to, it is not clear to me what the dose escalation guidelines are. It sounds as if you got 100 mg and you tolerated it, then you went to 200 and by 10 days you got 300. But I think that those guidelines need to be defined and it is not clear to me whether there was additional intolerability or bronchospasm or cough or wheezing due to a higher dose, or whether it was the vehicle itself.

It would be helpful I think to know what the tissue levels are. We have DTPA and scintigraphy that suggest that there are very good levels but it would be nice to know what the actual levels are because I am not really sure how you dose the drug. We are talking about can we get away with one time a month. I mean, I think we need to know what the level of the drug is and get a sense of the outcome of the drug. Since obviously systemic levels appear to be lower by inhalation, I am not exactly sure how to do that.

DR. SWENSON: Dr. Mannon, could you clarify which patient population?

DR. MANNON: It would be lung transplant recipients. You know, how would you label it? Preventing death? I mean, I think that would be really the only thing that you could honestly put in the label. Clearly there was no prevention of rejection. There clearly was no prevention, based on the data presented, of BOS, and there may have been an effect on OB but it is not clear to me that it was that, or whether you can say these are the limitations of this on the label.

DR. SWENSON: Dr. Gay?

DR. GAY: Most of my comments actually echo Dr. Mannon's. I think short-term safety seems to be reasonable. I have concerns about long-term safety issues, and with the fact that this will be a long-term drug I think that needs to be studied more fully and evaluated more fully.

It would have to be labeled for lung transplant patients and at this point, yes, clearly for improving survival. But with future studies it will probably be more for prevention of chronic rejection.

Dosing regimens have to be standardized at some point. With the concern that half the patients did not receive really long-term therapy, greater than 24 doses, that has to be looked at more closely with potential long-term risk of therapy associated with the disorder.

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: First, the question put to us is, is the agent safe? I just have to comment that if the survival benefit is real the drug is safe with reference to its benefit. But if the survival benefit is not real, then we have substantial issues, or if the benefit is much smaller than it seems we have substantial issues with local tolerability because, as has already been commented, it is striking that half the patients couldn't tolerate it for the long term. With respect to what should be done further--

DR. SWENSON: Let's get your vote. Yes or no on that?

DR. HUNSICKER: I would vote, since I voted no on the first, that I don't think that it

is shown to be safe relative to its known efficacy. If the efficacy is repeated and is there, then obviously it is safe because being alive is better than being dead.

DR. SWENSON: And this is a no vote?

DR. HUNSICKER: It is a no vote for the question or whether that issue has been answered. With respect to what more should be done, first of all, I think that there does need to be some more animal data specifically with respect to the lung toxicity of cyclosporine, and it is striking that there is no really long-term animal data on the tolerability of cyclosporine. That should be easy to be done. It isn't a definitive thing but it certainly is something that should be done along the way.

I am one who believes that things like cancer can really only be answered in postmarketing surveillance. I think it has to be done as part of postmarketing surveillance, along with all sorts of other bad things but I don't think there is any way that kind of question can be answered prior to its

approval.

With respect to question one, for which population, I agree with everybody that it should be lung transplants.

What information should be included on dosing, we have only had one dosing regimen and, therefore, I think we can only talk about one dosing regimen.

I do think that for duration we should say that this has only been shown to be useful up to two years. I think we can add on that there is no reason why the sponsor could not give us evidence about tolerability after two years. But right now what we have is data on tolerability, which seems to be actually sort of marginal, up to two years with half the patients going off of it at that time.

What information should be included on the labeling, I have sympathy with those who say the only thing you should say is that it prolongs life, however, it seems to me that to say that it prolongs life but we don't have any information

about what it does to chronic rejection or acute rejection is a little naive. I don't see how we can say that and not sound silly. So, if the agency is going to approve it, we should say that the outcome is that it prolongs life presumably due to suppression of chronic rejection. I think that would be the way I would phrase it. And, I think that you need to have an explicit statement in there that there is no evidence that it affects acute rejection because I am afraid that some people will think that this is something you should use for acute rejection, and if there is anything we do know is that it does not seem to affect acute rejection.

DR. SWENSON: Dr. Venitz?

DR. VENITZ: Again, I am a yes-man so I would vote in favor of safety having been demonstrated. I agree that the population would be the population of lung transplant patients at large. I don't think there is any evidence for subpopulations at a particular risk but, hopefully, that is a question that can be addressed in the

follow-up study that we alluded to.

As far as the dosing regimen is concerned, I think the dosing regimen that should be labeled should be the dosing regimen that was used, and that does include the initial escalating dose study to get patients up to 300 mg before they then start their three times weekly maintenance dose.

Something that I found interesting is that one of the patients during the open session mentioned that, because of seizures, he was put on phenytoin and he developed a rejection. Obviously, phenytoin is a known enzyme inducer which increases the clearance of drugs such as cyclosporine and lowers their systemic levels. So, as far as drug interactions are concerned, I do think that you have to stick with the current cyclosporine label for oral use even though we think the systemic experiences are low and unlikely to contribute to this effect.

I also have some concerns about the fact that at least the studies that we looked at were done with the same nebulizer. So, I think you are

looking at a fixed drug-device combination here. I don't think we can extrapolate that beyond any other devices since I have no clue what the aerosol dynamics--the mean diameter for example--might be in a different device. So, I think the device is pretty much locked in, and you have already heard some of the comments about the lidocaine briefly.

As far as 2(c) is concerned, I agree with my neighbor to the left. I believe they have demonstrated survival benefit. They have demonstrated no benefit on acute rejection and, therefore, maybe a benefit on OB.

A couple of additional comments, being a kineticist by training, I guess I miss some exposure measures in the preclinical studies that allow me to compare--and I am talking about pulmonary exposures, not drug levels or PG levels--some of those studies in the lung so I can make some extrapolations as to what that might be in humans. Is there any way that we can use some of those biopsies from lung to actually measure drug levels and to ascertain in humans what the

relative ratios of systemic exposure over topical exposure are?

On the last question that Dr. Albrecht wanted us to address about the study design, again given the fact that I am a yes-man on both questions, I don't see any reason why the follow-up clinical trial could not be an open-label trial. I happen to be a member on an IRB and I would think that most of my committee members, probably as a consensus, would not approve a randomized, placebo-controlled trial with this product. So, I do think an open-label trial ethically is more than justifiable, and I think most of the information, at least that I am looking at, especially as far as dose optimization concerns, could be gotten out of a non-randomized, open, prospectively designed trial.

DR. SWENSON: Miss Drittler?

MS. DRITTLER: On 2(a), I don't know what else to say except transplant patients. What information should be included on dosing regimen--I question whether each patient might have a

different dosing regimen as opposed to what has been shown in the study with the 300 mg for all patients. I just wonder if each patient could be different, and in that case it would have to be as directed.

Included in the labeling regarding expected benefit--so, that has not been proven. I agree that it should refer to longevity. As far as the carcinogenic impact, I pay little attention to that because everything I take has carcinogenic impact so we know that we are at greater risk for cancer when we are taking these drugs but that is one of the benefits of still breathing and living. That is it.

DR. SWENSON: And your answer to the original question is yes?

MS. DRITTLER: Yes.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: Well, presuming approvability, the answer to the first question is yes. It would be for long allo-transplant recipients.

For 2(b) I think it would be important to note that it would be used in the setting of standard systemic immunosuppression, perhaps with an insert noting that the data were essentially in patients on azathioprine, which is not going to be the standard practice now.

For 2(c) it should say that this may improve survival. It is not expected to be beneficial for acute rejection, and leave out anything else.

Can I just mention that postmarketing--you know, the FDA has one advantage here that you have built in 100 percent postmarketing surveillance through the OPTN. So, that is different from looking towards approval of other drugs where you sort of lose control of things a little more, and that is an important dimension to keep in mind.

DR. SWENSON: Dr. Moss?

DR. MOSS: I kind of agree with Dr. Hunsicker. I am not as concerned about the safety as whether there was really efficacy demonstrated in this trial. So, I would say no but I thought

the safety data was reasonable.

I really don't have a lot to add to what the other people said, except I think it is a good idea that there is already a cohort of patients you can follow-up for long-term follow-up.

There was some data about irritability and irritation of the airways and that could just be followed up better in a better controlled, randomized, multicenter trial.

DR. SWENSON: I will vote yes on this question and all the points that I would raise have already been raised by preceding members. Dr. Barrett?

DR. BARRETT: I will vote yes to the main body and for the population of lung transplant, like has been mentioned earlier.

With respect to parts (b) and (c), I think, again if we are going to recommend approval based on a single Phase II study, the description of the experimental findings unique to this study have to be clearly stated. However, in addition to that, I think there has to be information that says

explicitly that dose response has not been shown with this product, and I think it is going to be very important to decide how much of the oral or other route of administration of cyclosporine gets added to this label because I think we are going to have to make some choices. Dr. Venitz pointed out that in some cases the drug interaction piece will be very pertinent, but with others I don't think you can confer some of the information that is contained with the other routes of administration to this product. We are specifically fighting the issue of very limited patient exposures with this product and I think that is where the primary safety liability comes from.

Having said that, on (d), even though I answered yes, I think we still need to do more follow-up studies with respect to the propylene glycol as well as the product itself in longer term tox studies.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: On the safety, I don't really feel like I have a lot to say on the safety.

I would feel a lot more comfortable with more data than is available so far. I think that if there is an additional randomized trial that is larger, that would go a long way toward establishing safety. So, to me, I am not convinced that the safety has been adequately characterized.

I guess I would label it for survival and chronic rejection-free survival for lung transplant patients.

In terms of additional information, I sort of changed my mind on what kind of study would be a good follow-up study if, in fact, this is not approved. So, the question is what would you do next if it is not approved. I think that the essential uncertainty here, in this group, is due to the fact that is one study; that it is a small study; it is a single institution study; and that the endpoint was this unexpected endpoint. It seems to me that, given the actual data, you would choose a follow-up trial using the most powerful possible endpoint and that is basically chronic rejection-free survival. That had the lowest

p value. If you use that as an endpoint you would have the additional advantage that if patients then rejected, had a chronic rejection, you could give them drug so you wouldn't actually necessarily have to treat people until death. Treating people until death is a very unpopular way of running a study.

DR. SWENSON: Dr. Sampson?

DR. SAMPSON: I actually don't have much to add to what has already been said. I voted no on number one and I am ambivalent about the amount of safety data. I would certainly like to see more information on dosing to understand the relationship of the severity and occurrence of the adverse experiences that the patients experienced relative to dose.

DR. SWENSON: Miss Schell?

MS. SCHELL: My vote is no also, mostly because of the limitations of the study, including the variable dosing when the patient fell out and didn't take medication anymore, and also the length of the study, the long-term effects. So, it is no.

DR. SWENSON: Well, that concludes the

official questions and I will turn it back to you, Dr. Albrecht, for any further thoughts that you might want to pose to us. We are a little ahead of schedule--no one is going to complain, but we do have a bit of time for other pressing issues to be raised by members of the committee.

DR. ALBRECHT: If I could just ask a follow-up question, and I know I have heard a lot of discussion on this but I wanted to actually just specifically ask this one more time in case there were further comments. As you heard, Dr. Dilly proposed that the company, in the event of approval, would commit to conducting an open-label, multinational study of 250 patients. I know going around the table I heard different opinions about open-label studies, not comparative studies. I wonder if perhaps we could go around the table to see if the committee members would believe this was enough, or this in addition to comparative studies, randomized studies, dose-ranging studies. Could I ask the committee to sort of think about the proposal versus other studies that I sort of think

I heard mentioned, either dose-ranging studies or some other randomized studies?

DR. SWENSON: Well, if I could at least try to paraphrase the company's plan, it was 250 patients. Certainly it would be a broad number of patients that would address issues of confounders and all of that, but there really wasn't any explicit discussion of dosing either as to frequency per week or absolute amount per dosing. So, those questions sort of remain. I am sure the company probably doesn't know exactly what the answers are. Please?

DR. DILLY: We explicitly suggested 300 mg inhaled cyclosporine three times a week or the patient maximum tolerated dose. So, our explicit suggestion was--

DR. SWENSON: Just the way the first study was performed?

DR. DILLY: Yes.

DR. SWENSON: Okay.

DR. HUNSICKER: But it says for five years and, at this point, we have no information on five

years and at least a presumption that you don't need five years since the people who got short courses seemed to have benefited similarly. So, I would not agree with five years at this point. That is something that you might look to change as you accumulate more information.

DR. DILLY: One consideration here is we put in a single dosing element, if you like, 300 mg, three times a week for five years. It is perfectly within the realms of appropriate design to take a 100 mg arm into this design. It is perfectly appropriate to have a two-year cohort and a five-year cohort so we can actually test. Because, you know, we do agree that providing patients with access to potentially efficacious therapy is entirely appropriate at this stage so comparison of 100 versus 300 would be a very appropriate way to go; a comparison of two years versus five years we would see as both addressing our concerns about the ethics of withholding therapy, but also answering some of the key questions around safety of long-term administration

and what is the right dose for these patients. So, we are willing to refine this design.

DR. SWENSON: Rather than go around the table, I will just look to anybody with comments. Dr. Hunsicker?

DR. HUNSICKER: There are two issues and, therefore, I am not quite sure how to answer your question. One is what, in my mind, would be needed for approval given that I voted no. Then, the second is what is needed by the community, assuming that this does eventually become approvable for intelligent use. We have to keep these things separate.

With respect to approval, what I want is more evidence that, in fact, there is a real benefit here. I would actually agree rather strongly, surprisingly perhaps to some, that it need not be necessarily a placebo-designed study. I would be willing to accept, because there has been no change in chronic rejection if there is no change in chronic rejection over the next little while, an active treatment study against a

registry, contemporaneous registry control. I don't think that it really is needed to set it up as a placebo-controlled trial. So, that might ease the issue of doing another study if, in fact, the drug does not get to be approved.

In terms of its intelligent use, I think the outstanding issue is the amount of the drug and the duration of the drug. Actually, what is to me a rather attractive design is what has just been discussed which would be 100 mg, or some other dose that was designed to be somewhat similar to what you would have given with oral dosing as opposed to respiratory dosing, versus the higher dose. If you get a dose response--you know, if 300 is better than 100 then you have a clear answer to the other question as well.

The second is duration. I personally would like to see a trial that has two years--how shall I say?--if you are going to approve, I would approve for two years and then let them design a trial to take it to five years and see if there is an additional benefit.

DR. TISDALE: I just wanted clarification on your question. I think your question was, assuming approval, what study design would you envision as being appropriate as the next step, or did I understand you wrong?

DR. ALBRECHT: I apologize. I said that. Actually, I was thinking that the company's proposal was for a postapproval study but I was more interested, because the company had proposed a study that was an open-label study comparing to the registry, whether that type of study would be convincing to the committee or whether, when I heard discussion around the table about randomized studies, in fact, the committee felt that while that study might be informative, randomized studies, in fact, were what I was really hearing as the preferred approach to gaining further information, regardless of whether it be preapproval or postapproval.

DR. TISDALE: Well, I happen to agree that it would likely be problematic--you know, putting on my other hat as an IRB member looking at a study

that is a randomized study design, to repeat a randomized study that has already shown a striking survival benefit. I think most IRBs are not going to be capable of doing the post hoc analysis of the statistics and understand the limitations as they have been put forward today, and the majority of them would say, "look, you've already got a striking survival benefit, how are you going to go back?" So, I would look at that investigator and say, "hm, I wonder what it is they're trying to do? They want to look at mechanism. They want to do something else. And, they're going to take these poor patients and randomize them to placebo so that they can look at lung biopsies and try and figure out how cyclosporine is working locally when the question for survival has already been answered." I would really be wondering at that point whether they were putting their science ahead of the patient's benefit. So, putting on that other hat, I think it would be very difficult for me to look at a randomized, controlled trial in this setting with the survival being the primary outcome, with

my IRB hat on.

So, I think it is perfectly appropriate to go forward, either preapproval or postapproval, with a study that compares to contemporary patients. There will be plenty of patients who don't go on trial. I mean, I think it is striking that you got 50 percent. I think that is a really high percentage of patients to go on a clinical trial so I don't think you will have any trouble having controls. They will be the majority.

DR. SWENSON: Dr. Burdick?

DR. BURDICK: I mentioned this before, I am concerned that the sort of study that was proposed by the company, using cohort controls through OPTN data and so forth, is going to leave one, no matter how carefully it is put together, with a series of confounding variables to be interpreted and a more or less random conclusion that certain clinical settings work and certain others don't unless it is an extraordinarily positive benefit which is being predicted. And, as we have said, probably the next time around there

won't be quite such a big difference, then you are not going to be able to have the fundamental information about basic utility of the drug.

So, I think another randomized trial is the way to find that out. The argument that there is a huge difference in the trial we have been considering is true but, remember, we have seen that huge difference based on just a few patients because the numbers were so small. And, it is not quite as convincing as everybody is making it out to be. It is just too convincing to ignore but it is not that convincing. The way you really find out for sure is to do another randomized trial, somewhat larger numbers, pick your power, and then the rest of what is proposed in sort of cohort study, no control group study or dose escalation will go on in the transplant community anyway and we will get that information. It will evolve as immunosuppression evolves. It will have to be redone every two or three years, just as everything else works.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: I think Chiron has done as good a job as you could possibly do with this data that they have, and I am still not convinced. So, for me, I would need to see another randomized trial. I think the analyses that they have done, the sensitivity analyses, are very good and that is what made this so difficult for me. You pushed me right to the edge but you didn't quite push me over, although I am sure some of you probably want to push me over a cliff. But, to me, it is not strong enough and, to me, I would need to see another randomized, controlled trial. It would not be sufficient to see a one-arm trial for example.

DR. SWENSON: Dr. Moss?

DR. MOSS: Actually, I like the suggestion that Dr. Schoenfeld recommended. You know, I think the people that voted no, they would need to say that a randomized clinical trial needs to be done. I think having the endpoint be chronic rejection-free survival makes a lot of sense to me in the sense that then if people did develop the endpoint they could be done with the study, and if

they wanted to then do something off-label that would be a reasonable thing to do. So, I thought that was an excellent suggestion for a randomized, clinical trial.

DR. SWENSON: Dr. Hunsicker?

DR. HUNSICKER: It is always preferable to do a randomized clinical trial and my endorsement of the possibility of a one-arm study does not take away from the fact that is always preferable to do a randomized clinical trial. Sometimes it is not possible or feasible, or whatever you want to call it.

A way to get around the problem that Dr. Burdick raised, which is that if you use a registry control you are going to have some explanation to do, and if you have a close call it is going to be very unconvincing. One way to get around this is to stipulate a minimum difference. You know, what we are trying to do now is to see whether this idea that there is 70, or whatever it was, 75 percent reduction in mortality is credible. If you say that the mortality absolute difference--let's say

between 20 percent and 50 percent, I don't remember exactly what the numbers were--that there has to be at least a 15 percent difference in mortality that is observed, that will take care of an awful lot of messes in non-equality and will also get at the issue of whether this is really a robust finding. So, I think that there is, in fact, a rigorous way that one can do a single-arm, registry controlled trial by defining exactly what your outcome is.

DR. SWENSON: Dr. Proschan?

DR. PROSCHAN: In terms of the single arm or the non-placebo study, if you did dose ranging I would suggest trying to actually decrease that volume of propylene glycol. It seemed that even in the placebo patients it was poorly tolerated. So, rather than decreasing--you know, it is a small point--the concentration of cyclosporine, actually try to decrease the volume--it is something like 5 mL, which is a lot of stuff to inhale even though most of it is not being inhaled.

A second point is that if you are going to compare to the registry, is there a way to control

or at least partially control for systemic immunosuppressive drugs so that at the end of this clinical trial you don't have radically different systemic immunosuppression?

DR. HUNSICKER: The registry data on doses of immunosuppression is non-existent and is very low quality. I think all you can get is sort of what they were on.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I think, first, if you think that it is unethical to do a randomized trial we should approve this. I think if you can't do a randomized trial, then the drug should be approved now.

As a postmarketing study, I think the single-arm study is a great idea because basically, to use a baseball metaphor, the postmarketing study would tell us whether we hit a home run or just got to first base and that is an important thing to know because you want to know where to go from here, and a long postmarketing study would show us that. If survival was really, really good compared

to historical controls we would know that we had gotten a home run.

On the other hand, the fastest way to get approval has got to be a randomized, controlled study organized to be as quick as possible, with a sequential stopping rule, with an endpoint that occurs as early as possible. In this case it would be chronic rejection with lots of biopsies done so you can see it. If they do a single-arm study it will be a long, long, long time and then I think the results will be somewhat confusing.

DR. SWENSON: Dr. Sampson?

DR. SAMPSON: I just wanted to echo again the controlled, randomized, double-blind trial.

DR. MANNON: I just wanted to make a comment regarding the number of comments made around the table and also by the investigators regarding the ethics of this and what an IRB might potentially go along with. But I have to tell you that if I were sitting on an IRB and an investigator wanted to present a double-blind study and said, "I have this initial study and look at

the striking event," I don't think that I would find it inappropriate if I understood that the data presented represented some concerns and flaws and how the data was interpreted. And, look at us. There are 18 of us sitting here and we can't even come to an agreement one way or the other. We are all sort of split. So, that clearly means a number of intelligent people are interpreting this data in a variety of ways. So, I think that a standard IRB, presented with that kind of information, would understand the necessity for going on.

Then, as far as the patients, I think if I presented my patient with what they should take--we use a lot of things off-label--I shouldn't even say this but we use a lot of drugs in immunosuppression for transplant that are off-label based on a couple of case series, and you if present it to a patient and say this is the option and we are going to try this. Most will do what you recommend and it is not clear to many of the patients that this is the beneficial therapy. Therefore, I don't feel that everybody is going to run and say I can't be on

placebo.

DR. SWENSON: Dr. Moss?

DR. MOSS: I just want to echo what Dr. Mannon said. I think there is a lot in the literature about smaller Phase II trials which show that there appears to be efficacy and in a lot of those cases, or most of those cases, there were then larger multicenter studies done and they all got through IRB committees. So, I think there is very good precedent in the literature for orphan diseases, such as idiopathic pulmonary fibrosis, where this same scenario has happened where IRBs approved larger multicenter, randomized clinical trials. So, I agree with you, Dr. Mannon. To say that no IRB is ever going to approve a multicenter trail based on the data that we were presented today I think is incorrect.

DR. SWENSON: Well, that being the extent of comments here, Dr. Albrecht, anything more?

DR. ALBRECHT: No, just to thank everybody very much for all your thoughtful comments. You have given us a lot of food for thought and we will

take them back and discuss them internally.

DR. SWENSON: I would like to reiterate my thanks to everyone, the company, the FDA, the panel members, the audience and the patients who came here.

[Whereupon, at 4:30 p.m., the proceedings adjourned.]