UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + + +

ENDOCRINOLOGIC AND METABOLIC
ADVISORY COMMITTEE

+ + + + +

MEETING

+ + + + +

TUESDAY,
JANUARY 14, 2003

The Advisory Committee met at 8:00 a.m. in the Versailles Room of the Holiday Inn Bethesda, 8170 Wisconsin Avenue, Bethesda, Maryland, Dr. Thomas Aoki, Acting Chairman, presiding.

PRESENT:

THOMAS AOKI, M.D. Acting Chairman

LAURA BARISONI, M.D. Voting Consultant

THOMAS R. FLEMING, Ph.D. Voting Consultant

DEAN FOLLMAN, Ph.D. Voting Consultant

DEBORAH GRADY, M.D., M.P.H Member

LAWRENCE HUNSICKER, M.D. Voting Consultant

J. CHARLES JENNETTE, M.D. Voting Consultant

PRESENT (Continued):

| | |
|---|---|
| ADAM J. JONAS, M.D. | Non-Voting Consultant |
| KATHERINE KNOWLES | Acting Consumer Representative |
| LYNNE L. LEVITSKY, M.D. | Member |
| MICHAEL R. McCLUNG, M.D. | Voting Consultant |
| ALLAN R. SAMPSON, Ph.D. | Voting Consultant |
| DAVID S. SCHADE, M.D. | Voting Consultant |
| JERRY A. SCHNEIDER, M.D. | Voting Consultant |
| NELSON WATTS, M.D. | Voting Consultant |
| PAUL WOOLF, M.D. | Voting Consultant |
| ROBERT ZERBE, M.D. | Acting Industry Representative (Non-voting) |
| KAREN M. TEMPLETON-SOMERS, Ph.D. | Acting Executive Secretary |

FDA REPRESENTATIVES:

JOHN HILL, Ph.D.

DWAINE RIEVES, M.D.

AMY ROSENBERG, M.D

MARC WALTON, M.D., Ph.D.

KAREN WEISS, M.D.

SPONSOR REPRESENTATIVES:

NEIL KIRBY, Ph.D.

KATHLEEN LAMBORN, M.D.

ATUL MEHTA, M.D.

THOMAS J. SCHUETZ, M.D., Ph.D.

MELVIN SCHWARTZ, M.D.

RAVI THADHANI, M.D., M.P.H.

DOUG TRECO, Ph.D.

PUBLIC SPEAKERS:

JOHN BARRANGER, M.D.

JOE T.R. CLARKE, M.D., Ph.D.

JUDY COLLINS-STANLEY

RICHARD CORKUM

JENNIFER DICKINSON

AZZA EL SISSI

PAUL E. LEVY

RICHARD N. LIND, M.D.

AMADO MONTALVO

THOMAS STANLEY

ROLAND L. TUFTS

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:04 a.m.)

CHAIRMAN AOKI: Good morning. I'm Dr. Thomas Aoki, the Acting Chairman of this committee. I'd like to call the meeting to order.

The topic for today is Replagal from Transkaryotic Therapies, Incorporated, and to begin with I would like to ask the members of the committee to introduce themselves starting with, I guess --

DR. ZERBE: I'm Bob Zerbe. I'm CEO for QUATRx, and I'm the industry representative.

DR. McCLUNG: I'm Mike McClung, an endocrinologist at Oregon Health Sciences University in Portland.

DR. FOLLMAN: I'm Dean Follman, a statistician at the National Institutes of Health.

DR. BARISONI: Laura Barisoni, renopathology, Johns Hopkins.

DR. SCHADE: Dave Schade, endocrinologist, University of New Mexico, School of Medicine.

DR. FLEMING: Thomas Fleming, University of Washington.

DR. WOOLF: Paul Woolf, endocrinologist, Crozer Chester Medical Center.

MS. KNOWLES: Kathy Knowles, Health Information Network in Seattle, consumer representative.

DR. JONAS: Adam Jonas, biochemical geneticist, Harbor-UCLA Medical Center.

CHAIRMAN AOKI: Tom Aoki, University of California, Davis.

DR. TEMPLETON SOMERS: Karen Templeton-Somers, Acting Exec. Sec. for the committee, FDA.

DR. JENNETTE: Charles Jennette, renal pathologist, University of North Carolina.

DR. WATTS: Nelson Watts, University of Cincinnati.

DR. LEVITSKY: Lynne Levitsky, pediatric endocrinology, Mass. General.

DR. SAMPSON: Allan Sampson, Department of Statistics, University of Pittsburgh.

DR. HUNSICKER: Larry Hunsicker, nephrologist from the University of Iowa.

DR. SCHNEIDER: Jerry Schneider,

pediatrician, University of California, San Diego.

DR. RIEVES: Dwaine Rieves, Medical Officer in the Food and Drug Administration.

DR. WEISS: Karen Weiss, Food and Drug Administration.

DR. TEMPLETON-SOMERS: 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 interest in firms regulated by the Center for Drug Evaluation Research and the Center for Biologics Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exception.

Dr. Adam Jonas has been granted a limited waiver under 18 USC 208(b)(3) for his consulting for a competitor on an unrelated matter. He received between 10,001 and $50,000 a year. The limited waiver allows Dr. Jonas to participate in the discussions without voting.

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

In addition, we would like to disclose that Dr. Robert Zerbe is participating in this meeting as an acting industry representative, acting on behalf of regulated industry. Dr. Zerbe reports that he owns stock in Genzyme Corporation as part of his Salomon Smith Barney managed account.

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 exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

CHAIRMAN AOKI: The first speaker will be Dr. John Hill of CBER.

DR. HILL: Good morning, and thank you all for being in attendance today.

We are here to discuss Transkaryotic Therapies, or TKT, BLA's application for Replagal, gene activated human alpha galactosidase for the treatment of Fabry's disease.

I am John Hill, chemistry reviewer for this BLA submission. I will be presenting a brief overview of the CMC portion of TKT's application.

I'd like to start my presentation by summarizing the review milestones for this application. CBER received TKT's application on June 16th, 2000. Since CBER reviewed this BLA application, an interim review process encompassing extensive interactions between CBER and TKT has taken place. CBER reviewers have raised numerous comments during the course of this BLA review. These comments have been communicated to TKT in several complete response letters.

TKT's initial submission resulted in a complete response letter from CBER to TKT in December of 2000, communicating CBER's comprehensive comments. CBER stated that the clinical study data had not provided substantial evidence of efficacy and fully detailed the facts leading to that conclusion. CBER recommended that additional clinical studies be conducted.

After extensive discussions between CBER and TKT and submission of partial additional information from TKT, a complete response was received from TKT in May 2002. This information was fully reviewed and led to the second CR letter from CBER in November 2002 detailing CBER's comments.

This letter, again, stated that substantial evidence of efficacy had not been provided and that additional clinical studies should be conducted.

CBER also outlined the accelerated approval framework to TKT and the types of support needed for this approach. There have been discussions, requests, and responses between CBER and TKT on a more frequent basis than reflected in just these listed official regulatory milestones. This interactive review process is ongoing.

I would now like to summarize the biochemical features of the drug substance. Replagal is a gene activated human alpha galactosidase expressed in a continuous human cell line. Alpha galactosidase exists as a homodimer comprised of two approximately 50 kilodalton subunits.

The amino acid sequence for the recombinant protein is identical to the sequence for the endogenous enzyme.

And finally, there are three n-linked glycosylations.

Review of the CMC information provided by TKT indicates that this is a well characterized protein. There are no outstanding review issues concerning the drug substance.

I would now like to focus on the properties of the drug product. Replagal is provided as a sterile isotonic solution for intravenous administration. Each vial of the drug product contains 3.5 milligrams of alpha galactosidase, 12 milligrams of sodium phosphate, .8 milligrams of Polysorbate 20, and 31 milligrams of sodium chloride.

Replagal drug product is delivered into sterile saline solution for intravenous administration. There are no outstanding review issues concerning the drug product.

And, finally, I'd like to acknowledge and thank the members of the CBER review team for a job well done and a thorough review.

CHAIRMAN AOKI: Thank you, Dr. Hill.

Next will be the sponsor's presentation, with an introduction Neil Kirby.

Dr. Kirby.

DR. KIRBY: Thank you, Dr. Aoki.

Good morning. My name is Neil Kirby, and I am Vice President of Global Regulatory Affairs for Transkaryotic Therapies, or TKT.

On behalf of TKT, I would like to thank you for the opportunity to meet with you this morning to discuss the Replagal for the treatment of Fabry disease.

Fabry disease is a rare disease that is characterized by a deficiency in the enzyme alpha galactosidase A. Fabry disease is a progressive disease that affects multiple organs and systems and leads to death in the fourth and fifth decade of life.

Replagal, or agalsidase alfa, is the human protein alpha galactosidase A produced in a human cell line. Agalsidase alfa has the identical amino acid sequence to the endogenous enzyme.

Our presentation today will focus on the renal and cardiac aspects of Fabry disease, the major causes of morbidity and mortality in this rare disease. We will not present data today on the effects of Replagal on pain.

The data we will present today will demonstrate that Replagal improves renal pathology, a surrogate marker of clinical benefit in Fabry disease; Replagal stabilized renal function over 30 months; and that Replagal reduces left ventricular mass and improves cardiac conduction system function.

In addition, we will show that Replagal

has an excellent safety profile after up to two and a half years of therapy.

I'd like to take a few minutes now to describe the order of TKT's presentation to you. I would like to say that all the presenters and experts attending today's meeting on behalf of TKT are either TKT employees or receive consulting fees from TKT.

Dr. Ravi Thadhani is an Assistant Professor of Medicine at the Harvard Medical School and is Director of Clinical Research in Nephrology at MGH. Dr. Thadhani will give an overview of Fabry disease, including a description of the renal natural history of the disease. This overview will establish an important context for the consideration of the clinical data for Replagal.

Dr. Thomas Schuetz is TKT's Vice President of Clinical Affairs and is responsible for the Replagal clinical program at TKT. Dr. Schuetz will present an overview of the renal pathological findings of Fabry disease. He will then review the results of our clinical studies with Replagal in the treatment of Fabry disease.

We have invited several other individuals with expertise in specific areas discussed in today's presentations to be available during the question and answer session later today. They are:

Dr. Colucci, who is Chief of Cardiovascular Medicine at the Boston Medical Center.

Dr. Kampmann is Professor of Pediatrics at the Johannes Gutenberg University in Mainz, Germany, and is an expert in the cardiac aspects of Fabry disease.

Dr. Kolodny is Chairman of the Department of Neurology at New York University School of Medicine.

Dr. Lamborn is a biostatistician on the faculty of the University of California, San Francisco.

Dr. Mehta is a consultant in hematology at the Royal Free Hospital in the U.K.

Dr. Perrone is a nephrologist and Professor of Medicine at Tufts University School of Medicine.

Dr. Schwartz is Professor of the

Department of Pathology at Rush-Presbyterian-St. Luke's Medical Center in Chicago.

Now, I would like to introduce Dr. Ravi Thadhani who will give an overview of the clinical manifestations and natural history of Fabry disease.

DR. THADHANI: Thank you, Neil.

Fabry disease is an X-linked glycosphingolipid lysosomal storage disorder that results from a defect of the enzyme alpha galactosidase A. As a result of this defect, there is an accumulation of the critical substrate globotriaosylceramide, otherwise known as GB3.

The prevalence of this condition estimated by the incidence and the median survival of these individuals in the United States is estimated at 1,500 to 2,000 patients.

This is a progressive, multi-systemic disorder. As you heard yesterday, these patients suffer quite a bit. As a result of disease and damage to various organs, most notably the kidney and the heart, these patients die early.

There is no currently specific treatment for this condition, and patient care is generally restricted to palliation.

Let me review briefly the pathophysiology. As a result of parenchymal cell deposition of GB3 in various cells of the kidney, including the mesangial cells in the podocytes, there is progressive segmental sclerosis and subsequent renal failure.

As a result of deposition in the tubular cells, there are concentrating defects.

As a result of deposition in the myocytes, there is left ventricular hypertrophy, and deposition in the conduction system leads to QRS abnormalities and arrhythmias.

Pain is another component of this disease, and it results likely from a deposition in the autonomic ganglia.

This is a summary of the renal manifestations of Fabry disease. Early on there is proteinuria. In fact, in a large series published by Mary Branton and her colleagues at the NIH, 50 percent of individuals when they reach 35 years of age had evidence of proteinuria.

One hundred percent of those individuals who reach the age of 50 or thereabouts had evidence of proteinuria. Some of them went on to develop nephrotic range proteinuria and nephrotic syndrome.

Renal concentrating defects are also present, and that may lead to diabetes insipidus, although this often goes or often escapes clinical diagnosis.

And finally, there's a progressive decline in kidney function finally ending in end stage renal disease, which is shown here diagrammatically in this figure.

These are the stages of kidney disease as it progresses to end stage renal disease. On the Y axis is renal function, and on the X axis is time.

To put into context the results of clinical trials that you will shortly hear from Dr. Thomas Schuetz, I'd like to highlight two aspects of this schematic diagram.

The first is the slope or the rate of progression of kidney disease in these individuals, and the second is the mean age of onset of dialysis in this population.

To do so we turn to the best source we have, which is the literature. In a comprehensive literature search performed by TKT, 116 patients with Fabry disease were identified who had both age and renal function reported. In this review, the mean age of these individuals was 33.6 years, and their renal function is shown here.

But this population importantly can be divided into two separate groups. The first, a group that did not have end stage renal disease. Their mean age, 30 years approximately, and renal function showing compromise at 85 mLs per minute.

The second group in end stage renal disease, 62 individuals, and the age of onset of their renal failure was 36.7 years.

To understand the rate of decline, we have to focus on those individuals specifically that have serial measurements of kidney function, and of the 54 patients in the literature that were not yet on end stage renal disease or who had not yet developed end stage renal disease, 11 of them had serial measurements of kidney function, here shown by their age and their follow-up, and they were shown to have a rate of decline of approximately 21 mLs per minute per year.

Mary Branton in her series, a large series from the NIH, she had 14 patients in whom she had available information on serial kidney measurements, and these individuals, again shown by their mean ages, had a rate of decline of 12.2 mLs per minute per year.

Probably the largest experience though of untreated patients come from the placebo arms of three studies performed by TKT that you'll hear about shortly, and these patients, totaling 59, followed over a period of time, again shown by their ages, have a mean rate of decline of 8.3 mLs per minute per year.

Taken together, 84 patients in their mid-30s have a rate of decline of approximately 10 mLs per minute per year.

Let's look at that diagrammatically once again. Individuals in their mid-30s are expected to have a rate of decline that somewhere ranges between eight and 20 mLs per minute per year.

Dr. Tom Schuetz will come back to this diagram to show how patients who have been treated with enzyme replacement therapy compare to this natural history.

In addition, if it is the case that individuals in their mid-30s have evidence of renal insufficiency at this rate, you would expect that not too long thereafter they would develop end stage renal disease.

And, indeed, when we go back to the literature, 62 patients, individual case reports, the mean age of onset of dialysis supports that hypothesis, 36.7 years of age. In fact, studies that span over three decades, therefore accounting for interventions and medications that have been introduced, suggest that that mean age of onset of dialysis is rather consistent.

Let me focus on three particular studies, the first by Tsakiris, looking at the entire registry of patients on dialysis in Europe, and in that registry identifying patients with Fabry disease found that the mean onset of dialysis was 38 years of age.

Ojo from Michigan, looking at the mean age of first kidney transplantation among these entire registry of kidney transplantation patients in the United States, finding a similar age of 38.

And finally, a study that I did with colleagues from the New England Medical Center, looking at the entire registry in the United States of dialysis patients, finding that the mean age of these patients as they begin dialysis ranges from about 39 to 42 years of age.

Now, this range represents whether you include males or females in the population. Speaking specifically of females, it should be noted that 12 percent of individuals in the Tsakiris data from Europe and 12 percent from our series in the United States were females, and as you heard yesterday, these individuals, females specifically, can suffer from end stage renal disease.

Focusing on the 62 patients that had individual ages reported, we look at these individuals in a Kaplan-Meier-like fashion. Here on the Y axis we have percent of patients without end stage renal disease and on the X axis we have age, and we see that 50 percent of these individuals developed end stage renal disease by the time they're about 36 to 37 years of age, and this, of course, is in contrast to the mean age of onset of dialysis among individuals in the United States from other diseases, which is approximately 62 years of age.

Coming back then to the schematic diagram, again, the stages of kidney disease and the color, renal function on the Y axis and time on the X axis, we anchor this schematic diagram at the mean age of onset of dialysis, the upper 30s or 38 to be exact, and therefore, it make sense and the hypothesis stands that the rate of decline for these individuals in their mid-30s approximates about ten mLs per minute per year.

In the series by Mary Branton, again the largest experience probably to date, 105 patients reported at the NIH. She looked at individual that had renal insufficiency and then went on to kidney failure, and they did so on average over a period of about four years.

Now, this schematic diagram also brings up an important point, and that is individuals in their mid-30s, therefore, are expected to harbor fully pathological lesions that then lead to end stage renal disease.

And I point that out because Dr. Tom Schuetz will come back to a critical study in which the mean age of those individuals was approximately 34 years.

Therefore, in conclusion from the renal aspects, renal insufficiency probably begins on average in the mid-30s and declines at a rate here approximated at about ten mLs per minute per year, and the mean age of onset of dialysis in the upper 30s or about 38 from the data that I've shown you.

We now turn to probably the second most critically affected organ in this disease, and that is the heart. As a result of accumulation in the myocytes, there is left ventricular hypertrophy, and as you heard Professor Kampmann from Germany is here today, and he is an expert on the cardiac manifestations of Fabry disease and has shown that both in males and in females by the third or fourth decade, these individuals commonly have evidence of left ventricular hypertrophy.

As a result of deposition in the conduction system, there's widening of the QRS complex and bundle branch blocks, and we know from studies of patients with and without kidney that left ventricular hypertrophy is strongly and independently associated with mortality, and therefore, it comes as no surprise that in an autopsy series of patients with Fabry disease, 20 percent of them were found to have a primary cardiac cause of death.

Other manifestations of Fabry disease include the CNS system, with stroke and altered blood flow in the brain. Pain that is often refractory to medications is another complication.

The GI system as you heard yesterday so poignantly from a patient involving diarrhea and weight loss can affect these individuals.

And finally, hearing loss, a characteristic skin lesion called angiokeratoma, and lack of sweating or low sweating also affects these individuals.

Therefore, in summary, for the natural history Fabry disease is a complex multi-system disease, and as a result of progressive decline in kidney function and increase in left ventricular mass at an early age, these patients unfortunately suffer from an early death.

I'll turn the podium over now to Dr. Tom Schuetz.

DR. SCHUETZ: Thank you, Dr. Thadhani.

I would also like to echo the comments that Dr. Kirby made earlier and thank Dr. Aoki and the committee and FDA-CBER for the opportunity to discuss with you today the clinical development program for Replagal to be indicated for the treatment of patients with Fabry disease.

I will begin my presentation today with an overview of the renal pathology of Fabry disease. This overview of the renal pathology of Fabry disease will be important in order to put the results of clinical studies of the effects of Replagal on renal pathology into proper context.

In addition, this overview will provide important background information should a discussion of potential surrogate markers of clinical efficacy ensue this afternoon.

I will focus my discussion of the clinical development program today on the results of clinical trial of Replagal, focusing on the effects of Replagal on renal function, renal pathology, and cardiomyopathy, and I will finish the discussion with an overview of the safety profile of Replagal.

As Dr. Thadhani just discussed, Fabry disease is inexorably progressive clinical nephropathy, and there is a spectrum of progressive pathological changes in the kidney that mirrors this clinical syndrome.

In the kidney, Fabry disease is fundamentally an intracellular deposition disease of the nephron. The principal aspect of pathology in this disease is glomerular epithelial cell GB3 deposition.

GB3 deposition in the glomerular epithelial cells, or podocytes, is probably toxic, and podocyte injury likely initiates a cascade of events in the nephron that is first manifested by the appearance of glomeruli with mesangial widening.

As this spectrum of disease progresses, glomeruli with focal and segmental glomerular sclerosis are seen, and the ultimate culmination of this process in the nephron is the appearance of obsolescent glomeruli, a time at which the nephron is no longer functioning.

In addition, the tubular epithelials are prominently involved in this disease, and interestingly the capillary endothelial cells in this disease are relatively spared.

My next several slides present photo micrographs demonstrating this progression of disease in the kidney, but I'll introduce the concept of the kidney pathology of Fabry disease with two photo micrographs which show normal glomerular architecture and structure. All of my subsequent next slides are in this format with a PAS stain of a glomerulus on the left and a toluidine blue stain of a glomerulus on the right.

In a normal kidney, the toluidine blue stain is quite unremarkable, and I'll come back to this point in a minute, but normal glomerular architecture is characterized by a paucy (phonetic) cellular and sparse mesangial matrix, open capillary tufts, and an open urinary space.

In contrast, in Fabry disease, the earliest aspect of disease is podocyte deposition of GB3. You can see on the toluidine blue stain here on the right the dense deposition of GB3 which are highlighted bright blue by the toluidine blue stain.

And at this early stages of glomerular disease in the kidney, glomerular architecture is relatively well preserved in these patients despite the evidence of deposition of GB3.

As I mentioned, as the consequences of GB3 toxicity in the nephron progress, one of the earliest manifestations of disease are glomeruli with mesangial widening. You can see in the PAS stain on the left here expansion of the mesangial matrix and the cellularity of the mesangial space with expansion of the mesangial matrix, characteristic of mesangial widening.

On this toluidine blue stain here, you can see nonspecific stain in here of the matrix, expansion of the mesangial space, and dense deposition of GB3 within the podocytes.

As this disease progresses in the kidney, a more nefarious lesion appears, which is a focal and segmental glomerular scar here. You can see the perihilar (phonetic) scar here in this PAS stain and similarly here in this toluidine blue stain.

Interestingly, as this pathological process progresses in the kidney, there's actually evidence in the glomerulus of less deposition of GB3, suggesting that the initial toxic insult precipitates this cascade.

This process in the nephron ultimately culminates with glomeruli with this appearance, a completely scarred and obsolescent glomerulus, again, representing the demise of this individual nephron.

Thus, in the kidney the pathological progression of disease can be represented by a progress along this pathological spectrum. Early on in the disease when there's early deposition of GB3 within the glomerular epithelial cells, glomerular architecture remains relatively well preserved in this disease.

As patients age and the disease progresses, glomeruli appear with mesangial widening, and ultimately with continued progression of the disease, and as patients get older, there's the appearance of focal and segmental scars, which ultimately culminate in overt glomerular obsolescence, signaling, again, demise of this individual nephron.

I will now begin a discussion of the results of the clinical trials with Replagal conducted in patients with Fabry disease.

The clinical trials that we have submitted to our United States BLA are summarized on this slide. I have separated them on this slide based on the site at which these trials were performed.

Our initial Phase 1 study and, indeed, our most extensive experience with Replagal has been from studies conducted at the United States National Institutes of Health. The first study that was performed at the NIH was numbered 001, which was a Phase 1, open label, dose escalation safety study, which established the bioactivity of Replagal and the single dose safety profile.

Results from this study, in part, were used to establish the clinical dose of Replagal which was used in all subsequent clinical studies.

A set of studies numbered three, six, and 11 were subsequently conducted at the NIH in the same set of patients. The initial study numbered 003 was a randomized, double blind, placebo controlled study conducted over a short term period of about six months. This study enrolled 26 patients.

At the end of that six month period these patients were crossed over into open level maintenance studies, the first of which was number 006, and then continuing as 011.

Interim analyses are performed on these data on an annual basis, and we've submitted a one year interim analysis of the 11 study to the BLA, thus representing two and a half years of clinical trial experience in this patient population.

We've also conducted a six month randomized, double blind, placebo controlled study at Royal Free Hospital in London. This study was a study that enrolled 15 patients with cardiomyopathy and focused on the effects of Replagal on the cardiomyopathy of Fabry disease.

I'll point out that all of these studies were performed in male patients with Fabry disease. Study 14, which was conducted at the University of Mainz in Germany, was an open label, safety and efficacy study of Replagal performed in female patients with Fabry disease. This study also focused on the cardiomyopathy of Fabry disease and also enrolled 15 patients.

Thus, the data currently submitted to our U.S. BLA includes data on 56 unique patients who have been followed for up to two and half years.

We have also recently completed another short term, randomized, double blind study numbered 010, the results of which have not yet been submitted to our U.S. BLA, and I'll only discuss very briefly the preliminary results from that trial as that study was unblinded only about six weeks ago.

I'd like to briefly remind you of the relationship of the various NIH studies to each other, as I have several slides that are in this format. Again, the studies numerically were three, six, and 11. The first study was a randomized, double blind, placebo controlled study. Fourteen patients received Replagal. Twelve patients received placebo, and the duration of that study was six months.

At the end of that study these patients crossed over to open label Replagal therapy in the sixth study. An analysis was performed after one year of that study, and patients continue through today in the 11 study, and again, interim analyses are performed on an annual basis in that study, and we have submitted the results of the first annual efficacy evaluation in that study.

As Dr. Thadhani discussed earlier, the principal clinical manifestations of Fabry disease are the progressive clinical nephropathy, and many of our studies focused on the effects of Replagal on renal dysfunction in these patients, and I'll begin by describing the effects of Replagal on renal function as measured by creatinine clearance in the first NIH study. Those results are presented on this slide.

Patients randomized to placebo had a progressive decline in kidney function over the six months of this study, a decline of which is consistent with the natural history of disease, as Dr. Thadhani presented earlier.

Patients randomized to Replagal, on the other hand, not only did not decline, but had stable renal function during that time period.

Comparison of the two treatment groups yielded P equals .051 favoring Replagal. FDA has been somewhat critical of this presentation of the data, and they have pointed out various physiological implausible results in two creatinine clearance measurements in the week 23-24 time period of this study.

In order to address that concern, we had a plan in place that the NIH nephrologists put in place to devise an operational plan for excluding creatinine clearance evaluations that were considered under collections. Thus, there's a very straightforward explanation for what appear to be physiological implausible results, and by excluding those creatinine clearance samples at week 23-24 and with exclusions of other creatinine clearance samples, the presentation of these data can also be presented as follows.

Baseline, month two, month four, month six, again, a progressive decline in patients randomized to placebo, and stable renal function in patients randomized to Replagal with a very similar statistical comparison as the previous result.

We have also studied renal function in the 003 study with GFR, and those comparisons were not statistically significant, although qualitatively were quite similar. There was a progressive decline in renal function in patients randomized to placebo. There was a slight decline in renal function in patients randomized to Replagal. That was about three times less than the decline in patients who received placebo.

As I mentioned, we recently conducted a randomized double blind placebo controlled study called 010, which was also conducted over a six month time period, and the results of that study are shown on this slide. In this six month study, there was no difference between Replagal and placebo in terms of the effective therapy on renal function as measured by GFR.

Well, those are the short term effects of therapy with Replagal on renal function. What are the long term effects?

This slide has simply reproduced the creatinine clearance results from the original NIH 003 study, and as I mentioned, these patients have now been followed for an additional two years, and the results are quite important.

Focusing first on the patients who were randomized to placebo, there was a significant decline in renal function associated with therapy with placebo. Coincident with crossover to Replagal in this patient population, the decline in renal function was immediately blunted, and over the subsequent two years of therapy, there was a slight improvement in renal function over that time period.

Patients who have received Replagal over this two and a half year time period also have had stable or slightly improved renal function over that time period.

I will again remind you that the baseline age of these patients when they began therapy in the 003 study was about 34 years old, a time when we know from the natural history literature, as Dr. Thadhani discussed, that progression to end stage renal disease is quite rapid in these patient populations.

Thus, at this point these patients are now more than 37 years old on average, a time at which we know from the progression to ESRD these patients should be rapidly approaching end stage renal disease, but instead they have slightly improved renal function over that time period.

The results for GFR are quite similar. Again, the original randomized, double blind, placebo controlled study. Very similar results in the placebo population. A decline in renal function associated with placebo, and coincident with crossover to Replagal, this decline has not only been halted, but over the subsequent two years of therapy, there's a slight but not statistically significant improvement in renal function over that time period.

A similar effect in patients who have received Replagal for the full two and a half years of these studies. Stable renal function over the two and a half year time period.

Thus, in the two years of therapy in the six and 11 studies, whether renal function is measured by either creatinine clearance or inulin based GFR, the results are the same. Not only are patients not declining, but there's a slight improvement in renal function over that time period.

How do these results compare to the natural history of disease? That is, what would we have expected to happen to this patient population if they had not received Replagal in these studies?

This slide reproduces the slide that Dr. Thadhani showed earlier and is normalized to the baseline renal function of all of the patients in the NIH study at the time at which they initiated therapy, that is, the beginning of the three study for the patients who were randomized to Replagal, the beginning of the six study for the patients who were randomized to placebo.

Base on the data that Dr. Thadhani showed, in a patient population who is in their mid-30s, on average 34 years old at this time point, two and a half years of Fabry disease would be associated with a decline in renal function that would be expected to fall somewhere within this range.

Patients who have received Replagal are quite different. Again, initially there is initial stabilization of renal function, which is followed by a slight improvement in renal function, and this is the full two to two and a half years of therapy in these studies. Again, quite different from what we would have expected to have happened to these patients and very different from the patients who have received placebo in our clinical studies.

How do the individual patient results at two to two and a half years compare with the natural history of disease? What I have done on this slide is summarize the distribution of changes of renal function in the patients who have completed two to two and a half years in the NIH studies. The bottom of this line presents the expected magnitude of decline based on a rate of change of 8.3 mLs per minute up to 21 mLs per minute per year, as Dr. Thadhani discussed.

More than half the patients who received Replagal in these studies not only have not declined, but actually have slightly improved renal function over that time period.

In addition, about another quarter or so of patients are declining at a rate that is less than we predicted from the natural history literature and the behavior of placebo patients in our clinical studies.

A small number of patients probably are not responding to Replagal in the kidney, but I will point out that of these five patients who may not be responders in this case, four of these five patients have had reductions in cardiac mass based on MRI and have evidence of a response in the heart data, which I will come to in a minute.

Well, as Dr. Thadhani discussed, as

patients are progressing to end stage renal disease in their mid to late 30s, the ultimate consequence of this disease is progression to end stage renal disease. How do the patients who have received Replagal compare to the patients in the literature?

This gray line presents the Kaplan-Meier analysis of the 116 individual patients reported in the literature, presenting the percent of patients without ESRD as a function of age. The yellow line presents patients in the NIH studies who have received Replagal.

None of these patients have progressed to end stage renal disease during this two to two and a half year time of observation, and indeed, since progression to end stage renal disease would be considered a serious adverse event, since it would qualify as an important medical event, our ongoing safety surveillance of this study can tell us that these data are valid up to about three and a half years of therapy in these patients.

Thus, for three to three and a half years of therapy a time at which patients are now about 38 years old on average, none of these patients have progressed to end stage renal disease.

In order to determine whether or not the patients treated with Replagal are significantly different from the patients described in the literature, we performed an at risk analysis in which we used this curve to determine the conditional probability of progressing to end stage renal disease, given the probability that a patient was not in ESRD at baseline. Being in ESRD was an exclusion criteria for the 003 study, and the results of that analysis are shown on the next slide.

Firstly, in the study 003, there were 12 patients who received placebo in that study. The sum of the probabilities of progressing to ESRD in those 12 patients, on average 34 years old, over six months is 0.7. The sum of probabilities then represents the number of expected events in this patient population.

Thus, we would have expected .7 patients to progress to ESRD during that study, and indeed, we unfortunately did observe one event in a patient randomized to placebo who progressed to end stage renal disease during that study.

For the 24 patients who have received Replagal in the three, six, 11 series, based on their average age and the period of follow-up of three and a half to four years, that is, current to today, we would have expected about 4.7 patients on average to progress to end stage renal disease during this time period of observation, and as I mentioned, we have, in fact, observed zero events, and the probability of observing zero events based on the natural history data is 0.006, suggesting that Replagal has significantly delayed the time to progression to end stage renal disease in this patient population.

Having discussed the effect of Replagal on renal function, I would now like to discuss the effect of Replagal on kidney pathology in these patients. This slide simply reproduces the slide I showed earlier to remind you that in the kidney where there is an inexorable clinically progressive nephropathy in these patients, there also is a histological progression of disease that can be characterized as follows.

Early in the disease when patients are relatively young there's GB3 deposition within podocytes and preservation of glomerular architecture.

We then seek glomeruli with mesangial widening, which ultimately progress to glomeruli with focal and segmental glomerular sclerosis, and then ultimately culminating in overt glomerular obsolescence.

It was this aspect of the pathology of disease that will be the focus of the effects of Replagal on renal pathology. I'll begin with a brief review of the kidney pathology procedures in study TKT 003.

In that study, patients underwent baseline and month six renal biopsies. Outcome measures included assessments of lipid deposition and also an assessment of the standard glomeruli histopathology of disease in which glomeruli were categorized into one of these four mutually exclusively categories. Glomeruli were categorized as either normal, with mesangial widening, with segmental sclerosis, or overtly obsolescent.

Importantly, I'll point out that a mean of 24.3 glomeruli were examined per biopsy specimen.

Just to review the procedures for this study in some more detail, as I mentioned biopsies were performed at baseline and week 24 of this study. The biopsies cores that were taken were immediately fixed and imbedded by pathologists at that AFIP, Armed Forces Institutes of Pathology.

All blocks were then assigned a unique random number, and when the blocks were sectioned and stained, the slides retained the random number assigned to the individual blocks.

Following completion of the dosing portion of study TKT 003, the investigators amended the planned analysis to include an assessment of standard glomerular histopathology which the investigators felt was more important in this disease rather than simply studying the effects on lipid deposition.

In addition, the investigators modified the study so that the slide were read in one batch. That is, the study initially intended the biopsy specimens to be paired, but the investigators felt that this would be a more rigorous assessment of these slides, and therefore, the pre and post study biopsies could not be paired in this analysis, and two renal pathologists at the AFIP subsequently read all of the slides in one batch, and consensus was reached on the determination of glomeruli.

The results are shown on the next slide. Patients who were randomized to placebo in this study had a decrease in the fraction of glomeruli that were considered normal. This is not surprising, given the fact that we know that these patients had a decline in renal function during this time period, and this suggests that this measurement of renal pathology correlates with the measurement of renal function in these patients.

Patients randomized to Replagal, on the other hand, had an increase in the fraction of glomeruli that were considered normal, and this difference was significant.

In terms of the pathologic component of mesangial widening, the results were quite similar, namely, patients who were randomized to placebo had an increase in the fraction of glomeruli with mesangial widening, and patients randomized to Replagal had a decrease in the fraction of glomeruli with mesangial widening, results that were also significant.

These first two panels suggest that the pathologic aspect of mesangial widening is, in fact, reversible with therapy, perhaps not unlike diabetes mellitus and the effects of pancreas transplantation.

Progression of disease in placebo patients associated with an increase in the fraction of glomeruli with mesangial widening, improvement of the pathology of disease in patients randomized to Replagal with glomeruli with mesangial widening essentially becoming normal following six months of therapy with Replagal.

In terms of segmental sclerosis and obsolescence, not surprisingly these two aspects of the kidney pathology are not reversible. There was a small increase in the fraction of glomeruli with segmental sclerosis in the patients randomized to Replagal and a small decrease in the patients who received placebo. This did favor placebo. However, I think this is really an artifact of these glomeruli in the placebo population progressing to obsolescent glomeruli, changes that were, of course, not significant.

In determining whether or not a potential surrogate marker is reasonably likely to predict clinical benefit, it's important to determine whether or not measurements of that marker correlate with function.

On this slide we have plotted the baseline renal function in all of the patients who were enrolled in study TKT 003 as measured by creatinine clearance versus the fraction of glomeruli that are normal, and what we've discovered is that there is a significant linear correlation of the fraction of normal glomeruli with renal function. That is, the larger the fraction of glomerular or kidney biopsy that are normal, the better the renal function.

Not surprisingly, the lower the fraction of glomeruli that are considered normal, the lower the renal function in these patients.

In terms of the pathologic aspects of

disease, exactly the opposite result is seen. We've discovered a significant negative linear correlation of renal function with the fraction of glomeruli that are sclerotic and obsolescent. That is, the larger the fraction of glomeruli that are sclerotic and obsolescent, the worse the level of renal function in these patients, and lower fractions of glomeruli with these aspects of disease, the higher the level of renal function in these patients.

Thus, in the kidney therapy with Replagal is associated with the following effects. Replagal at least stabilizes renal function in these patients, and again, I will point out that the patients enrolled in these studies were on average age 34 and today are on average about age 38. Thus, this represents a true therapeutic effect of Replagal in this patient population.

Some of these patients improve renal function over that time period.

Replagal may delay progression to ESRD in these patients not surprisingly, given its effects on renal function at least compared with historical control patients.

Replagal therapy significantly improves the renal pathology of Fabry disease, and importantly, standard renal glomerular histopathology is reasonably likely to predict clinical benefit since measurements of renal pathology in this way correlate with renal function.

I will also add that since Replagal was approved in the European Union in August of 2001, we've treated over 200 patients with Replagal and have followed them in a registry database, and we have very intriguing data which we're happy to share with you that suggests that patients with abnormal renal function perhaps have the most therapeutic benefit of Replagal.

Having discussed the effect of Replagal on renal structure and function, I'd now like to turn to a discussion of the effects of Replagal on the heart. As Dr. Thadhani mentioned, Fabry disease is a hypertrophic cardiomyopathy characterized by elevated LV mass in this patient population.

The first study of cardiomyopathy we

performed was study TKT 005, which was conducted at Royal Free Hospital in London. Fifteen patients were enrolled in this study, which was a randomized, double blind, placebo controlled study conducted over six months.

There was one important selection criteria difference between this study and the NIH studies, and that is patients were required to have left ventricular hypertrophy based on echocardiographic evidence of increased wall thicknesses. Thus, these patients at baseline had markedly abnormal LV masses at 262 grams at least 50 percent above the normal range, consistent with severe cardiomyopathy in these patients.

The primary endpoint in this study was a reduction in cardiac GB3 content as measured directly in endomyocardial biopsy specimens. These results favored Replagal, but were not statistically significant.

The principal secondary endpoint of this study was the effect of Replagal on LV mass as measured by MRI. Patients randomized to placebo had an increase in LV mass during this study, and patients randomized to Replagal had a decrease in LV mass during this study.

Patients who received placebo with a baseline LV mass of about 250 grams gained 20 grams in LV mass during the six months of this study. Data that are emerging from studies of patients in Europe and additional Phase IV studies in Europe suggest that this change is consistent with the natural history of the progression of cardiomyopathy in this patient population.

Similar to the effects of Replagal in the kidney, there was a decrease in LV mass as measured by MRI in this study, and the comparison of these changes was significant.

We also studied the effect of Replagal on cardiomyopathy in the NIH studies 003 and 006. As I mentioned earlier, there wee no selection criteria for abnormal LV mass in these studies. So patients had a slightly lower LV mass at baseline, but still quite abnormal at 219 grams on average.

Twelve to 18 months of therapy is

associated with significant declines in LV mass compared to baseline in this patient population.

Of the 16 patients enrolled in this study who had elevated cardiac mass at baseline, 13 of these patients have declines in LV mass with 12 to 18 months of therapy.

In addition, in half of these patients 12 to 18 months of therapy was associated with a decrease in LV mass into the normal range from abnormal.

Of interest in the original 003 study, we also saw a significant effect of Replagal on cardiac conduction system function as measured by QRS complex duration. The most common aspect of cardiac conduction defects in these patients are prolongation of the QRS complex which leads to bundle branch blocks, and involvement of the QRS complex duration is associated with dysrhythmias in this patient population.

Therapy with Replagal reduced QRS complex duration therapy with placebo, was associated with a progression of the QRS complex duration, results which were significant.

In terms of the effect of Replagal on LV mass in the three and six studies, those results are shown in this slide. I'll mention that we no longer did cardiac MRIs in the 11 study. So this represents 12 to 18 months of therapy in this patient population.

Firstly, in terms of the double blind portion of the study, there was no difference between placebo and Replagal in this patient population. However, long term therapy has demonstrated a significant decrease in LV mass in these patients.

In patients who initially received placebo in the three study, there was a progressive decline in LV mass that was significant after one year of therapy

In the patients who initially received Replagal, 18 months of therapy was also associated with a significant decline in LV mass based on the change from baseline.

A third set of patients in whom we have studied the effects of Replagal on cardiac mass are the patients enrolled in study TKT 014, conducted at Mainz, Germany. Again, I'll remind you this was a study of female patients with Fabry disease. Patients enrolled in this study had a mean LV mass at baseline of about 254 grams, thus again consistent with the observation of many described in the literature that female patients have a very similar clinical syndrome as male patients with Fabry disease.

Six and nine months of therapy were associated with significant declines in LV mass from baseline. I'll point out that the echocardiograms in this study were read in a blinded fashion, although this was an open label study.

There were also statistically significant declines in other measurements of cardiomyopathy, including cardiac mass index and various wall thicknesses, including the left ventricular posterior wall and the inner ventricular septum.

In 12 of these 15 patients with elevated LV mass at baseline LV mass declined in all 12 of those patients and normalized in four of the 12 patients.

Similar to the 003 and 006 studies, there were also statistically significant declines in QRS complex duration during this study.

In terms of the effects of LV mass, those results are shown on this slide. The first thing I'd like to point out is that the number of patients who have completed the various milestones in this study progressively decreases. Enrollment into this study was staggered, and then the study was terminated following approval of Replagal in the European Union.

So although 15 patients were enrolled at baseline, 11 patients completed month six and seven patients completed month nine.

Regardless, there's a significant decline and progressive decline in LV mass in these female patients with Fabry disease with six to nine months of therapy.

Importantly, since the long term effects of Replagal have demonstrated more significant improvements in patients compared with short term therapy, these patients have all been followed in various Phase IV studies at Mainz, and Dr. Christoph Kampmann, who has led those studies, is here today, and results of the continued follow-up of these patients in Phase IV studies is shown on this slide.

Thirteen patients originally enrolled in Study TKT 014 have now completed one year of therapy with Replagal, and there has been a progressive and significant decline in LV mass from baseline in these 13 female patients who have completed one year of therapy with Replagal.

Thus, in the heart Replagal at least initiates the reversal of cardiomyopathy in these patients. Evidence for this includes regression of left ventricular hypertrophy, which includes normalization of LV mass in many patients treated for 12 to 18 months.

I will also add that Dr. Kampmann has completed an additional Phase 3B/4 type study of now a fourth patient population, males with Fabry disease, and has seen similar results in that Phase 3B/4 study.

We've seen significant improvements in cardiac conduction system function in each of the patient populations that we've treated. Thus, in at least four different patient populations in multiple different clinical studies we've seen consistent effects of Replagal in the regression of left ventricular hypertrophy, including the normalization of LV mass in many patients treated.

Briefly I'll discuss the metabolic effects of Replagal. As Dr. Thadhani described, the GI involvement of Fabry disease often leads to a syndrome characterized by chronic weight loss. In the original 003 study, placebo patients continued to lose weight while patients randomized to Replagal had weight gain in that study, results which were significant.

This was also associated with anecdotal reports of improvements of GI symptomatology, including decreases in diarrhea, and these long term effects were confirmed in the 006 study.

We've seen GB3 declines in plasma, urine sediment, and we've seen trends favoring Replagal in kidney and cardiac biopsy tissue specimens.

I'll conclude the discussion today with an overview of the safety profile of Replagal. The safety profile of Replagal has been excellent. We have now treated over 300 patients worldwide with Replagal in a combination of clinical trials, compassionate use programs, and over 200 patients have been followed in the FOS registry system in the European Union.

And Dr. Atul Mehta is here today, one of the FOS investigators, who can discuss some of the safety data with you.

The most common adverse events in clinical trials are consistent with the natural history of Fabry disease. The vast majority of adverse events were mild to moderate in severity, and the majority of adverse events were assessed as not related to study drug.

The most common adverse events are infusion reactions, which are associated with the intravenous infusion of Replagal. I will point out that the routine use of premedications is not required with therapy with Replagal. Thus, our estimates of the incidence of infusion reactions are not masked by the routine use of premedications in this patient population.

We see mild infusion reactions in about ten percent of patients treated, and this has been confirmed by the FOS registry data in which over 200 patients have been followed, representing over 6,000 infusions of Replagal in that patient population.

The most common adverse events are chills and rigors and facial flushing. The correlation of these adverse events with antibodies is not so clear, but we don't have a real clear association of the association of antibodies with these infusion reactions.

Importantly these reactions are very easily managed with a simple oral regimen of antihistamines and/or corticosteroids, and patients often tachyphylax to these infusion reactions with time.

In terms of the patients at the NIH who had a slightly higher incidence of infusion reactions as they received 20 minute infusions of Replagal, this two by two table shows the association of antibodies with infusion reactions in that population. Among ten patients who have had infusion reactions, six are antibody positive; four are antibody negative, and of ten patients who are antibody positive, six have had infusion reactions and four have not.

In terms of the antibody response to Replagal therapy, among the patients who have been followed for the longest period of time, which is the patients enrolled in the initial 03 study at the NIH and the 005 study at Royal Free Hospital, we have data on 40 male patients up to two and a half years of therapy.

About 30 percent of these patients develop a persistently positive IgG antibody. We've never seen a positive IgE antibody and have never seen a clinical syndrome that would suggest an IgE mediated syndrome.

The vast majority of these IgG antibodies are quite low titer, about one to 50 or one to 100. We have a single patient who is positive at one to 2,500, and none of the female patients who have received Replagal have developed an antibody to Replagal.

The generation of immune response to Replagal, of course, begs the question of whether or not these antibodies affect clinical efficacy. Some patients who have persistently positive antibodies do have lower decreases in glycosphingolipid levels a measured in plasma compared with patients who are not antibody positive. These are the long term data from study TKT 011.

I'll point out that these n's for these means are different. So these time points are not comparable. So it's best to compare the experience at time zero to month 24.

As we've discussed in our briefing booklet, measurements of plasma GB3 do not correlate with any measures of clinical efficacy, and indeed, plasma GB3 represents an extremely small component of total body GB3, perhaps less than one percent of total body GB3.

The more important question is: do these antibodies affect any measure of clinical efficacy?

In terms of the effect of Replagal on renal function as measured by creatinine clearance, this slide separates patients who are persistently antibody positive versus patients who are antibody negative, and again, there's no difference in the stabilization of renal function in patients who are antibody positive or antibody negative.

This difference at month 30 again is an artifact of the difference in the n's of patients who have completed those time points. Similarly, very similar results are seen in terms of the effect of antibodies on the regression of left ventricular hypertrophy in these patients. The same problem here.

So focus on the time from zero to month 12. Patients who are antibody negative or patients who are persistently antibody positive have no difference in the regression of left ventricular hypertrophy. Thus the formation of a low titer IgG antibody has no effect on the clinical efficacy of Replagal as measured by either renal function or cardiomyopathy.

In terms of the generation of antibodies to Replagal, about 30 percent of patients develop a low titer IgG antibody. As I mentioned, we have never seen an IgE antibody or a clinical syndrome that would be consistent with an IgE mediated phenomenon. It's interesting to speculate that this may reflect the fully human glycosylation profile of the molecule.

We've seen no clear correlation of IgG antibody response with infusion reactions, and although in a small subset of patients IgG antibody formation can affect plasma GB3 levels, there's no effect of these low titer IgG antibodies on measurements of clinical efficacy based on the effects of Replagal on renal function or cardiomyopathy, and importantly, with long term therapy we have seen no evidence of immune complex formation in this patient population.

This slide summarizes the clinical development program for Replagal and the results in patients with Fabry disease. The data that I've shown you today demonstrate that Replagal improves standard glomerular histopathology in these patients, and measurements of glomerular histopathology correlate with renal function and, therefore, are certainly reasonably likely to be a surrogate marker for clinical efficacy.

However, Replagal also affects kidney function. Based on the stabilization of renal function and the improvement in some patients at 30 months, in a patient population in their mid-30s, a patient population that would be expected to be declining quite rapidly and progressing to ESRD.

On the contrary, patients who have received Replagal have not progressed to end stage renal disease. Thus, Replagal delays the time to progression to end stage renal disease in these patients.

The effects in the heart have been quit consistent in multiple different patient populations and multiple different studies. Replagal clearly reduces left ventricular mass in these patients and improves carduction (phonetic) system function based on narrowing of the QRS complex duration.

We have not surprisingly concomitant metabolic improvements in these patient populations, and as I discussed, the safety profile of Replagal in clinical studies and in post marketing safety surveillance has been excellent.

Thus, the benefits of therapy with Replagal overwhelmingly outweigh any risks associated with therapy, and this benefit-risk profile strongly supports approval of Replagal in the United States at this time.

Thank you.

DR. KIRBY: That concludes the formal presentations from TKT this morning. We look forward to answering any questions you may have either now or later in the session.

Thank you for your attention.

CHAIRMAN AOKI: At this time the committee can address questions to the sponsor.

Dr. Barisoni. Please turn on your microphone.

DR. BARISONI: I have a few questions on the pathology. First of all, the mesangial widening that you show us is quite mild, and I wanted to know how you quantified the lesion when it increased and when it decreased after the treatment with Replagal.

DR. SCHUETZ: The question is how is mesangial widening quantified?

DR. BARISONI: Yes.

DR. SCHUETZ: Each glomerulus was assessed as falling into one of four mutually exclusive categories, either with normal architecture with mesangial widening, which required a diffuse increase in the mesangial matrix. That was the definition that was utilized in order to categorize glomeruli into that category with segmental sclerosis or with obsolescence.

So each individual glomerulus was categorized as either with mesangial widening or not, with something else.

DR. BARISONI: The reason why I'm asking though is because the mesangial widening is very mild compared to what we will see in other diseases, and I was wondering how this mild mesangial widening can influence the renal function.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: Along this same line, I want to address the issue of a correlation with function because it has been suggested that the changes in pathology might serve as a surrogate, and that might be useful because the changes in function correlate with or at least the structure correlates with function.

I'd like to point out that the change in structure that we were shown was a decrease in the fraction of glomeruli that are classified as having mesangial widening in the patients that were treated. So the major difference is this difference in mesangial widening.

I then went back to your briefing booklet on your page 59 where you show the correlation, which is the critical correlation between the degree of mesangial widening and function, and I saw no very convincing relationship there.

Now, it would be expected that there would be correlation between total structure and function. That is to say if you lose glomeruli either totally in the total obsolescence or with focal sclerosis or whatever, you would expect that to be associated with changes in function, but those weren't changed in either group. The real critical issue is whether this change in structure is associated with a change in function, and I see no convincing evidence for that.

I also would like to add to that challenge, I suppose, to you the question of interstitial changes. My recollection is that there were not many differences in interstitial changes, and it is well recognized that the best correlate with function is actually the state of the interstitium rather than the state of the glomeruli.

DR. SCHUETZ: I have two comments on the first part of that question. Firstly, the changes in kidney pathology were driven by not only a decrease in the fraction of glomeruli with mesangial widening, but also an increase in the fraction of glomeruli that were considered normal.

So those two changes, that was really the critical change.

You're referring to this figure from our briefing booklet which is, I think, quite a complicated figure, but I think is consistent with our interpretation of the data, and I think that you can see from this figure which correlates the fraction of glomeruli with mesangial widening with GFR in these patients that there's really almost a classic boomerang type curve.

That is, having a glomerulus with

mesangial widening is consistent with either normal renal function or severely compromised renal function. So that as patients begin to lose GFR, the fraction of glomeruli with mesangial widening increases, but then at some point, perhaps in this level of GFR, these glomeruli then become glomeruli that are sclerotic and obsolescent. Thus, as GFR falls further, there's a decrease in the fraction of glomeruli with mesangial widening going in this direction on the graph, consistent with progression of these glomeruli to glomeruli with obsolescence and mesangial widening.

And the data that I showed earlier suggests that the highest fraction of glomeruli with sclerosis and obsolescence occur at very low GFRs not surprisingly.

DR. HUNSICKER: Well, I must confess that's a very creative explanation, and it may even be true, but the underlying fact is that you cannot correlate the fraction of glomeruli with mesangial widening with function, and that was the assertion.

DR. SCHUETZ: No, I'm sorry. I did not

mean to assert that. The correlation was between the fraction of glomeruli that were normal and the fraction of glomeruli with sclerosis and obsolescence. And I agree with you. I find this correlation fascinating in terms of I find this scatter plot fascinating in terms of the pathological regression of disease. It is not my intention to be creative. Clearly there is no correlation, as it were, in this data, but I think these data are consistent with the progression of disease.

DR. HUNSICKER: And relation of interstitial changes and whether there were any differences in interstitial changes?

DR. SCHUETZ: We did not see any differences in interstitial changes.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: Several questions. The first concern, a couple of parameters of renal dysfunction that were mentioned in the introduction, but not mentioned as being evaluated in outcomes. There was a mention that there are renal tubular defects that occur in these patients, and I wonder if you monitored those and saw any changes.

And there was also mentioned that a substantial number of patients, especially those at this stage of disease who have proteinuria. So did you monitor proteinuria as a measure of changes in function or dysfunction?

DR. SCHUETZ: So the question is: what are the effects of Replagal on measurements of tubular function? And second, what are the effect of proteinuria?

Regarding the first part of that question, I have a two part answer. The first part is we did not rigorously study concentrating defects in this patient population. So we did not, in fact, do water deprivation tests sa a part of the study. So we didn't study that.

Although we have seen a decline in urine sediment GB3 content, it's unclear what the functional significance of that is, but we've seen a decline which represents decreased in GB3 tubular epithelial cells.

In terms of proteinuria, these patients

have an incredibly broad range of proteinuria. I believe the range at baseline in the 003 study was something like 200 milligrams to almost ten grams per 24 hour.

So because the variability was so great in the patient population, we have not seen any differences in proteinuria. However, we have followed a number of individual patients over time, and this graph simply shows an individual patient in these studies followed over two years who had a relatively low level of proteinuria, although still abnormal at 350 grams of total protein for 24 hours and a little over 200 grams of microalbumin over 24 hours, and over the one to two years of therapy this patient had a progressive decline in proteinuria. Again, this is just one patient, but we have seen that effect in multiple patients and in several studies, gut we've seen no effect in the population as a whole.

I think this reflects the broad range of proteinuria in these patients.

DR. JENNETTE: And one final question. Again, in the introduction the point was made that the prime mover in this process is the accumulation of the substrate within cells, but you mentioned only in passing observations about the bulk of lipid before and after treatment. Could you comment further on your conclusions about whether or not there was a real reduction in the amount of substrate in cells?

DR. SCHUETZ: Sure. We looked at a number of different cell types in this study. We studied vascular endothelial cells in the interstitium and quantified that based on a semi-quantitative zero to three scale. Patients randomized to Replagal had a significant decline in GB3 content in vascular endothelial cells, and patients randomized to placebo had a slight increase, and that difference was significant, demonstrating a decline in vascular endothelial cells.

We also studied capillary endothelial cells in the glomerulus, and in terms of the effect on the capillary endothelial cells in the glomerulus, the results were quite similar, and that was also quantified on a zero to three scale and patients randomized to Replagal had a significant decline --

this is the wrong slide -- had a significant decline in glomerular endocapillary GB3 deposition. Patients who had received Replagal had a score of 1.2 at baseline, which declined to 0.5; no change in the placebo population, which was significant.

So in terms of the effect of Replagal on interstitial and glomerular or capillary endothelial cells GB3 content, Replagal significantly reduced those inclusions as well.

DR. JENNETTE: What about podocytes?

DR. SCHUETZ: We did not see in the population a significant improvement in podocyte GB3 content, although we've seen some qualitative differences. There were no quantitative differences that were significant.

CHAIRMAN AOKI: Dr. Barisoni.

DR. BARISONI: In the picture in the slide number 51, you said that the renal function is tabled and there is a delay in progression, and also there is an improvement in renal pathology.

However, in slide 48, you show that there is an increase in focal segmented sclerosis after six months of treatment, and focal segmented sclerosis is part of progression, of chronic progression of renal disease, number one.

And number two, I want to know whether you correlated the amount of segmented sclerosis with the amount of proteinuria.

DR. SCHUETZ: In terms of the second part of your question, we did not do that correlation. The data to which you refer is here. I think these are the data. There was a slight increase in the fraction of glomeruli with segmental sclerosis in the treated population, but I think this simply tells us that there are some aspects of mesangial widening that are not reversible and that there are some aspects of the kidney pathology of this disease that are not reversible.

And I think segmental sclerosis and certainly glomeruli obsolescence are two components that are not going to be reversible.

CHAIRMAN AOKI: Dr. Sampson.

DR. SAMPSON: I actually wanted to follow up a question of Dr. Hunsicker's, and that is: did you do any graphics of the -- you have data on change in fraction of normal glomeruli over six months. Do you have graphs of those versus change in GFR that we could see a correlation in that?

DR. SCHUETZ: Yes, we do.

I will also add that the correlation of GFR with kidney pathology at week 24 was quite similar to baseline. That is, there was no linear correlation of the fraction of glomeruli that were normal, and a negative linear correlation of the fraction of glomeruli with segmental sclerosis.

And you're asking for the correlation of the change in GFR with the change --

DR. SAMPSON: In the percentage.

DR. SCHUETZ: -- in these measurements of kidney pathology, and we have that for our treated patient population, and those show that the change in the fraction of normal glomeruli is consistent with what you would expect. That is, there is a positive correlation, namely, an increase in the fraction of normal glomeruli is associated with positive improvements in GFR.

And for mesangial widening, it's just the opposite. There is a negative correlation. That is -- I need the slide with the two correlations, please, the two correlations on the same slide -- there is a negative correlation. That is negative changes in the fraction of glomeruli with mesangial widening are associated with improvements in GFR.

This is a very complicated slide, and the correlations are not quite so statistically compelling because the n's are a little bit lower here, but you can see that this slide is divided into the change in the fraction of glomeruli that were normal and the change in the fraction of glomeruli with mesangial widening.

So the axis here is zero right here and zero here. So, again, the slope is positive for the change of normal glomeruli with the change in GFR. So positive, normal, positive GFR.

And in terms of mesangial widening, exactly the opposite, that is, a negative correlation is seen, a negative slope is seen so that lower fractions of glomeruli with mesangial widening correlate with better GFR and vice versa.

DR. SAMPSON: Is there a P value for the percentage normal for that correlation? It looks like it might be insignificant because --

DR. SCHUETZ: It is not significant for the change of normal, but for mesangial widening the P value is .06.

DR. SAMPSON: the other question I had is just perhaps a much more simple one, but at baseline in Replagal the percentage is right around 40 percent. In placebo, it's 60 percent. Are those significantly different? They look quite different beyond what one might expect by chance, but I think --

DR. SCHUETZ: Those are standard error. The bars are standard error.

DR. SAMPSON: In comparing the baseline, would you have a --

DR. SCHUETZ: They are not significantly different. Also I'd add that all of the analyses were ANCOVA that utilized the baseline value as the only covariate.

DR. SAMPSON: Thank you.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I'd like to return to the proteinuria for a moment. I realize with such a broad range that it will be impossible to show significant differences in the mean levels, but surely you can show us the percent changes from baseline or the direction of change from baseline among the patients who were treated.

DR. SCHUETZ: We looked at that. The percentage changes are really -- the mean percent change is kind of all over the map because we had so many patients with nephrotic range proteinuria. So we had patients who varied over the study between three, four, five, eight grams of protein. So we didn't see anything in the mean percent changes either.

DR. WOOLF: How about comparing the changes versus the baseline? What you're saying is --

DR. SCHUETZ: The changes versus --

DR. WOOLF: If the baseline were mild proteinuria to begin with, then perhaps you might see a better change, percent change.

DR. SCHUETZ: We haven't done that.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: I'm just trying to get my data clear here. As far as I can tell here, you have three randomized trials, right? That's 003, 005, and 010.

DR. SCHUETZ: Yes.

DR. GRADY: And they contain 26, 15, and 80 patients.

DR. SCHUETZ: Yes.

DR. GRADY: So really a lot of the data is coming from this trial 010, which is completed but you're not presenting; is that right?

DR. SCHUETZ: We only unblinded that study about six weeks ago. The only result I presented from that is the effect on GFR. I haven't presented any other data from that study.

DR. GRADY: Right, and that's another thing that bothers me a big, is you seem to have sort of selected things to present. So I'm trying to also get clear changes in creatinine clearance and GFR, and you presented both of those for study 003, in which there was a statistically significant or close to it anyway improvement in creatinine clearance, but not in

GFR.

Don't you have those similar results from 005 that you could present to us? Those are, you know, to some extent the main outcome of your research.

DR. SCHUETZ: The results from study 005 were quite consistent with the results from 003, but the patients in the 005 study had really very normal renal function at baseline, and there were only 15 patients in that study. So that individual study did not show a difference.

DR. GRADY: And what about creatinine clearance from 010?

DR. SCHUETZ: I don't have that data.

DR. GRADY: So you have the GFR but not creatinine clearance?

DR. SCHUETZ: Yes, the GFR was the primary endpoint.

CHAIRMAN AOKI: Dr. Barisoni.

DR. BARISONI: I have a question on the mechanism. How do you think the Replagal works on the regression of mesangial widening or other pathologic findings?

DR. SCHUETZ: That's an interesting question. I think that whatever precipitates the cascade of events, at the mesangial widening stage, that cascade can be interrupted. In terms of what the precise mechanism is, I assume it has something to do with GB3, but I'm not certain what the mechanism of this progression is. So it's interesting to speculate, but I'm just not sure on what the mechanism by which Replagal improves renal pathology.

CHAIRMAN AOKI: Dr. Hunsicker?

DR. HUNSICKER: I have an opinion about the creatinine business, which I will express, but I also have a question, and I don't want the question to get lost as I express the opinion. So let me put the question first. The question actually has to do with the establishment of dose in your dose response study. It has been noted that the dose that you're using is not the dose that was tested in the dose response study. In fact, you could argue that the dose might not be enough because the amount of change that you see is possibly less than you might have seen had you had a higher dose.

So the issue of selection of dose is a major issue here because that is one of the things that we have to know going into this. Is the dose the correct dose? I don't want to lose that.

I want to speak to the issue of creatinine clearances in the I guess it was 003. I don't keep the numbers straight, but the study that is really the critical study where there was a difference -- yeah, 003 -- in creatinine clearance.

It has been pointed out by the FDA that there is an anomaly here in that there was a substantial difference between the creatinine clearances in the last two weeks, two successive weeks, which are biologically implausible, and there has been a response to that in terms of selection of certain values that should be used and certain excluded.

There are several issues to be made or several points to be made with respect to all of this creatinine business. The first is that the state of the art in the United States right now is to use either serum creatinine or transform serum creatinine rather than to use creatinine clearances because actually doing creatinine clearances adds more noise to the study than it does information.

Now, this is particularly true when you're talking about sequential creatinines or measurements within a certain patient. The point of the clearance, that is, measuring the urinary excretion, is to correct for differences in patient size, something that's not likely to have been striking over the period of time in the study.

So you get greater precision without losing much accuracy by looking at the serum creatinine changes themselves over time.

The serum creatinine changes which are really primary data -- they are not calculated data -- were not significantly different between the two groups at any of the time points.

The issue of removal of implausible creatinine clearances has been addressed previously by the MDRD study, which looked at numerous algorithms for being able to remove outlying creatinine clearances, and none of them were found to be statistically robust.

So I think that the sum of this is that the removal of those values is suspect. There is an unexplainable biological fall between the last week, and when you look at the serum creatinines which are primary data, they do not support the idea that there was a substantial change or a difference in the amount of change in renal function between the two groups.

Now, that I said was a statement. You are, of course, free to respond to it, but I do want to hear about the choice of dose.

DR. SCHUETZ: Let me just very briefly address the algorithm that was used for the creatinine clearance over and under collections in this study for your reference.

The nephrologists institute an operational definition, which was that over and under collections would be defined by a greater than 35 percent difference between the mean total urine creatinine of a suspected over or under collection compared to the other five creatinine clearances that were performed in the study for that patient.

The two clearances of question in these two patients at week 24 who for the other five creatinine clearance measurements during the study had a level of urine creatinine in their 24 hour urine of 17.6 milligrams per kilo of body weight and 25 milligrams per kilo of body weight, respectively, and in the two collections in question for this patient, it was 11 milligrams per kilo, and for this patient, 12.9 milligrams per kilo. So this was clearly a half collection in this patient.

So that was the definition, and I certainly agree with FDA that these two collections reveal physiologically implausible results.

The second part of your question was the question about using transformed serum creatinines in this study and those results are shown on this slide. Using the six variable MDRD equation, we estimated GFR based on the serum creatinine in these patients, and we saw, I think, quite consistent results with the results of both GFR and creatinine clearance.

Baseline GFR by MDRD in the Replagal

patients, 96, for a slight decline over the six month period, and a much larger decline in the placebo population with P equals .098 for the comparison based on the transformed serum creatinines.

The third part of your question was the question of dose. We mentioned that in our Phase I study we did a dose escalation study, and subsequently we chose a higher dose than the highest dose used in that Phase I study.

One of the results of the Phase I study that we used in part to help determine our selection of dose was that we discovered that progressively increasing the higher doses, there was a progressively lower fraction of dose delivered to the liver. Those data are shown on this slide, which estimates based on 75 kilogram patient the amount of the dose present in the liver at the five different doses we tested in the Phase I study, and from those data we constructed this curve, and at the highest dose approximately 15 percent or so of the administered doses were recovered in the liver.

We know that the liver is not an organ

that is involved in this disease. So our thinking here was that we wanted to maximize biodistribution away from the liver, and that's what went into our thinking of selecting the dose at .2 based on extrapolating this curve. We estimate that ten percent or so of the dose or less perhaps would be delivered to the liver, and that in part went into our dose selection thinking.

We also based on dose selection on rodent biodistribution data, GB3 clearance in the knockout mouse and some inherited pharmacokinetic studies that we did, but at the end of the day, the dose that we studied of .2 milligrams per kilo has effects on renal function and renal pathology and has clear effects on the cardiomyopathy of this disease.

And in addition, that dose, in part also based on our Phase I study, has been demonstrated to be quite safe. So .2 is the dose that we've studied in our studies, and the data that I've shown you today suggests that that dose is not only quite safe, but has strong evidence of efficacy.

CHAIRMAN AOKI: Dr. Sampson. I'm sorry.

Dr. Fleming.

DR. FLEMING: Thank you.

I'd like to have you show a few of the slides that you showed during your presentation as I'd like to explore just briefly some of the conclusions that you had raised in slide 69. So could you go to slide 53 first?

As you do, one of the conclusions on slide 69 was the reduction in LV mass that is claimed to have been established. In slide 53 it's interesting that there seems to be a baseline imbalance where the placebo patients had an on average lower LV mass.

Isn't it true, however, that in this sample size of eight versus seven you've left a patient out in the placebo -- can I finish please? -- where that patient had at baseline 457 grams, dropping to 395 grams at 13 weeks, and you primary specified analysis was a last observation carried forward? Where if you, in fact, followed your previous protocol specified analysis and put that patient back into the analysis, we would see comparable levels at baseline and nonsignificant differences in LV.

Is what I'm saying accurate or inaccurate?

DR. SCHUETZ: Yes, that's accurate.

DR. FLEMING: Okay. Could I go to the second? Could you go to slide --

DR. SCHUETZ: Could I just add one part to --

DR. FLEMING: Sure, sure.

DR. SCHUETZ: The imputation technique was for the primary endpoint in that study. So it's not quite as clear as you stated, but it is accurate that one patient because of claustrophobia did not have a week 24 MRI in the placebo population, and if you do last observation carried forward to that patient, the results are not significant.

DR. FLEMING: If we could go to slide 34, a second of your conclusions on slide 69 was that the stabilization of renal function had been established, and we had seen on slides 36 and seven that GFR in 003 and 010 weren't significantly affected.

On slide 34 what we see here is over the period of the randomized comparison no changes over time in the intervention group. In the placebo the

FDA in their briefing document on page 10 provides the overall creatinine clearance components for weeks zero, nine, 17, 23, and 24.

Now, your slide here indicates that on the placebo there's a linear decline. The FDA document indicates that the week 23 value was not very different from the week zero, and then there was this very interesting biological effect where all of a sudden from week 23 to 24 you had a substantial decline.

Is the FDA document inaccurate here? Is it, in fact, truly a linear decline as your slide indicates?

DR. SCHUETZ: The data that we've presented, the data as presented both in FDA's briefing booklet and in our briefing book, the data are the data.

DR. FLEMING: Well, I guess my fundamental question, because I know the Chair wants to keep us moving, and I have two more question: is the data accurate in the FDA document that indicates it's not a linear decline?

DR. SCHUETZ: I do not believe those data are accurate.

DR. FLEMING: Okay.

DR. SCHUETZ: And the reason is there are two reasons. Presented on this slide are the FDA's presentation of the raw data as presented in their briefing booklet and the data as we have presented them. There are several differences between these two presentations.

Firstly, the FDA analysis includes the two clear under collections that we discussed.

Secondly, the n's at this time point and this time point are different. So that these two means are not directly comparable. There are 11 patients here and 11 patients here, but they're not the same 11 patients.

So what we have done is used last observation carried forward to normalize the n's at each time point so that the means are directly comparable.

In addition, patients had two creatinine clearance samples performed at baseline, and the analysis was to have included the mean of those two baselines. FDA has selected one of those two baselines to use the baseline value in order to present this analysis.

The mean baseline, so this is 12 patients, 12, 12, and 13, suggest a progressive decline in renal function over that time period.

DR. FLEMING: So your re-analysis is the solid line?

DR. SCHUETZ: Yes.

DR. FLEMING: Which then actually doesn't show the same magnitude of decline that your previous slide showed. This shows a magnitude of decline of about 12.

DR. SCHUETZ: That's correct.

DR. SAMPSON: Tom, can I just ask one quick question? Mine was about the baseline for placebo there. The FDA doesn't point out, but there are two baselines for placebo and creatinine clearance, and the second one is substantially higher than the first, leading to a higher average.

I can't tell how you computed the average, but that also leads to the appearance of the downward slope in the placebo, whereas if you just use the first baseline, you certainly don't get that appearance.

I was wondering if you could say just a little bit about this second baseline value of 129.7, which seems also biologically quite different from the first baseline value of 107 for the placebo.

DR. SCHUETZ: Yes. The two individual baseline means -- let me just answer one part of your question there. We calculated the mean creatinine clearance for each patient, and then used that to calculate the means for the baseline one and baseline two because the n's are not the same at baseline one and baseline two. So you can't look at the means of those two and calculate a mean.

In terms of the differences in creatinine clearance between the baseline one and baseline two, those are the data. None of those creatinine clearances fell into the category of potential over or under collections.

DR. FLEMING: Could we go to your slide

43?

Having served on the Cardiorenal Advisory Committee, we have on a number of occasions talked about evaluations for end stage renal disease, and often we're looking at thousands of patients followed for a long time. So it's fascinating to see a conclusion that we've delayed end stage renal disease when we've seen one event.

Can you explain exactly how you generated this yellow curve, which seems to suggest if you follow a cohort from age zero out to 50 there would be no end stage renal disease?

Methodologically, how did you generate that yellow curve?

DR. SCHUETZ: The one event to which you refer occurred in a patient randomized to placebo.

DR. FLEMING: Correct. That's what I understand from your next slide, but on this slide how did you methodologically generate that curve?

DR. SCHUETZ: These are the ages of the patients currently in the set of studies three, six, and 11. So this essentially -- and none of those patients have progressed to ESRD in that study. So this simply is a reflection of the top age in that study at the current time.

DR. FLEMING: But is the lower curve in essence a Kaplan-Meier curve?

DR. SCHUETZ: In essence, yes.

DR. FLEMING: And are you intending the upper curve to be a Kaplan-Meier curve, which typically would be generated when you follow if it's from time zero a cohort of people from age zero? I mean methodologically how are you generating that yellow curve?

DR. SCHUETZ: This yellow curve, well, yes, I agree with your point in terms of, you know, that you're making -- this is not intended to be a time to event necessarily because these patients --

DR. FLEMING: But it seems to suggest that there is evidence to indicate that there would be no progression to end stage renal disease over 50 years based on, I assume, data that you have.

DR. SCHUETZ: No, this is -- no. That's the patient at our latest follow-up. That's our latest. That's the oldest patient in that study. Perhaps I could ask Dr. Kathleen Lamborn, a statistician who is with us, if she can help.

DR. FLEMING: Briefly, briefly, but only if she can methodologically explain that curve.

DR. LAMBORN: The answer is there is no methodologic justification. That's really just a target to say we don't have any events in this. I think if you really want to ask for the methodological issue, it's on the slide that followed this.

So, yes, I would ignore the yellow.

DR. FLEMING: All right. thank you.

DR. LAMBORN: That's simply saying that no events occurred, but it is certainly not a Kaplan-Meier.

DR. FLEMING: Could we then finally go to slide 60?

It is of interest that this study evaluated a myriad of what I would call true clinical endpoints, including a primary endpoint, which just editorially in 15 years on numerous advisory committees, I guess you see something new all the time, but I've never seen a sponsor not present even the primary endpoint data, which I think was pain in your biggest study 003.

The one quality, the one clinical endpoint piece of information you did present here though is in the top of this slide on weight gain. If I understand though, you did collect weight gain information in 005. It went in the opposite direction where there was more weight gain, 1.3 kilograms versus .7 kilograms, which you didn't mention.

And is it true in this study that there was an excess of steroid use, eight versus two, more steroid use on active therapy?

Could steroid use have had any influence on this? Do you have any thoughts about this?

DR. SCHUETZ: Yes, you're correct. In the five study we did not see a difference in weight.

DR. FLEMING: Well, in fact, just to be specific because these are small studies, so we look at estimates. We're looking at a .3 of a kilogram difference in the favorable direction. It's a .6 kilogram direction in the opposite direction.

So, yes, it's true we didn't see statistically, but from an estimate perspective, it seems those data are as interesting as these, and in this setting, is there any thought that it's even plausible steroid use could affect weight?

DR. SCHUETZ: You're referring to the use of steroids as prophylaxis for infusion reactions in some patients in the treatment group.

DR. FLEMING: In eight, which was a large fraction of them.

DR. SCHUETZ: We did a subset analysis of those eight patients, and actually if you compare those eight patients to the six patients who did not receive steroids, the eight patients actually gained less weight than those --

DR. FLEMING: Well, I don't want to compare those two against each other. They're in the same treatment arm, and there could be selective use of steroids. I would like to compare them to a control.

So the fundamental question is: is there any plausibility that steroid use could influence weight gain?

DR. SCHUETZ: The steroid use did not drive weight gain in these patients. The weight gain was driven by the non-steroid use patients., and I think that I would also just add these patients took a dose of corticosteroids every other week, which I don't believe would likely have a metabolic effect to cause weight gain in these patients.

DR. FLEMING: So you have no explanation then for the inconsistency in the two trials.

DR. SCHUETZ: I don't.

CHAIRMAN AOKI: Dr. Sampson? Dr. Jennette.

DR. JENNETTE: Back to the issue of the optimum dose, your data on plasma GB3 levels indicated that there wasn't a return to normal, which would be absence in a significant number of the patients who received the agent. Do you think that's an indication that there might be a more efficacious higher dose?

DR. SCHUETZ: I don't know. You're correct in that our declines in plasma GB3 levels -- you know, patients did not get down to, you know, zero or two, et cetera.

But as I mentioned earlier, plasma GB3 is an incredibly minor of total body GB3. It's one percent or less of total body GB3 content, and I think it's fair to say that the effects of any therapy on plasma GB3 levels is -- the consequences of that, I think, are unknown, and you know, I would also add that although the pH optimum of the enzyme is at lysosomal pH is 4.5 or so, the activity at plasma pH is not zero. It's a couple of percent, and complete normalization of plasma GB3 may simply reflect in situ hydrolysis of GB3 in the plasma. So I think that's an equally plausible argument.

So I think that your sediment GB3 data, in fact, demonstrate that Replagal gets out of the blood stream, crosses the endothelial cell barrier, and gets to epithelial cells.

So, I mean, the data are the data. I don't know whether a higher dose would decrease plasma GB3 levels more.

DR. JENNETTE: Conceptually, where do you think the plasma GB3 is coming from?

In my perspective, it is evidence that some cells somewhere have been overwhelmed by their content of GB3 and it has spilled into the plasma. It would see if that is, in fact, the case, that it would be a surrogate marker of the status of accumulation of the GB3 within cells.

What's your --

DR. SCHUETZ: Within those cells, yes.

DR. JENNETTE: And as such, don't you think that would be a parameter that would be likely to be a marker for the efficacy of treatment?

DR. SCHUETZ: Well, as I mentioned, I'd just like to show one slide here, which is that plasma GB3 levels don't correlate very well with renal function as measured by GFR, but I would also add that in terms of the part of your question that asks for speculation regarding the cell type of origin of plasma GB3, it's really unknown, but the I think most commonly proffered hypothesis is that plasma GB3 probably originates in vascular endothelial cells throughout the body.

CHAIRMAN AOKI: We'll take only two

questions more because we have all afternoon to ask more questions. We're heading for a break.

Next, Dr. Hunsicker.

DR. HUNSICKER: I hope I'll make this quick.

To follow up on the serum creatinine business or the creatinine clearance business, it has come clear to me now that some of the difference between you and the FDA is related to the missing data and various people not having had studies done.

One way to get around this methodologically is actually to look at a mixed model analysis of slopes, of either creatinine or inverse creatinine or creatinine clearance or something which would resolve or remove the problems or deal with the problems of missing data.

Were anything done along this line actually to look at the slopes over time?

DR. SCHUETZ: We haven't done the analysis that you just described.

CHAIRMAN AOKI: Dr. Follman.

DR. FOLLMAN: You had a fairly striking

slide, number 41, which compared creatinine clearance in your trial participants who were on the study compound against historical controls. That's the one.

When I look at that and I'm reminded of the slide you showed earlier which showed, you know, a plateau in creatinine clearance or renal function for a long period of time followed by a precipitous drop-off, I look at that and I think, well, it could well be that the historical controls are sort of farther along as a group on that curve you showed earlier and hence, you know, slopes are more steep and the patients in these trials are somewhat earlier in this process, and so the two groups aren't comparable.

And the reason for the large difference there, which is certainly, you know, interesting and profound, is because the two groups are really not that comparable. So to what extent or what analyses have you done to look at that, whether they are comparable or not?

DR. SCHUETZ: Well, the principal analysis that we've done on that is age. We know that age is probably the most important risk factor, if you will, for progression to end stage renal disease and progression of the nephropathy. This is a progressive disease, and older patients are clearly worse than younger patients in sort of all aspects of the disease that have been studied essentially.

And importantly, the mean age of these patients in this set, which is the 84 patients that Dr. Thadhani described, is about 35 years old or so, and the mean age of these patients are about a little over 34 years old.

So I think based on that these patients are really quite comparable. I'll point out that the top of this line, which is the most conservative estimate of this decline are the 8.3 mLs per minute per year, which comes from the studies of our placebo population.

So those patients have been selected in similar trials to these patients.

DR. FOLLMAN: Well, if we focus in on the most conservative thing really, those patients were just followed for six months, and you are extrapolating out there for nearly three years.

And that earlier slide that I remember shows that it plateaued for a while, followed by a more precipitous drop. So it's not clear that the linear assumption makes sense here, especially when you're pushing it out so far.

DR. SCHUETZ: I think two comments on that. The important aspect, I think, about the schematic curve that we showed earlier in the talk is that patients in their early 30s and certainly patients in their 20s generally have normal renal function, and once they progress to their mid-30s is when accelerated loss of renal function starts to occur.

The second part of your question in terms of the potential linearity of this, you know, I think the range of decline here allows for some changes in the slopes, but interestingly, a study performed by the NIH by Branton, et al, which followed patients serially over the longest period of time that any patients with Fabry disease have been followed, they had nine patients in their series who were followed with serial serum creatinines up to five years in that study.

And if you look at each of the nine patients reproduced on this graph, this is reproduced from her paper; although there's some variability, many of these patients have linear declines. Here's a patient with a linear decline over a couple of years; another patient.

Most of these patients have relatively linear declines, which suggest that you can extrapolate slopes based on shorter time periods of observation to longer periods in order to make the inferences that we made on the first slide.

DR. FOLLMAN: But this is one over serum creatinine, and the other slide it was creatinine. So linearity on one wouldn't imply linearity on the other.

DR. SCHUETZ: Well, one over serum creatinine should have the same effect as creatinine clearance since serum creatinine is in the denominator of the calculation of creatinine clearance.

CHAIRMAN AOKI: At this time have you got a really short question?

DR. GRADY: I'm still concerned that, you know, study 010, which you didn't present, is the biggest randomized trial to date, and you state the primary outcome was renal function.

DR. SCHUETZ: Yes.

DR. GRADY: And there was absolutely no effect there, and that's quite different from the findings in study 003, which were the main ones you're presenting us.

So I'm wondering why you think that is and what it means.

DR. SCHUETZ: Well, we've done three short term studies conducted over six months. Two of those studies suggested that Replagal was better than placebo. One of those studies suggested that Replagal and placebo were equivalent.

So I think that what those three studies are telling us, I think, is that in some patient populations you can see a difference in the short term, but I think long term therapy is really required to be able to definitively show this difference.

DR. GRADY: The patients 010 had mild

renal dysfunction?

DR. SCHUETZ: Patients in the 010 study on average had GFRs in the 80s.

CHAIRMAN AOKI: At this time let's take a ten minute break.

(Whereupon, the foregoing matter went off the record at 10:08 a.m. and went back on the record at 10:22 a.m.)

CHAIRMAN AOKI: The next presentation will be from FDA. Dr. Rieves is the medical reviewer.

DR. RIEVES: Good morning. My name is Dwaine Rieves. I'm a medical officer within FDA's Center for Biologics and the lead clinical reviewer for Transkaryotic Therapies' agalsidase alfa.

Today I will present a summary of today's major observations from a review of the sponsor's license application.

This slide reiterates the proposed agalsidase alfa indication and dosage. The product is proposed for use as long term enzyme replacement therapy for patients with Fabry disease, and the proposed dose is the same dose studied in all major studies within the license application, 0.2 milligrams per kg IV every two weeks.

Overall reports from six clinical studies were submitted to the license application. This includes information from a Phase I single dose study, a study which provided pilot safety, dose selection, and bioactivity information and information from two controlled clinical studies, study 003 and 005, studies which provide the most notable clinical data in the application.

The primary endpoint focus of these two studies was an assessment of pain outcomes for study 003 and an assessment of certain heart biopsy findings for study 005.

Study 003 is especially notable because subjects completing this study were eligible to receive agalsidase under a series of two subsequent extension protocols, study 006 being the first year of agalsidase administration and study 011 being ongoing additional years of agalsidase administration. Data from study 011 were submitted as an interim report following one year of agalsidase administration.

Consequently the series of studies, study 003, 006, and 011, provides information through approximately two and a half years of agalsidase exposure, and these studies provide the bulk of the clinical data within the application.

As shown here, 26 subjects were enrolled into study 003, while 25 and 24 of these subjects continued on to enter the follow-up studies 006 and 011, respectively.

Study 014  was a noncontrolled clinical study conducted in Germany that collected data relating to the use of this study agent in female subjects.  All other studies enrolled solely men.

Although not shown on this slide, the sponsor has reported the recent completion of a third controlled clinical study, study 010, a study focused upon renal function outcomes.  These data have not been submitted to the license application for FDA's review and will not be discussed within this presentation.

There were many clinical outcomes assessed in the sponsor's series of clinical studies.  Rather than summarizing each major outcome study by study our presentation this morning will focus upon those outcomes most pertinent to our discussion request. These outcomes include the seven items listed here: pain outcomes, renal function outcomes, specifically creatinine clearance and GFV, renal histopathological findings, certain cardiac outcomes such left ventricular mass, weight changes, the antibody formation data, and the major safety findings.

It is especially important to note that four of the outcomes potentially related to efficacy, renal function, renal histopathology, cardiac outcomes, and the weight changes, represent findings from studies that in the controlled experience generally fail to show statistically persuasive treatment effects in primary endpoint analyses.

With respect to the two controlled studies, these four outcomes are selected for discussion today from a vast number of secondary and tertiary endpoints. Consequently, data from these outcome categories should be viewed in light of multiplicity concerns and the limitations associated with the study's primary endpoint findings.

Given these limitations, it is important to note that our purpose in discussing these specific observations today is to obtain input regarding the clinical data that, as will be shown, are most readily evaluable with respect to efficacy, that is, the renal function and histopathology outcomes and the cardiac and weight outcomes.

This slide and the next few slides describe outcomes from study 003, a study that provides important data related to all of today's major discussion topics. However, to place these topics in perspective, it is important to review study 003's design and primary endpoint finding.

Here the major design features of study 003 are summarized. The study was a single center, randomized, double blind, placebo controlled study conducted over six months. Eligible subjects had to be men with Fabry associated neuropathic pain.

Subjects were not required to have impairment in other body systems impacted by Fabry disease, such as kidney or heart disease.

During this study subjects underwent many evaluations, including the recording of pain scores, a baseline and end of study percutaneous renal biopsy, and various cardiac evaluations.

The study's primary endpoint was a comparison between the two study groups for changes in a pain score while the subjects were not taking pain medications. There were many secondary and tertiary endpoints, including the renal histopathology and renal function outcomes.

This slide summarizes study 003's prospectively defined primary endpoint analytical methodology. The placebo and agalsidase groups were to have off pain medication scores recorded at four time points during this study, baseline and three follow-up time points. The primary endpoint's comparison of the pain scores was to be statistically analyzed with a T test comparison of the area under the curve of pain score's change from baseline for the four off pain medication time points.

There were numerous exploratory analyses prospectively described, including a repeated measures analysis and analyses of all follow-up time point pain scores, that is, while subjects were either on or off pain medication and analyses using various methods for imputation of missing data.

This slide summarizes study 003's primary endpoint result as submitted within the license application. Shown in the two columns are the average AUC values for the 14 subjects randomized to agalsidase and the 12 subjects randomized to placebo.

As you can see, the average reported values for the agalsidase group were minus 22, and for the placebo group, minus one.

Statistical comparison of these changes were reported as showing a P value of 0.20. As we will see on the following slide, there were considerable limitations related to evaluating and verifying this outcome.

This slide summarizes two other major limitations of the primary endpoint data, limitations largely related to the fact that the primary endpoint pain scores had to have been obtained while subjects were off pain medications.

Firstly, the source data review revealed that it is impossible to accurately verify medication usage at the time of pain score assessments. There were striking inconsistencies regarding medication usage based upon comparisons of the specific pain score case report form pages, the medical records, other case report form pages, and subject's medication diaries.

The other major limitation related to the use of a highly problematic definition of pain medication. The sponsor's definition of pain medication made a distinction among certain types of analgesics. For example, certain common neuropathic pain medications versus analgesics more widely used for other types of pain.

In essence, this definition excluded the use of important analgesics such as the nonsteroidals and the many opiate analgesics. Hence, a subject could be receiving codeine for pain relief and be regarded for the primary endpoint analysis as off pain medication.

Despite these limitations, it is useful to examine exploratory and additional analyses of the major pain outcome as shown on the next slide.

This slide summarizes the findings from additional pain outcome analyses and exploratory analyses of the primary endpoint. In general, these analyses examined the primary endpoint outcome using an alternative statistical method, a repeated measure analysis, or analyzed the major pain outcome at time points when subjects were either on or off pain medications.

As noted in the text here, these analyses generally provided no support for a finding of efficacy in the reduction of pain.

This slide summarizes the major findings from study 003, primary endpoint of pain comparisons. There are two major conclusions. Firstly, the off pain medication data are uninterpretable because of the inability to verify medication usage and a very problematic definition of pain medication.

The other major conclusion, as shown at the bottom of this slide, is the finding that exploratory analyses of the major pain outcome, such as those using pain scores obtained regardless of whether subjects were on or off pain medications also provide no evidence for a treatment effect.

This slide concludes our summary of study 003's primary endpoint finding, and now we will move on to some of the other findings starting with the renal function outcomes.

The renal function outcomes from study 003 are shown on this and the next few slides. This slide shows study 003's creatinine clearance data. The table shows two outcomes, the change in creatinine clearance from baseline to end of study week 24 and the change from baseline to week 23. For agalsidase subjects there was no change in average values from baseline to week 24, while placebo subjects had a decline of approximately 20 milliliters per minute with a statistical comparison yielding a P value of 0.05.

These findings may be contrasted to those for the change from baseline to week 23. In this comparison both agalsidase and placebo subjects had little change in average creatinine clearance values, a difference that was statistically associated with a P value of 0.54.

This fairly striking difference in the two findings may be explored by an examination of the serum creatinine, as well as the creatinine clearance values as shown on the next slide. In this table agalsidase subjects are shown to the left and placebo subjects to the right. Under each group's heading, one column shows creatinine values and the other the creatinine clearance value. An especially notable finding is highlighted by the arrow.

As you can see, there was a fairly striking decline in the placebo group's creatinine clearance value within the final week of this study, a change that was not associated with an alteration of the group's average serum creatinine values. This observation suggests that there may have been inaccuracies within the collection of some placebo subjects' urine samples.

This point is illustrated more vividly on the next slide. Here creatinine clearance values are shown in a figure. The creatinine clearance is plotted on the Y axis against study week on the Ex axis.

It is important to note that only a portion of this figure represents study 003 as denoted here by the word "controlled" because most of the subjects completing study 003 began receiving agalsidase in a subsequent series of noncontrolled studies.

Additional weeks of creatinine clearance data are also shown in this figure. The placebo group is shown in yellow, and the agalsidase group in white. The figure illustrates the somewhat surprising finding of the difference between the placebo group's week 23 and their week 24 value.

The figure also highlights the placebo group's subsequent creatinine clearance values. It is important to note, however, that these post week 24 values were obtained while all subjects were receiving agalsidase.

Together these observations suggest that the statistical difference observed in study 003's creatinine clearance outcome may not be a robust finding. Notably creatinine clearance was also evaluated in study 005, the sponsor's other control clinical study.

However, these data are not evaluable due to inaccuracies in the study's collection of urine samples. As will be shown on the next slide, GFR data are available from both controlled clinical studies.

This slide shows the GFR results for both of the controlled studies. Study 003 findings are shown on the first row and study 005 findings shown on the second row. The columns contain average GFR values for the agalsidase group on the left and the placebo group on the right, along with the applicable P values from statistical comparisons of the changes.

As you can see, in study 003, both study groups had declines in their average GFR values, while in study 005 both study groups had increases in their values.

The comparison of GFR changes between the two study groups were not statistically persuasive in either study.

In a pattern similar to the creatinine

clearance data, most subjects in study 003 had GFR measured following the end of that study at a time point when the subjects were receiving agalsidase in a noncontrolled study.

These GFR findings are shown in this figure with GFR plotted on the Y axis and the week of follow-up shown on the X axis. As noted previously, study 003 findings are denoted by the word "controlled" and the follow-up time point findings denoted by the word "noncontrolled."

The placebo group, again, is shown in yellow, and the agalsidase group in white. Over all three time points were available for analysis, the beginning and end of study 003 and the end of study 006, study 006 accounting for a one year period of agalsidase exposure.

As previously noted during study 003, both groups had a decline in average GFR values. During the subsequent one year noncontrolled studies, there was no change in the GFR for the prior agalsidase group while the average GFR appeared to return to baseline for the prior placebo group.

These changes might be viewed as suggesting that the prior placebo group had an improvement in GFR following one year of agalsidase. However, this interpretation appears inconsistent with the controlled clinical experience which showed that at least over a six month time period, the average GFR appeared to decline despite agalsidase administration.

It is also important to note that the group receiving agalsidase in study 003 had no improvement in GFR despite a complete year and a half of agalsidase exposure.

This slide highlights the notable renal function changes from the noncontrolled clinical studies. These studies include the extension studies following study 003, as well s study 014, the study examining outcomes in women.

Overall, the duration of noncontrolled clinical study experience ranges from six months to two and a half years of agalsidase exposure. As very briefly cited here, there were overall no remarkable changes in either creatinine clearance or GFR outcomes.

It is important to denote that most of these study subjects had either normal or near normal renal function at baseline, and it is conceivable that such Fabry disease patients may experience little, if any, alteration in renal function tests over a relatively prolonged period of time.

Together the finding of a non-robust improvement of creatinine clearance in study 003, combined with no other controlled clinical data, suggests a beneficial treatment effect, and the noncontrolled clinical data generally showing no change in renal function leads one to propose that the renal function data do not provide persuasive evidence of an agalsidase treatment effect.

Alternatively, it may be considered that lack of deterioration in renal function over a prolonged time period reflects a favorable treatment effect. To address this consideration, the sponsor submitted certain historical data.

The applicant's historical data are summarized on this slide. There are three columns within this tabular summary, the first showing the data source, the second the number of subjects supplying data, and the third column, the rate of decline in either GFT or creatinine clearance. Four rows are shown, the first showing the result of an overall review of the published literature; the second, information from a publication by Branton that appeared following completion of the overall published literature review; the third, the placebo results from study 003; and the fourth row, the sponsor's weighted summary of these data.

As you can see in the top row, the overall review resulted in the collection of information from 11 subjects. The additional publication data shown in this second row provided information from 14 subjects. The third row shows the renal function changes for 11 placebo subjects.

From this information, the estimate of the average rate of decline of renal function was estimated at 18.7 milliliters per minute per year for subjects in their late 30s. These findings contrast to the study 003 follow-up clinical data showing little change in renal function with agalsidase administration over an approximately two year period.

Notably, the sponsor's clinical study data 010 are not included within this table.

The sponsor also noted that their review of published reports suggested that the average age for the onset of end stage renal disease in Fabry disease is 38 years. This is notable in light of the observation that most subjects within study 003 were, on average, approximately 35 years of age at initial enrollment, and since agalsidase was administered to most of these subjects for a time period of two years or more, the average age of these subjects is approaching one at which at least according to the literature review, some might be expected to have developed end stage renal disease.

However, no subject developed end stage renal disease following agalsidase exposure during the sponsor's series of clinical studies.

Certain caveats related to these historical data are especially pertinent to this summary. In addition to the inherent publication bias, it is important to note that there are small numbers of subjects in the literature review, an n of 25, and these subjects generally differed substantially in terms of their baseline renal function when compared to the subjects in the sponsor's clinical studies.

In general, most subjects in the literature review had profound renal impairment at baseline, while most of the subjects in the clinical studies had normal or near normal renal function.

For example, of the 11 subjects from the overall published literature review, all but three had baseline renal functional measurements less than 70 milliliters per minute.

Similarly, all 14 subjects from the Branton report were in chronic renal insufficiency at baseline with creatinines of 1.5 milligrams per deciliter or greater.

In contrast, within the sponsor's study 003, only three of the 26 subjects had chronic renal insufficiency at baseline using the Branton definition.

Consequently, the inherent bias associated with publication combined with the observation that the subjects in the publications generally had marked renal impairment at baseline profoundly limits the ability to make meaningful comparisons between the historical data and the data from the sponsor's noncontrolled clinical studies.

Together the data from the controlled and noncontrolled clinical studies do not appear to provide substantial evidence of efficacy based upon changes in renal function.

Next we will move on to a summary of the renal histopathology. All renal histopathology data comes from study 003. This slide shows that paired, meaning baseline and end of study samples, were available for 21 of the 26 enrolled subjects with paired samples missing for two agalsidase subjects and three placebo subjects.

The bottom of this slide shows the types of analyses performed.

Renal pathology was broadly analyzed within three major categories, two of which were prospectively designed, the acute lipid damage score or ALDS and the chronic damage score or CDS.

A third analytical category was exploratory, the standard histopathology outcome. The acute lipid damage score graded the renal slides for the deposition of GB3, while the chronic damage score graded the slides for the presence of certain chronic pathological changes.

The standard histopathology outcome was an analysis in which each glomerulus was categorized as falling into one of four possible categories. The chronic damage score yielded no notable findings and will not be summarized here. The outcomes of the acute lipid damage score and the standard histopathology are shown on the next few slides.

The ALDS outcome was a composite score of GB3 deposition within six cellular compartments, with zero being normal or no deposition and three being severe deposition. A better outcome at the end of the study would be reflected in a lower end of study ALDS score.

Consequently, the week 24 minus baseline value would be negative for a favorable outcome.

Here we see the average baseline scores which show out of a range from zero to 18 the GB3 deposition generally appeared similar between the two study groups, the score nine in the agalsidase group and eight in the placebo group.

The change to week 24 was, on average, minus two points, suggesting improvement in the agalsidase group and an average value of one in the placebo group, suggesting some worsening. The difference between these two changes did not reach persuasive statistical significance.

This slide shows the six components of the ALDS score with the most notable findings highlighted in yellow. The four columns in the table represent, firstly, the six components, the change from baseline for the agalsidase and placebo groups in the second and third columns, respectively, and the results of statistical comparisons in the last column.

The six ALDS components include glomerular endocapillary cells, other vascular endothelial cells, the glomerular epithelial cells, the proximal and distal tubular cells, and cells of the vascular media.

As highlighted, the comparison suggest that the agalsidase group had statistically notable decreases in GB3 deposition within those cellular components of blood vessel linings. On appreciable difference was detected in the comparisons for the other cellular components.

This slide summarizes the standard histopathology outcomes. Standard histopathology was an exploratory analysis in which all of the glomeruli on a slide were assigned to one of the four possible categories as noted here: normal appearance, mesangial widening, segmental sclerosis, or obsolescence.

In these assessments, the proportion of glomeruli on each subject's renal tissue sample that fell into each of these four categories was determined at baseline and at end of the study. The rows within this table show the change in proportion of the four categories on end of study samples minus the proportion on baseline samples.

For example, the agalsidase group's average value of 0.08 for the change in proportion of normal glomeruli means that the proportion of normal glomeruli for this group was on average eight percent greater at the end of this study than at the beginning of this study.

The second and third columns show the average changes in proportions of glomerular categories for the agalsidase and placebo groups, respectively. Highlighted in yellow are those outcomes suggesting a beneficial effect of agalsidase.

The proportion of normal glomeruli increased in the agalsidase group, but decreased within the placebo group.

Similarly, an improvement in mesangial widening was noted with the proportion of abnormal glomeruli declining in the agalsidase group, while that proportion increased in the placebo group.

There was no difference between the two groups for the obsolescence category, while the segmental sclerosis comparison tended to favor the placebo group. As will be subsequently noted, there are substantial limitations in the standard histopathology assessment methodology, such as a lack of criteria relating to the acceptability of a renal tissue sample for the assessment.

Additionally, it is important to recall that the renal histopathology outcomes are all secondary or exploratory endpoint findings and must be viewed in light of substantial multiplicity concerns.

The extent of the logistical limitations to the histopathology observations are summarized here. Firstly, we must remember that the renal histopathology data were obtained from study 003, a study that focused upon certain clinical outcomes. Hence far more of the study protocol details concerned these outcomes than the renal histopathology data.

The first bullet on this slide highlights one of the major topics for discussion today, and that concerns the clinical relevance of histopathological changes. More specific to study 003's histopathology outcomes are the subsequent points.

In general, these data were obtained with limited rigor. For example, there were no explicit prospectively defined criteria for assessing the severity of GB3 deposition or the criteria for categorization of glomeruli in the standard histopathology assessments. Pathologists were not trained in any study specific slide interpretation processes, and there were many deficiencies in the prospective plans related to specifics of slide reading, such as the number of slides, types of stained slides, or number of glomeruli within a slide to review.

Lastly, the source documents are not available for data verification.

In addition to these limitations, it is important to remember that there were small alterations in renal function during study 003, and this, combined with the extent of missing data from the renal histopathology assessments, largely precludes the ability to make interpretable comparisons between changes in renal function and changes in renal histopathology.

Nevertheless, the slide reviews were conducted in a blinded manner, and the results are notable. Over all the renal histopathology data suggests agalsidase administration was associated with diminution of vascular endothelial GB3 deposition and some improvement in certain aspects of glomerular architecture, but there are notable limitations in the ability to verify these outcomes.

This slide begins a review of a series of cardiac outcomes. In general, cardiac outcomes were evaluated in all of the sponsor's clinical studies. However, Study 005 was designed to specifically focus upon cardiac findings, and that study is summarized here.

Study 005 was similar in design to the other controlled clinical study in that it was a single center, randomized, double blind, placebo controlled, six month study. The study was unique among the group of clinical studies in that it required eligible subjects to have left ventricular enlargement on screening echocardiography.

The study's most notable evaluations included endocardiobiopsies, which were performed at baseline, mid and end of study, and several other assessments, including cardiac MRIs, echocardiography, and electrocardiograms.

The primary endpoint focused upon the cardiac biopsy result, that being a comparison of the change from baseline in the cardiac biopsy content of GB3.

The primary endpoint result for study 005 is shown here. This enrolled 15 subjects, but one of these subjects did not have a cardiac biopsy. Shown are the data for the 14 evaluable subjects. This tabular summary contains four columns, the first identifying the outcome as either change from baseline to week 13 or week 24. The second and third columns show the changes in GB3 content for the agalsidase and placebo groups, respectively.

Statistical comparisons are shown in the fourth column. As you can see, there was little change from baseline in either of the two study groups at either of the two follow-up time points, although the average agalsidase changes were negative numbers suggesting less GB3 content in the follow-up biopsy specimens.

However, the statistical comparison suggested no persuasive difference between the two study groups.

Several other cardiac outcomes were evaluated in study 005, as well as the other clinical studies. This slide notes that we will focus upon two of these outcomes, firstly, the left ventricular mass findings as assessed by magnetic resonance imaging and echocardiography, and secondly, certain electrocardiographic changes.

We will initially examine study 005, the major cardiac study, then examine the cardiac findings detected within study 003, the study that focused upon pain outcomes.

Finally, we will examine the data from the noncontrolled clinical studies.

This slide highlights study 005's findings related to end of study changes in left ventricular mass based upon MRI assessments. The first column within the table identifies the outcome with the first row showing the results of the left ventricular mass change in the entire 15 subject study population and intent to treat analysis.

The second row, the left ventricular mass change in the subset of 14 subjects without missing data.

And the third row shows the changes in left ventricular posterior wall thickness, again, for the subset of subjects without missing data.

The second and third columns within this table show the changes from baseline to end of study for the agalsidase and placebo groups respectively, and statistical results are shown in the last column.

The difference between the intent to treat analysis and the subset analysis relates to a missing data point for one placebo subject. This subject had an MRI assessment performed at baseline and at mid-study, but did not have an end of study assessment.

The intent to treat analysis uses a last observation carried forward approach to impute the missing data point.

As you can see from examination of the first row, the intent to treat analysis suggested an average decrease of approximately 12 grams for the agalsidase group, while the placebo group appeared to have an average increase of 11 grams.

The statistical comparison of these changes yielded a P value of 0.10.

The second row illustrates the relatively large impact a single missing data point had on the statistical comparison between the two study groups. As you can see, without imputation, the placebo group had an average increase in left ventricular mass of approximately 22 grams, and comparing the two groups in this analysis, results in a P value of 0.04.

The third row examines another measure that one might expect to correlate with changes in left ventricular mass, the change in left ventricular posterior wall thickness. Without using any imputation methods, both groups generally had very little change in wall thickness, with no statistically notable difference.

This slide shows the outcome for another technique of left ventricular mass assessment, the results of echocardiographic measures. Echocardiographic data were available for all subjects. So all three outcomes shown here are intent to treat analysis.

The first column shows the specific outcome, that being mass in grams in the first row; the mass as adjusted for body surface area or mass index in the second row; and in the third row, the left ventricular posterior wall thickness assessment.

As in the other slides, the second and third columns show the baseline to end of changes for the agalsidase and placebo groups, with the statistical comparison in the fourth column.

These echocardiographic data show, on average, mass decrease of approximately 20 grams for the agalsidase group, while the placebo group experienced an average increase of approximately 22 grams. Statistical comparison of these changes yielded a P value of 0.26.

The mass index data show somewhat different results, with both groups showing, on average, increases in left ventricular mass, approximately four grams for the agalsidase group and 40 grams for the placebo group.

The statistical comparison of these changes shows a P value of 0.66.

The echocardiographic assessment of left ventricular wall thickness showed on average a decrease of approximately 0.7 millimeters for the agalsidase group and an increase of approximately one millimeter for the placebo group, with a statistical comparison yielding a P value of 0.15.

As a reminder, study 005 focused upon cardiac outcomes, and all subjects had to have left ventricular enlargement in order to be enrolled.

The next slide shows the left ventricular findings from study 003, a study where subjects were not required to have left ventricular enlargement at enrollment.

Both MRI and echocardiographic changes for study 003 are summarized here. The first column shows the outcome MRI in grams on the first row and echocardiographic assessment of mass index on the second row. The changes from baseline to end of study are shown in the second and third columns for the agalsidase and placebo groups.

Within this study only baseline and end of study assessments were performed. One placebo subject had no end of study results, and this table shows the results for the remaining 25 subjects.

As you can see in the first row there was, on average, an approximately four gram increase in left ventricular mass in both groups with no statistically notable difference between the changes.

The echocardiographic data shows somewhat different results with an average increase in left ventricular mass of approximately 14 grams for the agalsidase group and a decrease of approximately eight grams for the placebo group, changes that were associated with the P value of 0.06 in the statistical comparison. Notably, the echocardiographic change appeared to favor the placebo group.

The bullet at the bottom of the slide notes that this pattern of changes was also detected when we analyzed the subset of study 003 subjects with evidence of left ventricular enlargement at baseline. This subset consisted of approximately half the subjects, seven in the agalsidase group and six in the placebo group.

Because six months is a relatively short period of time in what may be a fairly slowly progressive disease, it is useful to examine the data obtained over a longer period of time. One year of noncontrolled data are available for review. This result is shown in the next slide.

This slide shows the one year noncontrolled cardiac outcome data from study 006 and also the six month data from study 014, the noncontrolled study performed among female Fabry disease patients.

For study 006, the first column identifies the MRI and echocardiographic left ventricular mass changes, and for study 014, the echocardiographic changes.

The two study 006 outcome changes show the results for the change from the initiation of the study to the one year follow up time point. Since all study 006 subjects had to have completed study 003, the group may be divided into two portions, one, the prior agalsidase group and the other the prior placebo group.

As you can see, the average MRI assessment of left ventricular mass showed a decline for both groups of subjects within study 006, a decrease of 22 or 28 grams. The echocardiographic data are somewhat different, showing on the average an increase in left ventricular mass with an increase of approximately mass units in the prior agalsidase group and an increase of approximately 28 mass units in the prior placebo group.

At the bottom of the slide, six month echocardiographic change in left ventricular mass for subjects in study 014 is shown to be on average a decrease of approximately 23 mass units. Since there are no controls for these clinical data, no statistical analyses are shown.

The other notable cardiac outcome from these studies are shown on the next slide. This slide shows analyses of changes in QRS duration as obtained from electrocardiograms in the two control clinical studies. The top of the slide highlights the results from study 005, the major cardiac study, and the bottom of the slide highlights the finding from study 003. The study focused upon pain outcomes.

The rows show the changes in QRS duration from baseline to end of study in milliseconds. The agalsidase group is shown in one column, and the placebo group in the other column, with the statistical summary in the last column.

Looking at the study 005 outcome, we see that the QRS duration decreased on average approximately 13 milliseconds within the agalsidase group and increased approximately five milliseconds within the placebo group. However, there was considerable variability within these findings as reflected by the P value of 0.81 for the comparison.

At the bottom of the slide we see that within study 003 the agalsidase group had an on average decrease in QRS duration of approximately two milliseconds, and the placebo group had an increase of approximately four milliseconds, with the statistical comparison showing a P value of 0.05.

The asterisk in the agalsidase column highlights an important consideration in interpreting the statistical comparison of the study 003 outcome. As noted at the bottom of this slide, one subject within the agalsidase group had an intermittent bundle branch block prior to receipt of agalsidase since the QRS duration at baseline for this subject was very variable. The data shown in the table are those obtained when that subject had a QRS duration of 150 milliseconds.

Using this 150 millisecond outcome, a value one might expect to have been obtained when the subject was experiencing the bundle branch block results in the described P value of 0.05. This subject also had a QRS duration of 103 milliseconds recorded prior to the receipt of agalsidase, a value obtained when the subject was experiencing less conduction system delay.

The limited robustness of the statistical comparison resulting in a P value of 0.05 is illustrated by the use of the shorter baseline value of 103 milliseconds. If this shorter baseline value is used in the statistical comparison, the resulting P value is 0.08.

The next slide summarizes the noncontrolled findings for QRS duration.

This slide shows that noncontrolled electrocardiographic clinical data are available from two clinical studies, study 006 and study 014. Study 006 provides results over a one year observation period and, as noted, there was no appreciable change over this period.

Study 014 is the study performed among females, and within this study electrocardiographic data were obtained at multiple time points in follow-up, and of these multiple time points, only the week 27 value appeared decreased when compared to baseline.

Together the left ventricular mass findings and EKG findings conclude our cardiac presentation. In general, the observations from the controlled clinical studies appear to suggest no difference between the two study groups in left ventricular mass changes or electrocardiographic changes.

The noncontrolled clinical data similarly suggests little change from baseline observations.

The next couple of slides examine weight changes in the clinical studies.

This slide presents the weight change data from the two controlled clinical studies. The first row shows the changes for study 003, and the second row, the study 005 changes. The second and third columns show the agalsidase and placebo changes, respectively.

As you can see, during study 003, the average weight change was an increase of 1.6 kilograms for the agalsidase group and a decrease of 1.4 kilograms for the placebo group, with a statistical comparison yielding a P value of 0.03.

The study 005 findings are somewhat different with average weight increases for both groups, 0.7 kilograms for the agalsidase group and 1.3 kilograms for the placebo group. Changes associated with the value of 0.33 when compared statistically.

This slide summarizes the notable changes in weight from the noncontrolled studies. The top bullet shows the results for subjects completing two years of agalsidase administration through study 006 and 011, and the bottom bullet shows the changes for the subjects completing six months of agalsidase administration in study 014.

As noted in the top bullet, the average weight gain varied between 2.1 and 2.7 kilograms following two years of exposure to agalsidase. The bottom bullet shows that the 11 subjects completing six months of agalsidase administration in study 014 gained on the average 0.9 kilograms.

The next slide summarizes some important limitations of these data. The limitations of the weight change data generally relate to two major concerns.

Firstly, the use of concomitant medication, such as steroids and diuretics. The use of these medications was especially notable for study 003, the study that suggested a statistically favorable weight gain for the agalsidase group. Within that study systemic steroid usage was markedly greater for the agalsidase group than the placebo group, a difference mainly related to the treatment or prevention of infusion reactions.

Interpretation of the weight data from study 003 may also be confounded by the use of diuretics. For example, the largest weight gain in the study, a gain of 6.3 kilograms, occurred in an agalsidase subject who was taking 20 milligrams of furosemide at baseline, but has discontinuation of the medication during the study.

The other notable limitation to the data relates to the lack of other nutritional information from the studies. The importance of this information is emphasized by the notation that the baseline weight in both control studies was, on average, approximately 70 kilograms, a weight that may have been normal for many subjects.

Clinically, a small increase in weight among subjects with normal baseline weight may be viewed as inconsequential. The next few slides summarize the major safety findings and the antibody formation data. This slide highlights the most notable antibody formation data, specifically the data derived from study 003 and its follow-up series of extension studies.

Within study 003, antibody formation was assessed using three different assays: enzyme immunoassay and immunoprecipitation assay and a neutralization assay. The incidence of antibody formation in the study ranged from approximately 50 to 64 percent, depending upon the type of assay performed.

In general, the enzyme immunoassay provided the most comprehensive information, and this assay was associated with approximately 50 percent incidence.

The second bullet on this slide focuses upon the antibody formation data from study 003 and its follow-up studies 006 and 011, with all of the findings based upon enzyme immunoassay results. Overall, 52 percent of the subjects completing study 003 had antibody formation detected at some point during that study. These 13 subjects all participated in the follow-up studies, and as shown here, three of the 13 had reversion of their antibody assay outcomes to baseline levels, while ten of the 13 had consistently positive findings throughout the series of studies.

Notably, seven of these ten had steadily increasing magnitudes of antibody formation during the last year of observation as detected by greater blood antibody concentrations at the last follow-up time points.

The next couple of slides highlight the potential impact of the antibody formation upon certain biomarkers of Fabry disease. GB3, a glycolsphingolipid substrate for agalsidase, was measured both in the urine and plasma during studies 003 and 011. This slide shows the results for plasma GB3 concentration, and the next slide will show the results for the urine GB3 assays.

On this slide, outcomes are shown for the 22 subjects who completed the one year interim of study 011, a time period that represents 24 or 30 months of agalsidase exposure, depending upon whether subjects initially receive six months of agalsidase in study 003. These subjects are divided into three groups, those with persistent evidence of antibody formation throughout the follow-up time period, those with transient antibody formation, and those with no antibody formation at any time point over the follow-up period.

On the X axis, the months of follow-up are shown, and the plasma GB3 concentration is shown on the Y axis. In order to focus upon the pattern of changes, the Y axis origin begins at four nanamoles per milliliter. The zero time point on the X axis corresponds to the value obtained immediately prior to receipt of agalsidase.

As you can see, all subjects had a decrease in the plasma GB3 concentration after six months of agalsidase, and this decrease was maintained among subjects who had no evidence of antibody formation. However, subjects who had persistent antibody formation during the studies had increases in their plasma GB3 concentrations that at the 30 month follow-up time point was only modestly less than the baseline level.

The subjects with transient antibody formation had a pattern of plasma GB3 concentration alteration that was largely in between that of subjects with persistent antibody formation and those with no antibody.

Although not shown on this slide, of the 22 subjects shown overall, 11 belong to the no antibody group; eight belong to the persistent antibody group; and three subjects form the transient antibody group.

Urine GB3 results are shown on this slide, again, for the group of 22 subjects completing study 011 interim. Again, the subjects are grouped into three categories: those with persistent antibody formation, those with transient formation, and those with no antibody formation.

Also, similar to the prior slide, the month of follow-up is shown on the X axis and the GB3 concentration shown on the Y axis. As you can see, the urine GB3 content declined following the initial six months of agalsidase exposure for all three groups and remained at this lower value for the no antibody and the transient antibody formation groups.

However, the persistent antibody group had evidence of increases in urine GB3 concentration at 24 and 30 month follow-up time points, a pattern somewhat similar to this group's plasma GB3 results.

Although the clinical meaningfulness of alterations in the GB3 biomarkers is unknown, the urine and plasma GB3 findings raise questions regarding the impact of antibody formation upon agalsidase bioactivity.

The next slide summarizes the major safety findings. This slide highlights in three bullets the most notable safety findings. There were no reports of anaphylaxis in the clinical studies. However, the incidence of infusion reactions was notable. The highest incidence, approximately 60 percent, was reported in study 003. In general, the reactions were graded as mild to moderate severity, most manifest as various combinations of flushing and rigors. However, two of the infusion reactions were classified as serious adverse events, both events consisting of overnight hospitalizations for observation following the treatment of the infusion reactions.

During study 003, procedures were instituted in order to decrease the incidence of infusion reactions, including lengthening of the infusion duration and the routine use of prophylactic premedications. Using these procedures, the infusion reactions were decreased in incidents during the series of follow-up studies. The incidence of approximately 40 percent in study 006 and approximately 25 percent in study 011.

Notably, no infusion reactions were detected among the seven subjects receiving agalsidase in study 005 or the 15 female subjects receiving agalsidase in study 014.

The following few slides summarize the major findings from our review of the BLA clinical data. The most notable clinical data in the BLA are derived from the multi-dose studies. Within these studies 47 adult Fabry disease patients received agalsidase at 0.2 milligrams per kg on alternate weeks.

The major findings from the controlled clinical studies are summarized on this slide. As we have noted, there were two controlled clinical studies. Study 003 focused upon pain outcomes, and study 005 focused upon cardiac outcomes.

The primary endpoint of pain alterations for study 003 was largely uninterpretable, while the primary endpoint for study 005 showed no statistically persuasive difference between the two treatment groups, the endpoint being a comparison of the cardiac GB3 content in the myocardium.

As noted here, both studies provide additional clinical data, including renal, cardiac, and safety data. Within this presentation we have focused upon six major interpretable observations from the clinical data: renal function outcomes, renal histopathology outcomes, cardiac outcomes, weight change data, antibody formation data, and infusion reaction outcomes.

Each of these outcomes will be summarized in the next slides starting with the renal function outcomes.

This slide shows the renal function outcomes in the two controlled clinical studies. The two major bullets highlight the creatinine clearance and GFR outcomes first for study 003 and below it for study 005.

Our examination of creatinine clearance

data shows that for study 003 there was a non-robust evidence of a treatment difference between the two study groups in that the week 24 end of study outcome appeared biologically implausible when compared to the week 23 outcome. Study 005's creatinine clearance data were uninterpretable due to problems in urine collection.

The second bullet notes that GFR outcomes showed no difference between the study groups in either study 003 or study 005.

Renal function outcomes from the noncontrolled clinical studies are summarized on this slide. The sub-bullet notes that both GFR and creatinine clearance were generally unchanged when subjects received agalsidase in a noncontrolled manner over a period of time ranging from six months to two and a half years.

The second bullet on this slide highlights the previously noted major problems with the use of the application's historical data such that the ability to interpret the clinical meaningfulness of the noncontrolled renal function outcomes is very difficult.

These limitations largely preclude the ability to perform meaningful comparisons from the published data and the sponsor's noncontrolled clinical study findings.

Renal histopathologic outcomes are summarized on this slide. As previously noted, all renal histopathologic data are derived from study 003, a study with several methodological limitations regarding the ascertainment of these data. The two starred bullets highlight the most notable outcomes, the assessment of GB3 deposition and the outcomes from standard histopathological review.

As noted here, the GB3 deposition outcomes generally showed a decrease in GB3 deposition in the agalsidase group when compared to the placebo group. The standard histopathology findings generally showed improvement in two major components of the outcome with the agalsidase group having an increase in the fraction of normal glomeruli on the slides and a decrease in the fraction of glomeruli with mesangial widening.

Only a very small fraction of the glomeruli on the biopsy slides were classified as having segmental sclerosis, but the change in the fraction of affected glomeruli appeared to favor the placebo group.

The next few slides will summarize the major cardiac findings. Left ventricular mass outcomes from the control studies are shown on this slide for study 005 on the first row and for study 003 on the second row. The two columns summarize the findings of the changes in left ventricular mass as assessed first by MRI and secondly by echo cardiography.

Within study 005, the comparison of changes in MRI measures of left ventricular mass showed a decrease in mass for the agalsidase group when the comparison is performed solely among the group of subjects with evaluable clinical data. An analysis using imputation for the one missing data point suggested that there was no statistically persuasive difference between the two study groups.

The echocardiographic assessment of left ventricular mass within study 005, as well as both the MRI and echocardiographic left ventricular mass assessments within study 003 showed no difference between subjects receiving agalsidase and those receiving placebo.

Although not shown on this slide, you may recall that the noncontrolled clinical findings in left ventricular mass changes generally showed inconsistent changes that due to the noncontrolled nature of these data are substantially limited in their interpretability.

This slide summarizes another cardiac outcome, the change in QRS duration. The slide shows the changes in the controlled clinical studies. Firstly, we see that study 003, the study focused upon pain outcomes, generally suggested a decrease in QRS duration for the agalsidase group compared to the placebo group, while study 005, the study focused upon cardiac outcomes, suggested no difference in QRS duration between the two study groups.

As was previously noted, the study 003 outcome may be confounded by the results from a single subject who had an intermittent bundle branch block. Notably the noncontrolled electrocardiographic data generally showed no change in the QRS duration from baseline values.

The weight changes from the studies are summarized on this slide. Here the first two starred bullets highlight the observations from the controlled clinical studies, and the third bullet summarizes the noncontrolled observations.

The six months of follow-up of study 003 suggested a statistically significant gain in weight for the agalsidase group compared to the placebo group as reflected by the P value of 0.03, while the six months of observation in study 005 showed no difference in weight changes between the two study groups.

As previously noted, these observations may be confounded by the use of concomitant medications, especially for study 003 where there was extensive use of systemic steroids to treat or prevent infusion reactions.

The noncontrolled clinical data are

largely derived from study 006 and 011 and are most notable for suggesting an average weight gain from baseline of between 2.1 and 2.7 kilograms over a two year follow-up period.

The clinical meaningfulness of these small weight changes must be viewed in light of the groups having what might be regarded as largely normal, average baseline weights.

This slide highlights the major safety findings and the antibody formation data. As shown within the first two sub-bullets, the incidence of infusion reaction was approximately 60 percent within study 003, the larger of the controlled clinical studies, but was decreased during the extension studies that followed study 003.

The vast majority of all reported infusion reactions have been of mild to moderate severity. The most notable antibody formation data are also largely derived from study 003 and its follow-up extension studies. These studies show that approximately 30 percent of subjects exposed to agalsidase have persistent evidence of antibody formation over a 24 or

30 month observation period.

The last sub-bullet notes that antibody formation appears to impact certain biomarkers of Fabry disease, a finding that raises questions about the impact of these antibodies upon any clinical outcomes.

This slide concludes our overview of the clinical data. I thank you for your attention, and, Mr. Chairman, I now return the podium to yourself.

CHAIRMAN AOKI: Thank you. I think at this time we'll take questions from the committee because we want to go to the open public hearing fairly quickly.

Just the burning ones. Dr. Sampson.

DR. SAMPSON: Dr. Rieves, I actually have a very basic question I was hoping you might be able to help me with or someone from TKT. As a statistician, I would like to know if you could explain simply to me the differences in the genetic engineering technology of TKT's agalsidase alfa versus Genzyme's agalsidase beta, and in particular, how those differences if there are some might impact the dosage choice and the theoretical effects on immunogenicity.

DR. RIEVES: If I understand the question, I think you are asking actually about a product area, a manufacturing type area which I think we should perhaps turn over to some of our product reviewers who may, in part, answer that type of question.

DR. ROSENBERG: I'm Amy Rosenberg. I'm the Director of the Division of Therapeutic Proteins that did the product review.

And the products, as you know, as was stated, the TKT product is produced in a continuous human cell line. The Genzyme product is produced in CHO cells.

Immunogenicity with regard to these products is rather complex in the sense that we understand very well at this point that the potential for or immune tolerance to soluble proteins is based on the levels of such proteins during development, and so I think what speaks most strongly is the fact that in patients that have residual alpha galactosidase activity, such as the female heterozygote, the cardiac variance, you don't see antibody responses or certainly not potent ones, whereas in patients such as the hemizygous males who have very low levels of residual enzyme, you see antibody responses.

And I think it makes it very difficult to separate out issues regarding immunogenicity that may be based more on the derivation of the cell line. I don't think we have any strong reason to suspect that there are dramatic immunogenicity differences based on cell line considerations.

So I think more to the point, the immunogenicity of these proteins has to do with the level of endogenous enzyme in the patients that are treated.

DR. TRECO: Would you like me to clarify more on the differences?

Doug Treco from TKT.

As you may be aware, the type of manufacturing process has major effects on the glycosylation of proteins and the species in which you prepare the protein from has even greater differences. And for products like Replagal where its mode of action is to get into cells via the carbohydrate moieties, the carbohydrate is very important for uptake in the cells. We know that overall the carbohydrate, the mannose 6-phosphorylation, the linkages of sialic acid to galactose, all vary between the human product and the CHO cell product.

We expect that the human glycosylation pattern may actually have a favorable effect on the generation of antibodies resulting in most of the patients over time not showing antibodies to Replagal.

DR. ROSENBERG: Let me just -- I'm sorry. I just wanted to add one more thing. That is that, you know, antibody assays differ greatly depending on whose hands they are depending on, the type of assay, and specifically getting recommendations from the Biologic Response Modifiers Advisory Committee several years ago, we received a resounding endorsement for not directly comparing rates of antibody formation between companies with competing products because of issues regarding sensitivity and specificity, et cetera, of these assays.

So, you know, if you have an objective

third party outside group that takes two products and compares them in highly objective assays, having maximized sensitivity, having, you know, no particular competing interest. You know, that might be a viable way of looking at immunogenicity rates, but as of the way things are done now, I don't think it's fair at all to compare antigenicity rates between two companies that use completely different assays for assessing.

DR. SAMPSON: The other part to my question though was also with regard to dosage. If the difference in the genetic engineering would be related to the dose that's use.

DR. RIEVES: I think actually it might be best if we do turn those sorts of questions.

DR. SCHUETZ: I think that's a plausible hypothesis.

DR. WALTON: I think we simply don't have data. We really know about the effects of each product with the dosage that was studies, and I don't think that we can extrapolate dose to dose.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: A quick question. On slide 12 comparing study 003, you compared the creatinine clearance data to baseline, but you also showed us the creatinine levels, and in the placebo group, the creatinine went from 1.3 and was then stable at 1.9 for weeks 23 and 24. Were those differences statistically significant?

In the active group the creatinines were basically stable. They were initially one, and they went to 1.1

DR. RIEVES: I'm sorry. You're asking, again?

DR. WOOLF: Whether the creatinine -- whether the creatinine levels in the placebo group going from 1.3 to 1.9 were significantly different.

DR. RIEVES: To the best of my knowledge, as I recall I do not think those were a statistically significant difference. If I'm wrong, correct me.

CHAIRMAN AOKI: Microphone.

DR. RIEVES: Oh, I was just saying to the best of my knowledge those are not statistically different, and Dr. Schuetz is seconding that opinion.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: You made the comment that there were errors in the collection of the urine creatinine and the 005 study and that, therefore, they were noncomparable. I just want to comment and invite from the sponsor any comment on this, that if you look at the serum creatinines, which as I have said before within patient, from patient to patient should be fairly consistent, showed no significant differences between the two groups by either ANCOVA or by repeated measures.

So that if I am correct in interpreting that which is on -- this is your data here. This is the FDA's summary. On page 67, it would appear that that study not only has errors in collection of the creatinine clearance, but if you look at the creatinine again, there is not convincing evidence of a benefit.

DR. RIEVES: Your point is well taken.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: My question relates to the GB3 in urine in the antibody positive people. Could somebody tell me something about the GB3 assay? Because a lot of these people had massive proteinuria and whether antibody bound GB3 is going to be measured in the urine or not? I mean is this a valid thing to even look at in the urine of these people?

DR. RIEVES: The technology -- I think it's wisest that if we defer to TKT if they may explain the assay methodology.

DR. TRECO: The question was whether or not -- could you repeat the question?

DR. LEVITSKY: Because so many of these people had massive proteinuria, measuring GB3 in urine, it would be important to know whether you were measuring the protein bound substance, if there was antibody leakage, or what your actually measuring.

I mean, I don't know whether this is reasonable even to look at. If it's free GB3 or --

DR. TRECO: The assay is a reverse phase HPLC method, and it uses complex extraction procedures to purify the glycolipid. So I think that the possibility of protein remaining bound after the extensive extraction and purification is very low.

DR. LEVITSKY: But you would then be measuring GB3 that was pulled along with the proteinuria and not necessarily if it were bound to antibody in the urine.

DR. TRECO: WE are measuring actually urine sediment.

DR. LEVITSKY: Sediment. Okay, okay.

CHAIRMAN AOKI: Last but not least is Dr. Jennette.

DR. JENNETTE: Just a general question which demonstrates my ignorance about statistical analysis, but for example, in the analysis of the left ventricular mass in the control study 005, there was one study shown on page 9 of your handout at least that did show a statistically significant decrease in left ventricular mass by one methodology.

And the trends were always in that study using MRI in the direction you would expect if there were a beneficial effect, and there was some statistical support for that, but then in another method there was no statistical significance for the findings using echo. Yet the trends were still in the direction that you would expect if there were a beneficial effect.

At least in clinical method when there are two laboratory test that both give the same result, it adds support to the likelihood that the conclusion is correct. So even though there's no statistical significance in one of these two methods for determining a result, does the rigor with which one of them has to document that change if both of them have the same result?

Do you understand what I'm asking?

DR. RIEVES: I think I do understand. Most of us on the review team, you know, we look for consistencies and that provides some reassurance. I think you're raising questions about what is the differential meaning when there's not that consistency there, perhaps raising questions about which of the two is actually the most meaningful result.

And that's open to a number of interpretations between the technology involved in MRI assessments versus echocardiographic assessments, and I think that there are many clinicians who would have strong feelings one way or the other.

So what we generally do is try to look for that consistency pattern that you're talking about. If that's not there, then we're left with questions, and I think --

DR. JENNETTE: But when it is there, as in this instance, how does that affect your conclusion?

DR. FLEMING: But what's there? I thought we were talking about the MRI and the echo.

DR. JENNETTE: Right.

DR. FLEMING: None of the four are significant.

DR. JENNETTE: But the direction of change is the same in both procedures. There's a reduction.

DR. FLEMING: What's the change in 003 in MRI?

DR. JENNETTE: So in the treated group there's a reduction in left ventricular mass, and in the placebo group there's an increase in the left ventricular mass with a P value of 0.1. In the echo group there's a decrease in the mass in the treatment group, and there's an increase in the mass in the placebo group and the P value is 0.2.

So neither of those are significant with respect to statistics, but again, I'm asking when two separate methodologies come to the same conclusion, does that affect the likelihood that the result is correct even if individually they're not significant?

DR. FLEMING: Well, could we see that slide again that gives the LV mass, 003 echo result? I thought it was four and four, P of .93.

DR. WEISS: That's another study, Dr. Jennette. You were referring to study 005, and this is 003.

DR. JENNETTE: Oh, oh, five is --

DR. FLEMING: Oh, oh, five does not achieve statistical significance unless you violate the intention to treat analysis of including all people.

DR. JENNETTE: Right. But, again, the study I'm referring to is 005. The study that was designed to look at the effects of the agent on the heart. This study was designed, as I understood it not specifically for looking at effects on the heart.

So the patient selection for 005 is different than 003.

DR. FLEMING: And which direction does the echo do here?

DR. WEISS: Can we go back two slides.

DR. FLEMING: Just before we leave this slide though, could you go back just before you --

DR. JENNETTE: Yeah, there there is a discrepancy, but again, this is the study.

DR. FLEMING: And this 006 favors --

DR. JENNETTE: Yeah, but again, the study I'm referring to is 005 that was controlled and designed for looking at heart attack.

DR. WEISS: That slide, that slide right there.

DR. FLEMING: And so the valid P value is .10, and so there's a positive trend when the other study shows no difference.

DR. JENNETTE: But then the next slide using a different method comes to the same thing. That's the other direction.

DR. HUNSICKER: When it is one it is the

comparison of the echo and the MRI, both within study 005. That is what Dr. Jennette is talking about

DR. JENNETTE: So the next --

DR. WEISS: Dwaine, can you go back one, I think?

DR. JENNETTE: And then go back one more. Okay. So this study 005, in this slide it shows there was the trend you would expect if there were an advantageous effect of the agent here, by this method, the MRI, and then the next slide on 005 using a different methodology shows the same effect, which again is not independently statistically significant.

But I'm just asking since two independent methods come to the same conclusion, does that affect the likelihood that --

DR. FLEMING: So we have a trial with dozens of measures as secondary endpoints, and we have two secondary endpoints that do show positive trends, neither of which achieve significance, which in the 003 trial show no difference in the reverse direction. It's an interesting hypothesis generation, which actually leads me to my question, but I'm not to my question yet.

But I would call it an interesting hypothesis generation.

DR. FOLLMAN: I would say the consistency is expected because you're measuring mass in the same person using two different techniques, and so you know, I would be surprised if it weren't consistent, and the fact that they're both not significant, but trending in the same direction is completely expected to me. So I don't think there's any, you know, additional interpretation or you have to worry about you have two or three or one things pointing in the same direction.

CHAIRMAN AOKI: I'm trying to save time here. Is your question a burning question or can we go on?

DR. FLEMING: Well, it's a burning question, but I can ask it right after the open public hearing.

CHAIRMAN AOKI: Well, how about after lunch when we meeting again?

DR. FLEMING: It's up to you. It's --

CHAIRMAN AOKI: Okay. What I'd like to do is to go to the public hearing and then return back to these issues again so that we can spend it in a more continuous exposure.

So at this time let's turn to the open public hearing, and I caution the speakers to limit their time really to three to five minutes.

The first speaker is Dr. John Barranger.

DR. BARRANGER: Hi. Thanks for letting me talk to you very briefly.

I work at the University of Pittsburgh, and I have been a consultant to both TKT and Genzyme, and I'm just here to say that hearing the data presented over the last two days, I think there are a lot of questions that remain to be resolved, but as someone who has worked for more than 20 years in the developing enzyme therapies for lysosomal diseases and have seen the application come to really gratifying results in patients with Gaucher's disease.

I think the potential is here to apply these technologies to other diseases and particularly to Fabry disease, as you are considering it now.

So I just make the appeal that enzyme therapy for Fabry disease is very much needed by the patients that you heard from yesterday, and I think we'll hear from more today, and I hope the committee can provide that opportunity to provide them therapy.

CHAIRMAN AOKI: Thank you.

The next speaker is Roland Tufts

MR. TUFTS: I'm Roland Tufts. I'm 41 years old, and I was diagnosed with Fabry's in 1980. I had experienced a lot of the symptoms that are common with this disease in terms of pain in my --

CHAIRMAN AOKI: Lift the microphone.

MR. TUFTS: Pain in the extremities, lack of sweating, getting the GI symptoms and things like that.

I was involved in the clinical trial that was conducted from May -- excuse me -- December 2001 through May of 2002, and I continued on with bi-weekly infusions since then. I just want to share some of my experiences from this therapy.

With respect to pain, I have noticed a substantial reduction in the frequency, duration, the level of pain in my hands and feet. I've really noticed this in situations where there's a lot of heat or cold or I've been ill.

I very seldom take pain relief medication for this pain now, where I used to take it daily.

With respect to perspiration and intolerance to heat, prior to the treatment I had very little perspiration activity, even in hot and humid weather. This deficiency was confirmed through a sweat test conducted at the NIH.

Since taking the enzyme my perspiration activity has increased substantially, and I've noticed dramatic improvement in my tolerance to heat and humidity. This has allowed me to participate in a greater number of physical activities for a longer duration.

And while this improvement is most evident in the days immediately following the enzyme treatment I have noticed sustained perspiration activity, even ten to 12 days after the infusion.

With respect to GI symptoms, I've noticed substantial improvement in the GI discomfort which I lived with for many years. I have very few episodes of diarrhea now, which I used to have that quite frequently. I also have a lot less bloating and cramping, and these improvements have occurred without any change in my diet or eating habits.

With respect to my energy level, I think that the reduction in the pain, being more tolerant to heat, plus the reduced GI, I've had a much greater level of energy, particularly the first two or three days after getting the infusion. I have a lot less fatigue, and I am spending a lot broader level of activities, and I feel like I'm more productive at work as well as my personal life at home.

Also, I have not had any side effects at all from this infusion therapy at all.

In conclusion, I strongly endorse the approval of this product, and for the treatment of Fabry disease I think it's made a substantial contribution to my quality of life, and I endorse the approval of this product.

Any questions?

CHAIRMAN AOKI: Thank you.

MR. TUFTS: Thank you.

CHAIRMAN AOKI: Richard Lind.

DR. LIND: Good morning. I appreciate being able to speak here. I appreciate our country for letting our voices be heard and taken into account, and I appreciate all of you who have given your time and expertise.

I'm a physician, but I'm speaking as the spouse of a female heterozygote for Fabry's disease. Since she was a young child my wife had has problems with burning in her hands and feet. As she grew older these pains became worse, especially when tired or stresses. She also could not sweat, could not tolerate heat, could not tolerate cold, could not tolerate milk products, was under weight when she was adolescent and a child, and as an adult began developing ringing in her ears and began developing progressive deafness.

Most of all she had end stage renal disease. In 1993, she had a kidney biopsy, which was read by Dr. Jennette, who we are privileged to have here today on the panel. She had progressive renal failure and protein in the urine.

I researched the medical literature, learned of Dr. Desnick and Mt. Sinai, and we made a trip there in 1997. We were flatly turned down at that time for enzyme replacement therapy because it was only being offered to men.

Over the next four years, her creatinine -- excuse me. I'm skipping on that.

About six months after our visit to Mt. Sinai she began peritoneal dialysis, and in February of 1998, she received a renal transplant.

I will say that we very close to lost her in the first year, but since then she has done well. It was not until the fall of 2000 that I again began trying to get enzyme replacement for my wife. I made calls to everybody associated with this disease: the NIH, Mt. Sinai, the FDA, both drug companies, the FSIG and NORD.

Every time my question was the same: will there be a treatment available for females with this disease who have kidney transplants?

Always the answer was no. The only people gave me any hope were the people at TKT. I wore out their phone line, and they told me they were working on it.

Finally, in May of 2002, my wife was begun on treatment. I want to say that in the two years that I fought for my wife, I watched her decline. She grew tired. She couldn't do anything. She had constant pain, constant diarrhea, and I began to fear that I was going to lose my wife, and she has been on treatment since May. It is a short time, less than year.

I have seen a stabilization of her condition. Her hearing has stopped declining. Her GI symptoms are improved, and her pain is markedly improved, and she now has the energy to carry out her responsibilities as a wife and mother.

I believe over time if it is not denied her, enzyme replacement will give my wife a benefit equal to her kidney transplant. I believe it has saved her life. FDA must make agalsidase available to the American people.

Personally our experience has been with

Replagal. My reading of the literature and interaction with people make me to believe that Replagal is safer and easier to give than Fabrazyme.

On the other hand, at the end of the day as a physician, my take is both products will probably have similar efficacy, and that all of today's confusion can be explained by tiny studies over a tiny period of time in a lifelong disease.

We in the Fabry community cannot wait another decade for adequately powered studies to be done. Too many people will die.

I believe that in the free market economy practicing physicians like myself have integrity and patients like my wife have intelligence, and the better product will be selected by our break free market economy.

So please give us a choice.

Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Richard Corkum, reading a letter on behalf of Tamara Crabtree.

MR. CORKUM: Hello. My name is Richard Corkum. I've been asked to speak for Tami Crabtree. Unfortunately Tami has become hospitalized due to her illness and could not make the trip.

In Tami's letter to me she states, "I really want to be there, but this is an effect that Fabry's has on both genders. The ability to plan anything is stripped from our lives, even ones such as these, the most important of plans.

"I wish for the approval of both enzyme replacement drugs as it is in the best interest of patients and the medical community at large who are trying to help treat and study our very rare disorder.

"I know that we seem like a small patient population, but the thing about diseases such as Fabry's that run in family lines like this, when one new patient is found, there are often several more found affected within the family and then future generations to consider as well.

"Another fact I want to mention is the need for more study of females. The support of carriers, we are the ones that really continue to pass it on, and regardless of what the text might say about occasionally symptomatic female, we all know there are plenty of us out there that are just as affected if not more so than our male counterparts.

"I ask that they do grant the approval for both ERT drugs, that they also show the same compassion that they did for me and my sister and made this therapy available to both genders affected by this disease.

"There is so little actually known and so much more they are discovering each day about Fabry's how can we possibly determiner which drug is the right or the wrong one at this time? We need more studies, which can only come over time with the approval of both drugs."

Tami has mentioned to me that she had improvement in six months on therapy, and I know that this therapy is safe and effective. She had been on drug for several months and started to fail once again. She just received her seventh infusion.

Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Dr. Joe Clarke.

DR. CLARKE: Thank you very much for the opportunity to speak to you. I am Joe Clark. I'm a Professor of Pediatrics at the University of Toronto and the Director of the Genetic Metabolic Diseases Program there.

My way was paid here by Transkaryotic Therapies, Incorporated, but I have also received financial support as a consultant to other firms, including Genzyme for work related to lysosomal storage diseases.

Next.

My background with respect to -- Fabry disease goes back several years. When I did my graduate studies, I wrote my Ph.D. thesis on the structure of the liquid that's stored in patients with Fabry disease. More recently I have become involved in enzyme replacement first with Gaucher's disease and other lysosomal disease, and more recently with Fabry disease, and now also with MPS1.

All of the latter studies are industry sponsored.

Next.

With specific respect to enzyme replacement therapy in Fabry disease, I first became involved with six patients who were admitted to treatment on a compassionate grounds through the special access program of Health Canada. Four of them were female, severely symptomatic females, and two males. They're all still on treatment.

As a result of that combined with experience with patients on treatment in the course of the TKG 010 study and subsequent extension I have about 217 patient-months experience with enzyme treatment of the disease.

The issues with respect to safety are being well summarized before and our experience is not different from what has been reported. I will not go into detail.

With respect to efficacy, and this is important, as a practicing physician I saw these patients at least once a month and more often and usually more often than that, and I was unable honestly to detect any obvious clinical difference in patients before four and usually six months. They were highly variable in the expression of their disease.

However, ultimately almost all reported an increase in energy and exercise tolerance, decreased pain with concomitant decrease in pain medication and utilization without any selection for allegedly non-Fabry pain drug, increased temperature sensation and increase heat tolerance with sweating.

One of the most dramatic effects was the effects on the gastrointestinal track, which one of the other reporters has commented on. One patient, the only patient actually, who had severe renal disease exhibited a slowing of deterioration in renal function, and so far dialysis. although he had catheters put in over a year ago, he's still not on dialysis because of stabilization of his condition.

There are some things that did not improve, and there may be some other data to show on this, but patients with significant hearing impairment showed no improvement, and in fact, one patient actually lost hearing in one ear completely after 18 months on treatment.

I've also been impressed with what I would regard as an unexpected incidence of depression. Three of the patients came depressed, too, requiring psychotropic drug therapy.

The last thing is I've been impressed with the underemployment of patients who reported feeling better. Only one of those who was capable of going back to work actually went back to work, and this really requires further investigation.

Finally, this summarizes my overall comments, but one of the things that I feel rather strongly about is that the combination of the small sample sizes in the studies that have been reported, the high, tremendous inter-subject variability in the patients with Fabry disease in the short term of the studies that have been reported decrease the power, the statistical power of these studies enormously and increase the risk of missing a study effect that might be of tremendous value to patients with Fabry disease.

Thank you very much.

CHAIRMAN AOKI: Thank you.

The next speaker is Paul Levy.

MR. LEVY: My name is Paul Levy. Is this on? I'm a Fabry patient. I'm 52 years old, and my mother had Fabry. At least she had the pain in the extremities. I believe she did. She died prematurely. He mother died prematurely, and I have two daughters that have Fabry.

And the purpose of my coming here today is to encourage all of you to please, just as Jack Johnson said yesterday for FSIG, approve both of these enzyme therapies because our community needs these therapies. The results that we've seen, even if you discount them for the problems -- I'll call them problems or errors. I don't believe I saw any -- are encouraging, and if you use the same marker for both diseases, the reduction of GL3 or GB3, there's reason to believe that both will be equally efficacious, as I believe they will be.

I have had everything that one can have from Fabry that we've heard discussed, and some other problems as well. The pain in the extremities starting when I was a child. I won't detail them all, but no sweating, lung involvement, heart involvement. I've had a six-way bypass. Seizures, repeated daily seizures, as many as four a day, grand mal seizures for years and years, and then my kidneys, of course, have failed. I'm on dialysis and have been for several years. My hearing is gone in my left ear, as first happens to most Fabry patients, and I'm losing my hearing in my right ear.

Having said all of that, about a year ago, a little bit more than a year ago, New York Life Insurance paid off my life insurance policies under a provision which was designed for AIDS patients. When a patient is terminally ill and their doctors reach a consensus that the person will die within two years, you're able to collect up to 50 percent of your insurance. I don't know if you're familiar with this, but thank God for that I can only say.

I have used most of the benefit that I received, however, in obtaining Replagal treatments in Europe. Replagal's subsidiary, a Swedish subsidiary, TK5S, I believe, has made the drug available to me on a compassionate use basis. However, I have to pay for my way to Switzerland every two weeks. It is exhausting physically; it is exhausting financially, and it's another reason I encourage you to approve these drugs as quickly as possible, because those people who are not as fortunate as I am to be as resourceful as I've been to obtain the treatments or have the resources that I have to afford the treatments certainly are being left out in the cold if they live in this country as opposed to Europe, Switzerland, or Israel where the drug is available.

So that's the reason I've come here today. I must disclose, however, that I used miles, accumulated miles, to go to Switzerland this past weekend, and instead of coming back to Boise, Idaho where I live, I decided to stop in New York, and TKT is paying my way from New York to here and then back home to make that up to me, and so I do have to disclose that.

I have no stock or other financial interest in either one of these companies, and I encourage you to approve both of their therapies.

Now, since being on the therapy, however, I can echo the remarks that you've already heard. I've started to sweat, use antiperspirant for the first time since high school. I can handle heat. On the hottest day I can go out.

The quality of life is markedly changed. I have more energy, particularly right after the infusion, and it is subjective. I understand that, but there's no doubt in my mind that I feel that.

We Fabry patients are particularly sensitive to our own bodies because if you understand the history of the way this disease has been researched and so forth, you understand that most of the doctors that we've gone to and most of the hospitals we visited over our entire lives have denied there's anything wrong with us.

So we've had to advocate to each of our doctors these pain symptoms, heart symptoms and whatever, neurological symptoms in the face usually of denials, and I went to the Oregon Health Sciences University recently, just before starting Replagal and described the double vision that I've had, and their chief neurologist explained to me that he has no idea why I would be experiencing that.

And that is typical of our experience with doctors in the medical community until quite recently. I was only diagnose recently because my daughter turned out to have the GL3 deposition in her eyes, and so her ophthalmologist picked up that she had Fabry and so the rest of the family was tested because we understand it's a genetic disease.

I don't think I would be diagnosed even today if that had not happened. So having said that, my results with Replagal treatment are extremely encouraging.

One other thing I'll add. No one else has talked about this, and I can understand why, but I became sexually impotent about 17 months ago, but four months after starting Replagal I became impotent and sexually active just as I had been previously at a very healthy level. So, you know, I don't know if that's related to blood vessel damage or what, but it's a very significant and meaningful therapeutic benefit of this drug to me and I'm sure to other Fabry patients.

So in summary, I've encouraged you several times to please approve the drugs. We would appreciate it in the Fabry community. We're a small community understandably, but we need this help, and this is the most encouraging help that we've seen ever, and logically it seems that this should work, and the data is encouraging.

Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Azza El Sissi.

MS. EL SISSI: My name is Azza El Sissi. I'm 60 years old, and I have been on Replagal enzyme replacement for 22 months under the Canadian special access provisions.

The Replagal has been provided as treatment by TKT, and I'm very grateful for that. They also paid for my way here and the hotel. Otherwise I have never really had any financial interactions with them. Neither did I receive any gifts.

I am very grateful for, of course, being grateful to the Canadian government for giving me the special access, to TKT for allowing the drug to be administered to women, and for my very committed doctor, Dr. Joe Clarke, on you just hear from.

I was diagnosed 1981 through an eye test. They were trying to figure out what was wrong with me, and they were saying that I had lupus, and they were looking at my eyes to put me in chloroquine, and then they asked when they saw the ones they asked for, you know, figure out what the was, just the curiosity of the residents, and then Dr. Clarke diagnosed me.

At that time I was told I'm just a carrier and I don't have the disease, and I was put on steroids for the lupus, so-called lupus. I had severe, severe pains. Anybody who has not been labor without sedation would not actually, I think, imagine, or a colonoscopy without sedation. I've been through both.

The kind of pain and not only in the extremities. In the neck, in the shoulders, int eh muscles. You would really think, you know, Dr. Kevorkian, where are you?

And things were getting worse. The

fatigue was getting worse. I was slowing down in my job, which was a very demanding one. They said, oh, it's because of the stresses in my job. Well, it wasn't.

And then finally four years later, I was told that, well, yes, you do have the disease, and it's in your heart. And according to echo -- we're talking about echocardiogram -- before that several cardiologists, good ones I may add, they said that I have health heart as per echocardiogram. I had an abnormal muscle, but you obviously have been living with it as if, you know, if you have a big nose, it's a big nose, but it's still a nose.

Then finally, one doctor, Dr. -- he listened to me, and six weeks after actually I was told that you have a healthy heart. He told me after an MRI that I was having heart failure and I had to have a heart transplant, and six months later I did have a heart transplant.

So you would say that is very lucky. Well, maybe. I did not respond to the immunosuppressants at all. I was toxic to cyclosporine. I was toxic to everything. I was totally house bound. I couldn't move. I was like a rag doll, and I was in constant rejection.

When you see my daughter's wedding day, my only daughter, who is a carrier, by the way, that is the day that I always dreamed of. You would not see me in any pictures. I was just like a lump on a seat in a corner, and all the pictures of everybody around my daughter are my half sisters and my friends.

But then TKT came along and Dr. Clarke, and they decided to try me on Replagal. This diarrhea was so bad that the humiliation of the accidents. I mean, when we talk about diarrhea, it's not something that Immodium takes care of, and my cardiologist, actually my transplant specialist was adamant that I don't take the Immodium because it would affect the absorbancy and make things worse.

Well, I defied her because I could not handle it. I had to take Immodium daily or I would have accidents like a baby sitting in a restaurant.

The pain, the energy level was getting so bad. I also was having a lot of noise in my ear. I could not walk without a cane at all. My daughter wanted to buy me a walker, and I said, "No, I'm not there yet. I don't think so." But I think a lot of people thought I was.

After I got on the Replagal, slowly but surely my muscles started relaxing a bit. The pain started being controlled. The episodes are much less. The diarrhea has started ceasing, slowly. I mean things happened really slowly.

I think it, as Dr. Clarke said, it may have been six months before I actually did not have to take any Immodium anymore; I did not have to take any of the Tylenol that I was pumping, extra strength every three hours because I am, you know, sensitive to codeine and all of this stuff.

My body doesn't like drugs, but then a lot of other things started happening. The rejection stopped totally. I have acquired tolerance to the immunosuppressants. I take three of them.

CHAIRMAN AOKI: Can you come to closure?

MS. EL SISSI: Yeah. Okay. Anyway, I have a lot more energy, and I have joy in my life. I can look after my granddaughter, but the thing that worried me when I sit and listen really about debating if we allow it or we don't allow it is the rest of my family. My grandmother left 21 descendants. Eighteen of them are carriers. Only four, the males born to affected males are not, and that really worries me a lot.

I look at my daughter, at my granddaughter. What will happen to them? It's not just what will happen to me if it's discontinued. What will happen to them?

I have lost my brother. I have lost my mother. I have lost my sister. I have lost my cousin, that one to the stroke manifestation. I have lost enough.

It is not just the disease. It's watching others. That's what you really have to live with as well. It's not that you are being able to dance or to even laugh only. It's watching them go, too, and hoping, hoping that something can happen to stop that.

So please.

Thank you for listening.

CHAIRMAN AOKI: Thank you.

The next speaker is Richard Corkum.

MR. CORKUM: Hi. My name is Richard Corkum. I'm speaking on behalf of the Fabry Society of Canada. Fabry Society of Canada is an organization developed to bring awareness and to support Fabry's patients, families, and friends.

I would like to begin by saying that until two years ago I was a very sick and weak individual. I failed many grades or two grades in school due to missing many days from Fabry's disease.

I remember when I was about nine years old I was in the hospital for months during the summertime. I was constantly crying from the severe pain of the hands and feet burning and chronic diarrhea. The doctors had no explanation for my pain. The doctor told my mother I was dying.

I was release from the hospital. My parents took me to our summer cottage on the coast of the Atlantic Ocean. It is mostly cool there. My burning stopped. I appeared to be a healthy little boy, except for a few episodes of burning and the continuing cramps in my stomach.

I was running around, playing with my friends and no more tears. But the pain continued when I went back in the heat once again.

I have been dismissed from many jobs which was also due to my illness. Employers do not understand when you're working in the heat to the point of exhaustion and start to cry from the severe pain. This is normal for a healthy 22 year old?

Now after being on enzyme replacement for the past two years, I've gained over 25 pounds. I do not sleep most of the day from exhaustion. I've dug two ponds in my back yard and recently combined both of them into one.

All of this was done in the mid-summer in 80 to 90 degree weather. There was no way I could have done this without enzyme.

I know that enzyme replacement will have a great impact on all Fabry's patients. Patients that are not working due to the illness will be able to return back to work and have a quality life not known to us.

I am now able to do little things that people take for granted or hate to do, like shoveling snow, mowing lawns, or taking out the garbage thanks to enzyme replacement.

If enzyme replacement is provide to children, they may never have to grow up feeling the way we once did, nor will they have to worry about kidney failure, heart problems, or any other severe issues that follow this dreaded disease. Maybe with approval of enzyme replacement we can start planning our families.

No longer will we have to hide from the pain, the fear of people dying or just calling us lazy because we cannot do the things that healthy people can do.

Most people take their health for granted. I try to live mine each and every day to the fullest. I am one out of seven in my family that has Fabry's disease. Two of us are on drug. My mother, age 69, is on a double blinded study for almost one year. My brother, he's had a kidney transplant, three strokes. He is now on compassionate use. The other ones are not presently receiving drug.

I'd like to say that my nephew and I have traveled since 1994 to the NIH every six months from Canada, thanks to Dr. Brady and his staff. We've participated in every study that we could help to bring enzyme replacement to this day. We are only two of many others around the world that have also participate in these tests to help make this day possible.

We believe approval is long overdue and must need for quality of life we have never had until enzyme replacement.

I'm 34 years old. Usually death occurs in the fourth to fifth decade. With enzyme replacement I feel that I'm not faced with these fears. I am now well enough that I can hold down a full-time job with fewer symptoms.

I believe it's in the best interest of the patients to have both drugs approved.

I'd like to thank the FDA panel for allowing me to speak at this very important meeting, and I would also like to thank NORD for their financial support for my travel arrangements.

Thank you.

CHAIRMAN AOKI: Thank you.

The next speaker is Jennifer Dickinson.

MS. DICKINSON: Hi. My name is Jennifer Dickinson. I'm here from the U.K.

I have to let you know that TKT has paid for my travel and my hotel.

I'd just like to fill you in a bit on my case history. My father died from Fabry in 1966, age 48 with renal failure. I was only six years old at the time.

My cousin died from Fabry in 1987, also from renal failure, but he did go into a coma in the late stages. He was in his early 40s.

I also had a brother who died, age 13, of renal failure. At the time it wasn't diagnosed that he was Fabry. That we don't know.

At age 18 I was taken by my mother to see a doctor in London who, yes, confirmed that I was a carrier, but as a woman I would have no problems. I am only to consider when I have my own family.

I am now 42 years old. Five years ago I started to have severe symptoms. I had to give up full-time work at that stage. Symptoms, as we all know, the burning pain in hands and feet, legs and arms, and sometimes other parts of the body. I suffered flu-like symptoms, temperatures, nausea, and constant diarrhea; also very, very tired, just an absolutely sheer exhaustion.

And physical activity made me ill, and I spent a lot of time in bed. I also started to get rather depressed because at times on the outside I didn't look physically ill, but on the inside I was just hurting so much.

I had to give up playing sports and things that people normally do with their family, holidays, skiing holidays in the cold. I couldn't tolerate it. I was so profoundly uncomfortable in hot climates as I was unable to sweat.

As you can imagine this altered my family. I've got two children and a husband who works long distance from home.

Life since Replagal. Since I've started

my Replagal treatments I've been able to work more, and my quality has just improved dramatically. I've started to play sports again, and I can do all of the normal household activities that had made me a failure before.

The burning pains are now very infrequent, and if I do get them at all, they're bearable, and I just have so much more energy again.

Also, my diarrhea has stopped, and that was one of the first symptoms, and it stopped very quickly, as soon as I started treatment.

I'm also sweating again and having spent a holiday at the end of the summer in Turkey, my friends couldn't believe my excitement at being able to sweat. It's the first time I had ever experienced it. They thought I was rather mad, but it was just a pleasant sensation.

Also, my doctors have confirmed that my creatinine clearance has improved since I've been on the treatment.

Obviously everyone has noticed the difference. Colleagues at work, friends, but especially my family and the children. The infusion has now been administered by my husband at home, and they have just become a part of life. It's obviously very relaxing, rather than my five hour trip to the hospital, and my husband at last feels he's doing something to help, having spent so many years feeling so helpless.

And just to end, I wish the ERT had been around in my father's day, but I'm just very happy and fortunate that I'm having this treatment. And having spoken to many patients in the U.K. and several patients that at a recent patient symposium in Barcelona, they have also indicated to me that they are benefitting from the treatment, too.

And I just sincerely hope that patients in the United States will also be able to benefit from this treatment as soon as possible.

And I'd like to thank you for the opportunity to talk today.

CHAIRMAN AOKI: Thank you.

The next speaker is Judy Collins-Stanley.

MS. COLLINS-STANLEY: I would like to

thank all of you for letting me come to Washington. I have to tell you that TKT has never met me or heard of me that I know of.

I have heard of this enzyme through my nephew. So if you would allow me, I would like to tell you a little history. I'll be brief because I know it's your lunch.

My father died in 1965, and I started this long journey of finding out what was wrong with all of us. I am a carrier. I experience the burning of the hands and feet until it's intolerable. I have two uncles that have died with this disease. I have a cousin with a stroke. I have two cousins, I have one nephew, and my son.

I will dwell on my son as opposed to my nephew right now. My nephew fortunately has gotten the TKT compassionate treatment. He is thriving. He was little skinny, scrawny, sickly child growing up. I never saw him well. I thought he was lazy.

My cousin is the same way, very skinny, sickly, and everyone has called him lazy.

My son has been sick most of his life. He has had the diarrhea. He has had the chronic hands burning. They've all just eaten Tegretol just to try to get some relief.

The main thing I am here today for is to tell you that my son went into end stage renal failure at age 27. I nearly lost him. He had a kidney transplant after being on dialysis one year.

Now they tell us he's got tinnitus. He's almost deaf in his left ear. He has chronic fatigue, and he has the diarrhea.

My nephew that is on the replacement enzyme, that is on the compassionate treatment is thriving. He's gained a lot of weight. The reason I know this, he E-mailed me. He thanked me for harassing him to the point of going on one of these studies.

And I myself have participated in three studies, and my son has, but we have never gotten the placebo or the drug. We just gave our bodies, pictures, degradation, anything we could give for this cause.

So I'm here today begging you to please

vote for this. Even if it should do harm to one, it's a better quality of life as you have heard.

I thank you for your time.

CHAIRMAN AOKI: Thank you.

Our next speaker is Thomas Stanley.

MR. STANLEY: I'm here just to speak as a husband and a father. I can't add much to what my life has just said or the rest of the people.

And as far as all the problems go, everybody knows this, everybody that's in the room. My son is 27. He hasn't yet had anything real serious, but he has to take eight to ten Tegretol a day just to function. He has never kept a job for more than six months, and that's one thing several people have mentioned.

It's very hard, especially in the heat. He likes to -- he did like to do construction work and work outside. He just can't do it.

And if it helps one person, whether it be him or anybody else, if you could approve one or both of these things, if they help one person, it will answer a prayer I've had for 37 years and that prayer was for something to happen to help these people out.

Thank you very much

CHAIRMAN AOKI: Thank you.

The next speaker is Amado Montalvo.

MR. MONTALVO: I would like to thank the committee for letting me come here and speak. I'd like to also thank NORD for helping me with my travel arrangements to get here.

My name is Amado Montalvo, and I am a 42 year old Hispanic from West Texas where the summers, it gets up to 107 degrees.

I was diagnosed with Fabry's disease in 1987 at the age of 27 by Dr. Stanbaugh in Lubbock, Texas. Dr. Stanbaugh had been treating a brother and cousin of mine at the time with Fabry's. I have had a brother, two cousins, and two uncles die from this disease.

I suffered as a child from the pain and symptoms associated with the disease which caused a lot of discomfort. My parents were taking me to the doctors only to be told that nothing was wrong with me and that everything was in my head.

This would become very frustrating. Ever since I could remember, I knew that something was wrong with me because of the things that I felt were not normal.

One of my main complaints was not being able to tolerate the heat. My body did not perspire. My hands and feet would burn and hurt with a pain so severe that at night I would get in the fetal position and cry myself to sleep.

The doctors would not give me anything for my pain due to the fact that they still believed that it was all in my head.

As a child in school I was not able to have any fun when I played in sports because of my disease. I would run out of air, and I would experience extreme pain, but I was determined that much more to push myself and try to do better. Sometimes it would work, but the majority of the time it did not, and I was really limited to what I was able to do.

In 1992, I was contacted by the National Institutes of Health in Bethesda, Maryland, and was asked if I would be interested in participating in a study that they were doing on Fabry's disease. I agreed to do so. I felt that if the research could help find a cure or help ease the symptoms and increase my quality of life, it would be well worth my time.

I have been on Replagal for three years, and it has made a big change in my life. For example, my gastric problems have improved to the point that I have put on 25 pounds of good, healthy weight. My body has begun to perspire, and I will never forget the first time that I did perspire. I felt a breeze and it felt cool to me, and I thought to myself, "So this is how sweating is supposed to feel." It was great.

I know I can now tolerate the heat a lot better, and I'm able to coach my daughter's basketball and softball teams. I myself play in the men's softball league, basketball league, and umpire Little League baseball games.

I am currently walking two miles daily and riding my bike the same distance. I feel a lot better and have a better quality of life. My friends and colleagues at work in the church tell me that I look health and I look better since I have been on Replagal.

Replagal is the reason for me having a better quality of life. I have come here today in hopes that I can make a difference in the way that Replagal will be looked at. My goal in 1992, by being a participant in the research, was that the researchers would be able to help not only me and my family, but my ten year old daughter is beginning to suffer from some of the symptoms, but also other children and adults.

I now know that there is something that can help, and just as I have been helped, and the difference that it can make in their life not just to prolong life, but to have a better quality of life.

I mentioned my daughter in what I have said, and not only for me am I hoping that you will really look at this close and approve it, but I do not want her to suffer as I did as a child, and if you all do approve it, I feel like that they can take the time to do other studies and take children in to where they will be able to help them.

Thank you for letting me speak.

CHAIRMAN AOKI: Thank you.

I think at this time we will break for lunch and return at 1:30.

(Whereupon, at 12:36 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

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

(1:32 p.m.)

CHAIRMAN AOKI: Okay. Please take your seats. We'd like to get started.

Okay. I thought I would try something very unique. It seems that yesterday I tried one tactic and that met with a certain amount of success. So I thought I would try something very different. I thought we would go straight to the questions.

Hearing no dissent --

(Laughter.)

CHAIRMAN AOKI: Okay. On the first question I have been asked to read it for the record.

Oh, Tom had a leftover question.

DR. FLEMING: Well, I guess now I have two. I guess I now have two burning questions. I mean, one of them is --

PARTICIPANT: Talk into your microphone.

DR. FLEMING: I had a burning question now maybe I have a second.

CHAIRMAN AOKI: This is not a burning bush. This is only a burning question, and there are no follow-up questions to his burning question.

(Laughter.)

CHAIRMAN AOKI: The floor is yours.

DR. FLEMING: Well, I have always found the most valuable part of these Advisory Committee sessions the opportunity to hear perspectives from colleagues and also to share perspectives, and obviously we can do that through the questions, but do we not want to take a fair amount of time to do additional discussion of issues before we get to answering questions?

CHAIRMAN AOKI: I think the strategy might be let's see how we do. Yesterday I think was exceptionally long, and let's deal with your burning question first and then let's launch into the questions, and then if we have issues to discuss, let's discuss them.

DR. FLEMING: But don't the issues, in fact, potentially influence the answers to the questions?

CHAIRMAN AOKI: It does, and I thought yesterday we had this open discussion before, and actually we answered many of the questions, and then when we tried to answer the question, it was as if we had never seen the questions before.

So I was just wondering this time to kind of be a little bit more efficient if we might just -- if there are some questions that you'd like to deal with right off the top, then let's address that because I know that you had a question, especially following this morning's presentations.

DR. FLEMING: All right. I'll phrase my question, and if you sense that it would easily come out through these other questions, I'm happy to defer.

CHAIRMAN AOKI: Okay. Fair enough.

DR. FLEMING: Basically my fundamental question was to the FDA in terms of where are we from a regulatory perspective here. We have seen two randomized trials, the 003 and the 005 studies, respectively randomizing 14 people and seven people to active intervention. The first study 003 targeted as a primary endpoint pain, and in the aggregation of results certainly didn't show any clear signal on that primary endpoint.

The second study had a primary endpoint of cardiac GB3 content, and also yielding P values around .4, .7, in that range. So also falling well short of providing clear evidence of benefit on its primary endpoint.

Both studies then having dozens of secondary measures. In a certain sense it's fully appropriate in a Phase 2 study, in an early Phase 2 study, to explore the data and to learn as much as possible, realizing what you're learning is hypothesis generation.

So I find myself a little agitated when looking at some of these results and having results interpreted almost as though they're providing some conclusive evidence of benefit, which in a sense when you're bringing an application before an Advisory Committee, the Advisory Committee is, in essence, having to answer that question.

But it just seems as though this development plan is being evaluated at a stage of what I would traditionally think has just finished its Phase II screening trials, generating hypotheses for sample sizes that could be adequate and study durations that could be adequate.

There is another trial, the 010 trial, that actually has some substantive sample size, although unfortunately its limitation may be a short follow-up period. There isn't a study that we see in place here that would provide 60 to 80 people followed for three years, so to speak. One has here the 010 study, but even at that we're not presented anything other than the fact that its primary endpoint, which is certainly an important primary endpoint relating to creatinine and GRF changes, is negative.

So is this being developed in an accelerated approval strategy, in which case what is the study that's in place that ultimately is going to give clinical endpoints, or is the 010 supposed to be that study?

But then we've already seen that it's negative, very impressively negative on the primary endpoint. So I'm perplexed here because it looks like we're looking at Phase II exploratory hypothesis generating data as the essence of the information that we're looking at.

DR. WALTON: I think that you've summed up things quite well and that the FDA viewpoint is very similar to what you've been saying. The framework in which we are bringing it to you is that this BLA was submitted to the agency asking for a conventional approval on the basis of the clinical data that was supplied to us.

We have brought that forth to you here today, and I think that we've been reasonably clear in the manner in which we are viewing this data. As you've heard, our viewpoint is not entirely shared by the company, and I think, therefore, it is valuable to hear the committee's perspective on the clinical data.

CHAIRMAN AOKI: And in this particular case, I think if we do address the first question, we do cover the issues.

Okay. I will read the first question and the question that stems from the reading. Data from two placebo controlled clinical trials, TKT-003 and TKT-005, have been submitted to the license application. TKT has recently completed a third placebo controlled clinical study, TKT-010. Study TKT-003 was designed with the primary objective of demonstrating a meaningful effect in the reduction of pain.

Data were also collected on renal function, cardiac function, and other clinical outcomes. The pain outcome in study TKT-003 did not indicate a treatment associated effect.

Study TKT-005 was designed with the primary objective of demonstrating a biochemical effect on GB3 content in heart biopsies. Data were also collected on renal and cardiac function outcomes. The study results did not demonstrate a treatment associated effect on cardiac GBG3 content.

While some renal function or renal histology outcome suggested a treatment effect, there were secondary or exploratory endpoints in these studies and were inconsistent and/or contradictory with multiple other endpoints.

These data prohibit reaching clear conclusions regarding beneficial effects of treatment on these organs. FDA determined that the data do not provide substantial evidence of efficacy.

The primary endpoint of study TKT-010 was evaluation of progression of renal impairment. While FDA has yet to receive the complete study report, TKT has stated that the results of the study do not provide statistically significant evidence of efficacy on progression of renal dysfunction.

Please discuss the available clinical data and any conclusions you are able to draw from these data regarding efficacy of the product. Do you find that TKT has provided substantial evidence of efficacy of agalsidase alfa in the treatment of Fabry's disease?

We will be voting on this after discussion.

Dr. Grady.

DR. GRADY: Yeah, I just wanted to ask the FDA. You know, in your presentation there were a whole lot of I guess what I thought were fairly substantive methodologic issues with both of the trials conducted with regard to this product.

And there was a site visit and lots of

other issues raised with the data and the methods, and I'm just wondering if you can give us some global assessment of how serious those were, you know, with regard to even the positive findings.

DR. WALTON: I think that I would note first that the fact that there was a site visit is not at all unusual. It is standard practice within marketing applications for the FDA to go out to some portion of the sites to examine the records at the site.

And in this case, study 003 was a single site. So we, in essence, could inspect the entire study with one site visit, and that's a little unusual, but the fact that we did have a site visit is not in and of itself unusual.

I think that Dr. Rieves conveyed to you that on that study the site visit helped us in interpreting the information provided to us and determining that we feel on the primary endpoint the data are not interpretable. We can draw no conclusions at all from it on that endpoint.

With regards to the other data, I think

we've highlighted that there are certain concerns about things like urine collections being adequate, for instance, on the creatinine clearance.

On the clinical data, there were not on the other endpoints major methodologic problems identified. There were on the histology endpoints. Dr. Rieves highlighted that there are methodologic difficulties that we feel are severely impairing our ability to interpret those findings.

Nonetheless, because they may have importance in evaluating this product for this disease, we certainly did present them, but in terms of the methodologic problems, it probably is primarily limited to the pain data and to the histology, and that is not in terms of how those samples were collected, but rather how the actual reading of those slides are.

And that question is actually going to be a portion of what we ask in a later question, your recommendations about that aspect of those data in terms of giving our concerns or does the committee feel able to interpret that or is it worthwhile returning to those slides in a more structured manner?

So I think that that's on that study. On the other studies I don't believe it's the methodologic problems that are giving us pause. It is the outcomes in the data themselves, the apparent weakness of the results and some of the inconsistencies between the findings.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: Continuing my tradition of trying to summarize where I am at the beginning, I'm going to actually read or not read, but discuss a set of opinions that I have that would form the basis for a vote and invite my colleagues to amplify, discuss, critique, challenge, whatever it happens to be.

I want to say that first I am speaking to the issue of whether the sponsor has demonstrated solid evidence of clinical efficacy. I want to say before I do this for the sake of some in the audience who may not understand what we're after, that absence of proof does not constitute proof of absence.

That is to say if the sponsors have not today convinced us of clear evidence of efficacy, that does not exclude the possibility of efficacy. It simply states that as of this moment can we or can we not establish efficacy.

And it's going to be my contention that we cannot at this moment establish evidence of significant clinical efficacy. We can't exclude it, but we cannot establish it.

I make that opinion based first on the controlled trials, and I'm going to talk first about the renal and then the cardiac business, and then general considerations that weaken the data still further.

With respect to the renal, the primary claim seems to be riding on the creatinine change in the 003 study. I've already expressed myself on this. I won't be redundant. I'm very skeptical that that is a robust change, that change at the end of the randomized period for all of the reasons that we've discussed.

In addition, this is not consistent across studies. We don't see it with respect to the GFR. We don't see it with respect to the serum creatinines.

We don't see it in the other study. So I do not believe that we have solid evidence from that study of a renal physiologic change.

We go to the renal histologic change. The one thing that is significant is the difference in the fraction of glomeruli that have mesangial thickening.

Now I have to get to the issue of a significant clinical outcome, and what I would assert is that I don't exclude the possibility of using histology as a significant clinical outcome, but I would assume that that would be irreversible damage, that is to say, clear-cut evidence that this is on the way to fibrosis, and at the best what you can say is that a difference in mesangial expansion is not tantamount to progressive fibrosis.

We don't know what the meaning of this is. This could be a surrogate of some sort. We can discuss that later on, but it is not established clinical change that would warrant a finding that there is a definitive beneficial clinical effect.

If I go on to the cardiac things, I point again to the inconsistencies that we have talked about both within studies and between studies, and so I do not find the data that were presented convincing that there is a clear-cut, pretty solid clinical benefit.

The general things that I would then qualify those two things is that in neither study was the primary outcome significant, and one always has to devalue the P values that you find in specific components underneath that by the fact that there are very large numbers of other examinations.

Therefore, even the solidity of the finding that we see is attenuated by the fact that there are many, many tests. I repeat this does not exclude the possibility of effectiveness. It just goes to my conclusion that as of today this claim is not yet established.

Now, the long term studies are an important issue here, and you've heard, I suspect, most of you have heard us discussing yesterday the issue of whether you can use historical controls as a solid comparator. I want to give you two reasons why I think in both of those cases that this is probably very -- both the case of the heart and the kidney why this is tenuous.

In the case of progressive renal insufficiency, a very clear issue is that the rate of progression is going to be a function of where you start at least early in the disease. Patients who are close to normal renal function will typically lose function rather slowly initially and only until they get into that sort of terminal slope, if you will, with a creatinine that is definitively in the abnormal range, can you assume that there will be the higher rate that we saw in the studies that came from NIH and the like.

The two groups of patients are clearly non-comparable with respect to that. The patients in the follow-on study had lower creatinines at the outset, and it does not surprise me as a nephrologist at all that there is a difference in the rate of progression in that group of patients who were studied at an entrance creatinine of one to 1.1 compared to the patients who were seen later at 1.6 and above in the NIH study.

So I do not believe that we can use the

historic data as a basis for expectation of what would happen.

In addition, as we've heard, as we said yesterday, there is a whole world of difference between even 2000, let's say, or 1998 and 2002 in terms of the use of converting enzyme inhibitors, the blood pressure control, and so forth.

With respect to the heart my argument is different, and I first of all let you know that I'm not a cardiologist, and so what I say is based on what I know from my colleagues in cardiology about what's happening in the management of cardiac failure, and that is that within the past ten years, there has been a very substantial difference in the treatment of and outcome of cardiac failure so that today it should be anticipated that a person coming to an experienced cardiologist with congestive heart failure will improve with standard therapy.

What we don't know is whether the people who we see in this study will have improved more than the people who would have improved had they received only the current standard of therapy. This is unknown.

And, therefore, I believe that it is unreliable to use an historic database to compare outcomes and to say that we would not have expected improvement.

Based on all of that, I have to say that there are no data here that serve to leave me absolutely convinced of a clinical benefit, and therefore, I do not believe that they have achieved solid evidence of effectiveness.

CHAIRMAN AOKI: Do we have any other comments?

Dr. Woolf.

DR. WOOLF: I'd like a point of clarification from the FDA. This is not an accelerated application?

DR. WALTON: This application was not submitted with a request for accelerated approval.

DR. WOOLF: So we must demonstrate clinical efficacy and not a surrogate marker with efficacy proven later?

DR. WALTON: This first question is, yes, is with regard to the evidence of direct clinical benefit. I'm sure you've read through the other questions, and you can see that the second question is going to be asking about the idea of a surrogate marker, and that second question was put there in light of the fact that we were bringing two applications to you and of what the, you know, main discussion of the first application was going to be and the potential advice that we might have received on the first day.

We thought it might be valuable to receive your comments on that topic as well on this application. However, that is not the way the application was submitted to us, nor is there any verification study underway.

DR. WOOLF: With that caveat, I agree with Dr. Hunsicker's assessment.

CHAIRMAN AOKI: Dr. Jonas.

DR. JONAS: I think that there's some reason for optimism that this pharmaceutical could be effective in that it is a replacement for an enzyme that's not being produced. It's the same sequences as the enzyme. It goes to the right spaces that the enzyme or right compartments, at least some of them, that the enzyme is supposed to be in, and it does seem to have an effect on storage of material in vascular endothelial cells at least in some of the material that we've reviewed.

So all of that gives one some reason for optimism. However, I must agree that the material presented to us in these studies is not persuasive regarding an clear-cut effect. Now, that may be a problem of the amount of time allowed for the study. That may be also related to even something like dose of the agent used, but I must agree that I don't see a compelling effect other than the things that I mentioned in the data that was presented.

CHAIRMAN AOKI: Dr. Barisoni.

DR. WALTON: Dr. Aoki.

CHAIRMAN AOKI: Yes.

DR. WALTON: May I clarify the comment that I made previously?

CHAIRMAN AOKI: Absolutely.

DR. WALTON: Although this application was not brought to us primarily for accelerated approval, that that idea was raised during review in discussions with the company and in the briefing document that they have provided they have expressed an interest in that consideration as well, and it should not be -- I really may have given an incorrect impression in my answer about focusing just the initial presentation and not the later discussions.

CHAIRMAN AOKI: Okay. Thank you.

Dr. Barisoni.

DR. BARISONI: If we agree that there is no solid evidence for the data that is being provided, and in particular I'm talking about the histologic data, I was wondering whether there is a chance to review those data and review those slides and reevaluate them and see whether it's possible to come up with some scoring system that might tell us something more about the effect of this drug at least histologically.

DR. WEISS: Doctor, actually that is one of the questions actually specifically for this committee to see, I believe, about whether or not there is an opportunity to reread. One of the advantages of having biopsy samples is that you can engage in rereads in certain matters, and one of the specific points of advice we'd like from the committee is whether or not that would be something that we should have discussions with TKT about.

So we would be very interested in hearing those comments.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: Well, I find this all kind of confusing and odd because if you remember yesterday, what we were presented, what we were really struck by yesterday was the fact that the company had developed a product which clearly replaced an enzyme deficiency, and I think none of us would argue that this product does the same thing or has the same potential and has the same compelling sort of theoretic and biological potential.

Yesterday also we were presented data that showed that the effect of the drug was to reduce aggregation of GL3 in certain cells of the kidney, but not all cells of the kidney. In fact, we've been presented similar data here in that if you look at the FDA slides, there was a statistically significant decrease in lipid in endocapillary cells of the kidney and in vascular epithelial cells. It's pretty much exactly the data that we were shown yesterday.

There was not a statistically significant effect in other cells of the kidney.

CHAIRMAN AOKI: But I caution you that each of these --

DR. GRADY: Well, I know that, but I'm just saying that with regard to what we know, it seems to me we know sort of similar things, and we perhaps know a little bit more in that some of these short term studies did not who any effect on renal function, and I find the pain data just completely uninterpretable.

On he other hand, it just seems like an odd position to be put in because I think that we do have the same compelling biologic plausibility, and we do have effects on some cells, not others.

CHAIRMAN AOKI: Point well taken.

Dr. Schneider.

DR. SCHNEIDER: Well, I mean, to start, to answer the specific question, my answer would be no, that we've not been provided substantial evidence. But I think I want to go one step further.

After these two days or day and a half I'm fully convinced that enzyme replacement therapy works in Fabry's disease. The problem is that neither group has really presented the kind of evidence we'd like to see.

I suspect that one reason for this is this crazy situation where only I'm told that whoever gets approved first, the company has lost millions of dollars and has to wait seven years. Consequently, they've both gone much too fast.

Knowing the natural history of this disease, obviously what we all want is a controlled study. And the natural history of this disease is so bizarre of normal kidney function for a very long time and suddenly all of a sudden fall-off and with improvements in treatment the patients with renal disease, we all know that this sudden fall-off might occur a few years later in 2002 than it did in 1996.

It's very likely that a controlled study to give the answer we want would take several years, many years. I don't know, and obviously we can't go back and do that anymore.

I think the fact that the drug is available in Europe. We have people flying to Europe to get treatment. Once we approve one drug it's going to be impossible to keep patients in a controlled group, in a controlled study.

Personally, I think it's time to approve this drug and get to the kind of answer we really want in post marketing, very careful follow-up of patients, which could take years. I think we will eventually get the answer. It's a shame that we're doing it this way. I don't think we have any choice at the moment.

We have hundreds of patients who need this drug. So it's obviously going to help them, and I think we're just being a little too pedantic in trying to demand the type of thins that we'd all love to see. I think we really should approve one of these. Personally I'd like to see them both approved. I don't know if that's possible.

If I had to choose between the two, the group yesterday, pick the primary endpoint and as best I could tell, a close collaboration with the FDA. They met that endpoint very nicely, and then we had a big fight whether that was the right endpoint or not, and we overwhelmingly voted that it was.

Again, I have no reason to believe that one drug is any better than the other. It's just one company, I think, maybe by luck, maybe by smarts has ended up with a better application than the other, but I really would like to see this drug approved, and I think it's a disservice to the patients and really it sort of throws mud in our own faces to hold off on this.

I think there should be approval of this drug. So that's my vote.

CHAIRMAN AOKI: Dr. McClung.

DR. McCLUNG: Let me just amplify the issues about the quality of the data from the clinical trials, not so much the endpoint, but one other issue is that I'm uncertain about the dose particularly with this drug. There is no clear dose response curve where above the dose response curve that was studied, and I'm not sure where we are on the dose response curve.

Moreover, the serum and urine levels of the substrate were reduced, but not to normal, and while it's possible that there is a threshold effect where suppression of a certain amount would result in clear or even optimal clinical benefit, I'm not certain that that's true, and the combination of those two things at least makes me uncertain about that even if the drug is approved -- and I agree that the plausibility that it will work is true, but I'm not sure that this is the correct dose.

And while it is unfortunate to withhold therapy from patients who might benefit, it's just as uncomfortable to expose patients to the wrong dose of a drug that encourages both expense and potential toxicity without clear evidence of benefit.

DR. HUNSICKER: I'd just like to clarify one thing. I addressed specifically the question of whether we had currently solid evidence of efficacy. I concluded and I will maintain that we do not.

I will just clarify I said precisely the same thing yesterday. So the issue of whether there is a surrogate is something that we can discuss when we get to the surrogate, but right now the issue before me at least, as put in this thing here, is has the sponsor established efficacy as of now.

And my belief is that they have not yet.

CHAIRMAN AOKI: Since I don't see Dr. Fleming --

(Laughter.)

CHAIRMAN AOKI: I do see Dr. Fleming.

DR. FLEMING: Well, actually my comments can be much shortened significantly because almost verbatim what Dr. Hunsicker has said at the beginning was the assessment that I was going to articulate.

I might just add that certainly as well the pain data which were the primary endpoint in their largest pivotal study was also unfavorable.

We've had a number of comments made about kind of the philosophy of what strength of evidence we should have in life threatening disease settings, and in settings where there is considerable difficulty in being able to enroll because of small numbers.

It seems to me that we have had put before us regulatory standards, and those standards do accommodate the fact that this is an orphan drug setting, and yet in an orphan drug setting it's very clearly indicated that there still needs to be substantial proof of efficacy.

Are all enzyme replacement regimens the same? If, in fact, Regimen A was proven through rigorous clinical trials to establish benefit, does that mean that any Regimen B that comes along we will automatically assume carries the same benefit?

I mean, we just heard one aspect that should give us pause. If the dose is not proper, we may not achieve the same efficacy. We had discussion about the fact that is it ethical to randomize people on a life threatening disease to a control regimen over two or three years. It's not unique to this setting.

There are a number of settings where we've had life threatening disease settings in an unmet need, and yet it was determined to be wise to determine whether there was adequate proof of efficacy before interventions were approved.

If we worry about a small number of people on a placebo being disadvantaged by being on that placebo, should we not worry about the possibility of approving an intervention that, in fact, isn't established to be beneficial where it could be widely used and, in fact, be a placebo?

How ethical is it to have people on a placebo for years and have it a large part of the population where they're getting bi-weekly infusions, especially if there's another regimen out there hypothetically for which there is benefit? Is it not important to understand that if an agent is approved that there is adequate evidence of efficacy?

And as I understand from a regulatory perspective, that is, in fact, the declaration. So I understood our challenge here was in the context of what has bene put before us even in an orphan drug. Is there substantial proof of efficacy?

That's the question that we're being asked to answer, and I think Dr. Hunsicker's response provides a very clear answer to that question.

CHAIRMAN AOKI: Seeing no further discussion, then why don't we start with the votes, starting with Dr. McClung.

DR. McCLUNG: Let me see what the question is so that I'll know whether yes or no is correct.

CHAIRMAN AOKI: Yes or no. Do you find that TKT has provided substantial --

DR. McCLUNG: I understand the question, and the answer is no.

DR. FOLLMAN: No.

DR. BARISONI: No.

DR. SCHADE: No.

DR. FLEMING: No.

DR. WOOLF: No.

MS. KNOWLES: No.

CHAIRMAN AOKI: No.

DR. JENNETTE: No.

DR. WATTS: No.

DR. LEVITSKY: No.

DR. SAMPSON: No.

DR. HUNSICKER: No.

DR. SCHNEIDER: No.

DR. GRADY: No.

CHAIRMAN AOKI: The vote is 15 to zero.

Turning to the second question, I've been asked to read this as well. I hope you're enjoying me reading this.

In the controlled study TKT-003, renal tissue biopsies were collected, and multiple histologic features analyzed as secondary or exploratory endpoints. Only a portion of the analysis methods were prospectively planned in detail. The data suggests some effects on renal pathology, but the exact degree of treatment associated change is unclear.

Data regarding endpoints other than clinical efficacy may, under some circumstances, be used as an unvalidated surrogate for efficacy. The accelerated approval regulations provide for marketing of a product based on such data.

The first question is: please discuss the quality and strength of these data. Please discuss the potential predictive meaning of the histologic findings obtained by TKT. Please include discussion of the importance of the renal vascular epithelial cell type as compared to other renal cell types or tissues.

And we are going to be asked to vote on, with clarification, are any specific elements of the histologic data reasonably likely to predict clinical benefit -- i.e., I assume it is the surrogate -- in the manner intended under the regulations for accelerated approval.

DR. WALTON: Dr. Aoki.

CHAIRMAN AOKI: Yes.

DR. WALTON: Given the flow of the discussion that's been occurring, it occurs to us that our breaking up of this question into three parts may not serve the committee well in how they might feel more comfortable about discussing things. If you would prefer to sort of open discussion up to all three aspects, all three subparts of this question if you think it might be more efficient, we would be happy to have it done that way.

CHAIRMAN AOKI: I think that would be

reasonably well received.

Okay. That was -- I read Part A and Part B. Part C is if you do not feel the histologic data at present is reasonably likely to predict clinical benefit, do you recommend that any further evaluations of the existing biopsy samples be performed, with the possibility that these additional evaluations might be a suitable basis for an accelerated approval?

If the answer is yes, then please discuss the types of re-analyses that would be most useful for TKT to perform.

Dr. Hunsicker.

DR. HUNSICKER: Okay. I'm going to start with a question. I will after I hear the response probably be ready to give an answer.

I read Paragraph 601.41 that we've had distributed to us, which is approval based on a surrogate endpoint or on a clinical endpoint other than survival or irreversible morbidity. The FDA may grant marketing approval for a biologic product on the basis of adequate and well controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely based on epidemiologic, therapeutic, and so forth, as I read yesterday, basis.

So it seems to me as I read this that to approve at this moment, to recommend approval of this agent on an accelerated basis conditional upon later validation would require not only that a surrogate be designated, but that there be now convincing evidence that at least the surrogate had been affected; is this correct?

DR. WALTON: Yes. We would hope you would find that the data you have in hand now on some particular piece of information is convincing to you that there has been an effect on that surrogate and that that surrogate, that particular surrogate you view as reasonably likely to predict clinical benefit.

DR. HUNSICKER: Okay. Then if I may, I'm going to respond to the issues that I put. So I will start out off the cuff saying that I have the suspicion that has been shared by many of us that these enzymes are likely to be very similar; that there is some kind of a priori the likelihood that they're going to do the same thing if they're properly dosed.

But I'm going to stick with what I've been told to do by the instruction today, which is to evaluate is there some surrogate that I can pick out of the data today for which the evidence is convincing, for which there is a rationale for a relationship to ultimate outcome and for which there is convincing evidence that there has been a change.

The first part of those two is rather easy. I can go through. I told you yesterday that I thought that it was rather arbitrary to choose one pathophysiological hypothesis. I personally believe that the pathophysiologic hypothesis put forth yesterday by the Genzyme corporation is probably the more credible of the ones that are put forth simply because there is the experiment of nature evidence from the cardiac variant, and so forth that that might be correct.

But I am not what I would call highly persuaded that we have any clear evidence that any one particular surrogate is better than another one. So I have to be very open minded as to what surrogates might suffice amongst the ones that we have here.

Of the ones we have here, the one I find most likely to be persuasive to me is the change in pathology. That is because I suspect that the sponsors may well be right that the expansion of the mesangium might well be a prelude to further fibrosis and that that would be indicative of long term outcome.

So if we were to choose that, then I have to look at the issue of pathology, and I want to be very clear about one thing. Were there a change in overall, across the whole series of severities, including the irreversible changes, I would be very persuaded, if there was significant change in the total scarring within the kidney, just as I would be persuaded if there were a change in renal function; I would be persuaded that that was a very good surrogate and that it might lead us on.

I'm willing to believe that the change in mesangial thickness might be just as good a surrogate as we accepted yesterday. The problem is that the evidence in favor of that being a significant change is much weaker.

So I come up with -- and I'm open to discussion on this -- I come up with I cannot as I read through this find a surrogate which both has some credibility as a predictor and for which there is clear evidence that the intervention has made a substantial change.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: Well, with respect to the specific questions, asking about the quality of the observations and the strength of the evidence that there is an effect and that it might be a marker of clinical outcome, with respect to the quality, there clearly were some methodologic problems, and there clearly were some changes in the observations that were ultimately made relative to the ones that were proposed to begin with.

And as the FDA review pointed out, probably the major change was a shift from the chronicity study with the deletion of some very important categories, glomerular sclerosis, both segmental and global, from that approach which was semi-quantitative, as I recall, zero to three-plus, and then the construction of an ad hoc set of observations which in fact focused on the glomeruli as well where it was more quantitative looking at the percentage of glomeruli that had segmental sclerosis or global sclerosis or no lesion and adding in the mesangial expansion factor.

So there clearly was an ad hoc shift. Just as a matter of opinion I think that was an improvement. Now, again, it broke with protocol, and so from that perspective, it has a problem, but basically what in effect was done was to shift from a semi-quantitative scale of zero to three how much segmental sclerosis was there to a zero to 100 scale for how much sclerosis there was with a counting of the glomeruli.

So it was replacing in my view a semi-quantitative score, zero to three plus segmental sclerosis to a percentage of glomeruli with segmental sclerosis.

So to me it improved the precision and

interpretability of the data to modify that. So as far as that methodologic issue, that's my perspective on it.

Now, I don't think that change probably had any significance on any outcomes because, as was pointed out by Larry, there was no clear-cut change in the degree of sclerosis and glomeruli brought on by the treatment regimen.

However, just thinking about what I would expect to be likely to change in a six month period of time, I would have been very surprised if there had been substantial change, especially reduction, possibly more likely an increase in, but certainly no reduction in the amount of sclerosis in an observation period of six months. I'm not surprised by that.

What I would have expected if it is, and as with Larry, I'm not sure there's evidence that it is, but the mesangial expansion could more reasonably change in that interval of time, but I share his position that we have no strong evidence that there is a linear progression from mesangial expansion to glomerular sclerosis. So with respect to it being a surrogate marker, I can't feel too confident about it.

Now, the quality of the observations, just in general when you look down the actual scores on page 11, I guess, of the FDA review, in some respects it's remarkable there is no significant change in a lot of these scores, which suggests to me that there was no significant difference in the reproduceability of the assessment of the pathologists when they went down through this.

So there was pretty good reproduceability here in identifying the same amount of an injury that didn't change. So in some respects that validates that these pathologists who looked at this at least can reproduce their opinions about how severe a particular lesion is looking at its expression.

The change that is most impressive, as has been pointed out several times is something that we would expect, given our conclusion yesterday that the presence and amount of endothelial inclusions is a marker for exposure to replacement therapy by this enzyme.

If it had not been observed here, then the explanation would be that we were wrong in our conclusion yesterday or the observations were not correct r the agent that was used in these patients isn't the same.

So it is comforting to me to see that the conclusion is the same in this study as the study yesterday, that is, that there's a highly statistically significant decline in the amount of endothelial inclusions of the substrate for this enzyme, the GB3, in this study.

So moving down into these questions about is there potentially a surrogate imbedded in the data here, I think that the surrogate that looks the most likely here is endothelial inclusions.

I don't share Larry's preference for the hypothesis for pathogenesis that was presented yesterday. I have other opinions, but I think that's somewhat irrelevant because if this is a surrogate, it doesn't necessarily have to be a prime mover in the major pathogenic mechanism to be effective.

So that, I think, to a certain extent is irrelevant, but nevertheless, you know, to summarize what I have said, recognizing that there have been some methodologic problems, I feel reasonable comfortable with the observations that were made and reported here and with the likely validity of them, and the one observation that looks to me to be the most likely surrogate marker for an effect by this enzyme replacement is endothelial inclusions.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: I just --

CHAIRMAN AOKI: What? You'll wait?

DR. WOOLF: I think we do have a potential surrogate. I think it's a different one than has been discussed by the two previous speakers, and I refer you to graphs 49 and 50 of this morning's presentation from TKT, that is, comparing the two graphs, mean baseline creatinine clearance versus normal glomeruli and the inverse mean baseline creatinine clearance versus segmental sclerosis and obsolescent glomeruli.

These have correlation coefficients of roughly .7, which in the realm of biology is pretty good. I would like to hear from our statisticians about the details of those analyses. They didn't change with time, but if I were looking at a point in time, I have a surrogate that correlates with some clinical outcome. That is, the more normal glomeruli, the better the creatinine clearance and the more abnormal glomeruli, the worse the creatinine clearance.

So to me, speaking as a non-nephrologist, that seems like a pretty good surrogate if the data is solid.

And so I think that there are data here. I would personally like to have -- I realize there are not a whole lot of patients who have been biopsied, although there were a lot of glomeruli per patient. I would personally like to have an independent review of those slides redone because of the ad hoc nature of the change in the protocol, but I think it's a reasonable surrogate.

DR. SCHNEIDER: Which is the surrogate, the creatinine is a surrogate for the normal glomeruli or the normal glomeruli is the surrogate for the creatinine clearance?

Why don't you just give the serum

creatinine? Why biopsy the kidney?

DR. WOOLF: Well, I'm not particularly interested in the glomerulus as much as I am in what the clinical state of the patient is. So I'm more interested in the creatinine, and the glomerulus seems to give me that.

CHAIRMAN AOKI: So are we basically talking about free surrogates, potential surrogates, mesangial thickening, capillary endothelial inclusions and the number of healthy glomeruli?

Dr. Fleming, are you yielding?

DR. FLEMING: Well, I'll just comment on this just to understand just because I have the same confusion here.

What we're saying here is that the normal glomeruli has a trend in the right direction. By the way, segmental sclerosis is a trend in the wrong direction. We've got data on creatinine clearance indicating no differences, and in fact, an enriched data set in the 010 trial showing no differences.

So if we're going to use these as surrogates for short term creatinine clearance and we know that there's no effect on short term creatinine clearance, that would make me wonder about why these are good surrogates.

Ultimately, ultimately a surrogate is a good surrogate if a treatment induced effect on that biological marker is accurately predicting treatment induced effect in the clinical endpoint. And what do you say about the creatinine clearance?

Obviously we could say we haven't observed it long enough, and that's very true. We are uncertain here about whether we followed long enough.

There are additional measures that have been put forward. The primary endpoint in the 005 trial was the cardiac GB3 content, and that shows a modest reduction with a P value of .42. In the 003 study, the kidney GB3 was reduced modestly with a P value of .27.

We talked a lot yesterday about plasma, about the plasma GL3 as potentially being a good marker. As you know from my comments yesterday, I was at least not currently persuaded even with yesterday's data that we really can say we have a surrogate that's adequately established in large part in my own view because of the absence of longer term clinical outcome data by which we could make a more reasoned assessment of correlation.

But yesterday we were looking at capillary endothelial scores in the kidney, heart, and skin that we're dropping to zero in 70 to 100 percent of cases, and it was, in fact, the primary endpoint. It wasn't one of a wide array of secondary exploratory measures.

And I understood -- maybe I misunderstood -- but I had understood that the rationale yesterday was the very striking -- in fact, the FDA had, in fact, prospectively said you must show large fractions of people moving to zero, and they did, and we heard discussions about the plasma GL3 yesterday, and by my recollection, it dropped from 15 to two.

Here we're looking at plasma GB3 in the 005 trial. It was the strongest statistical signal. It was actually confirmed in both studies at the 01 level, but it was a drop of 50 percent. It wasn't a drop to zero.

And so is this a biological marker? Well, one of the challenges that's a reasonable surrogate at least for accelerated approval, well, as I was discussing yesterday, historically where we've so often been misled with markers, you know, it's patency stupid. It's not just patency. It's how much, how long.

And so I'm confused. I mean if we're going to look at these changes, these changes look far more modest in magnitude than what I saw yesterday. Does that matter? How can we be convinced if we see a given change?

And, you know, I'm interested in clarification. In fact, maybe I'll just stop at this moment to say at least in summary when I look at the focus, one of the focus measures in 003 which is kidney CTH and in the 005, which is the cardiac CTH, and I see modest percent reductions and then I see the plasma GB3, but the reductions are relatively modest in magnitude. How do you interpret that?

CHAIRMAN AOKI: We have about eight people lined up to respond. First is Dr. Schneider.

DR. SCHNEIDER: Well, here you have a

lysosomal storage disease where you know you have a defect of a lysosomal enzyme, and the material that the lysosomal enzyme is supposed to degrade is accumulating within the lysosome, the GL3. This to me is a logical surrogate.

So plasma GL3 is a surrogate of the lysosomal CL-3 and eventually it's a lot easier to take a couple of milliliters of blood rather than get a kidney biopsy, but if you're actually looking for the real surrogate, to me the only logical one is the interlysosomal accumulation of GL3.

DR. FLEMING: And the same pattern though exists, i.e., what we're seeing is a partial or a modest reduction that, in fact, isn't even statistically significant. I was referring to the plasma because of discussions that had been raised yesterday, although even though this was statistically the consistent signal by the sponsor's own analyses in their slide 23(a), it didn't correlate with GFR, and they acknowledged that the clinical consequences are unknown.

For what marker do we have known clinical associations and very substantial reductions?

CHAIRMAN AOKI: I'd just like to interject at this point. It is my understanding that the Replagal and Fabrazyme are exactly the same molecule, and I'm willing to stand corrected if they're not.

DR. WALTON: For review purposes, the FDA regards the different biologic products as being different products. Under the specific terminology and definitions of orphan drug regulations, both are regarded as presumptively the same drug, but that's a different question than I think you're trying to get at.

We feel we need to regard the information about each product as being about that product itself.

CHAIRMAN AOKI: With that as a cautionary, let's continue with this list here.

Dr. Grady.

DR. GRADY: Well, I guess this is also confusing because I think we have three potential possibilities. One would be endothelial GB3 accumulation, the problem there being the company nicely showed us they had no correlation with creatinine clearance.

So I mean then we have plasma GB3, which there was a statistically significant decrease in of about 40 percent, which did correlate with creatinine clearance with a sort of smallish correlation coefficient, however, with .17, and I think the final one we have are percent normal glomeruli, which is what I think the company was aiming for as their main surrogate. That did have, although, you know, there are multiple testing issues, a statistically signification decrease and a correlation with change of creatinine clearance.

So to me that seems like the most logical choice for a surrogate, but the very confusing thing is we're saying it's a surrogate for a change in creatinine clearance, and we're looking at the correlation coefficient with creatinine clearance, but there was no effect on creatinine clearance that we can tell.

So I think in order to come to a surrogate, we have to throw out the actual outcome where we're looking for a surrogate for and assume that there wasn't long enough follow-up or it wasn't quite the correct population, which is possibly true, and choose a surrogate based on that.

But it's awfully strange to have sort of information on the actual outcome you're looking for and try to choose a surrogate despite that.

CHAIRMAN AOKI: I agree.

Dr. Follman.

DR. FOLLMAN: Regarding surrogacy, I think we're just in an impossible situation, frankly, because the sponsor didn't come up with a prespecified surrogate as far as I could tell. They did their study on their primary endpoint. It wasn't significant. They did many, many analyses, and out of that we end up with a few P values that are less than .05 on renal histology.

I can't see how in a study you can both pose a surrogate and validate it within the same study. To me it seems an impossible task, and now we're discussing, you know, what could be possible surrogates. Even at the end of the day here, I think the most we can do is say this might be a useful thing to look at in TKT-010, but I just don't see that we can come up with a surrogate here after so much has been looked at and it wasn't specified prospectively.

CHAIRMAN AOKI: Dr. Schuetz.

DR. SCHUETZ: Thank you. Thank you, Dr. Aoki.

I think it is very important if I could perhaps refer you to page 90 of our briefing book which shows in Table 20 and 21 in terms of the comparison of the effects on capillary vascoendothelial cell GB3 levels.

In our study we had quantified on a zero to three scale, and we did not look at what fraction became normal or nearly normal, and in addition, no capillaries were excluded from that analysis. So that includes all of the capillaries in the biopsy.

So in Table 21 is reproduced from the publication in the New England Journal of Medicine on the effect on essentially the same cell type, the effect of Fabrazyme, and I think you would agree that those changes are quite similar.

In addition, if I may, we have looked at individual capillaries, and if I could ask Dr. Melvin Schwartz to make a comment on the clearance of GB3 from the vascular endothelial cells, I think that might be important at this point.

DR. SCHWARTZ: My name is Mel Schwartz. I'm a renal pathologist from Chicago.

I was not involved in the histological evaluation of this material at the NIH, but I had the chance to look through all of these slides, and I want to point out to the committee -- most of you are not morphologists -- that, you know, when you do a semi-quantitative morphometric study like we're talking about, and there's several different types that we would be talking about here, you know, they are really valuable when you have a difference that's obvious to somebody who just looks at the slides and they can see the difference.

If there are small differences, it's going to be an inconclusive study. Well, on the left side here you see, on the left side -- I'm not sure that I'm technologically adept enough to work this. Okay. Here we go.

On the left side there arrows mark deposits within endothelial cells, and I point out to you you have to go to oil immersion to see these things because they're not the same big, huge deposits you'll see in the glomerular epithelial cells. They're very small and, you know, we're not talking about pathogenesis here, but they're very small, and they seem rather inconsequential.

But be that as it may, after 24 weeks of the enzyme, you see there are no deposits in this field. Now, I realize pathologists can choose fields, but we looked at slides to take these pictures, and this is a reproducible observation. So this field shows zero deposits, and for the committee members who's worried about the doses, I will say that this is the dose that was given in this study.

Also, these endothelial cells to my eye at this power have returned to normal in appearance.

CHAIRMAN AOKI: Thank you.

DR. FLEMING: Just before we leave that point, I mean, even the sponsor is drawing our attention to what they want us to selectively look at doesn't make the point because comparing these two agents, one is reduced to 40 percent, the level, and the other one 15 percent, the level, and even that's not quantitatively the same.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: Actually Dr. Schwartz mentioned the issue that I was going to address, but I've got a couple here, and let me still address it from my own perspective.

But let me begin by saying I am concerned that there could be a problem with dosing here, and so I think that's an open question, but as far as the data on endothelial inclusions addressing that point, I think it's difficult to compare because, as I noted yesterday, zero is not zero in the study that we considered yesterday. Zero excludes the most severely affected endothelial cells before you even start looking, and then it allows for a few inclusions elsewhere.

So zero is really somewhere in the lowest segment of observable changes. The data here were on a scale of up to three plus, and the reduction, as I recall, went from something around two plus as sort of moderately severe to less than one plus, and so if you had concluded that you're going to report anything less than one plus as zero, then it would have been a better strategy for the company today to use that designation of zero for a small amount, and then it would have been comparable to yesterday.

The point I'm making is I'm not sure we can conclude that what was reported yesterday as zero inclusions is, in fact, more or less inclusions than what's being reported today as .8 plus inclusions, just with respect to that point.

Now, with respect to a surrogate, you know, I mean my understanding is we're just asked, you know, what's going to be reasonably likely to predict a beneficial outcome at some point. I absolutely agree today there is no correlation between any of this pathology with compelling evidence for a substantial change in clinical outcome in the observed data.

But if there were, we wouldn't need a surrogate from the histology. If the creatinine clearance already correlated with exposure to the replacement therapy, we wouldn't need a histologic surrogate. It would be a moot issue.

But none of the clinical parameters in the window of observation so far show an effect, and so I understand this question to be, well, since we don't have any good clinical parameter for positive benefit, is there a histologic surrogate that might reasonably predict that if we keep looking at the outcomes in these patients, at some point there will be a beneficial effect that will be observed?

And my conclusion today is the same as my conclusion yesterday. That is, looking at the pathologic changes that were observed, which one is the most robust in showing that something has happened since treatment that may be a beneficial effect and that may predict ultimately a good outcome?

And, again, it looks like the endothelial inclusions.

Now, I like the comment about the normal glomeruli. It's, in fact, a concept that seems pretty intuitively sound, but it's remarkable that pathologists, as bright as they are, have never really used that as an important parameter until recently.

And actually now in the literature, especially with respect to aggressive glomerular nephritis, instead of looking at the percentage of glomeruli with severe injury, what's being looked at are the percentage of glomeruli that have no apparently injury, and that's correlating better with outcome than the previous approach over hundreds of years of looking at the percentage of injury of glomeruli.

So you know, that's another attractive possibility for consideration. So I do agree with that point.

Now, one other thing with respect to the dosing, and my concern about that which was raised, in part, by the plasma levels which do appear not to have been depressed as adequately as with the other agent we've considered, but as far as the endomyocardial biopsies, endomyocardial biopsies of necessity are pretty difficult to obtain. You know, you've got a little device in the chamber of the heart, and you're biting away at the wall of the heart, and you're mainly at the endocardial surface, and it's hard to know where you are and how deep you're getting.

And my concern, and maybe someone in the company can address this concern, is whether or not those endomyocardial biopsy orders were really obtaining tissue that adequately represented the content of the substrate in the myocardial cells, and I'm worried there might have just been quite a bit of endocardium and not much myocardium.

So was there any assessment of the amount of myocardium in those endomyocardial biopsies?

DR. SCHUETZ: There was. Light microscopy was done in all of those endomyocardial biopsy samples, and the principal component of those was myocardium. Actually in the briefing booklet, I think it's Figure 5 is an example of a biopsy specimen from one of the patients in that study.

DR. JENNETTE: Now, what was the method for separating out the tissue for quantitative analysis versus histology?

DR. SCHUETZ: The cardiologist attempted

to obtain up to four or five endomyocardial biopsy specimens. That was not always possible because of the difficulties that you raise.

Because GB3 storage was the primary endpoint, those were taken first. So the first two samples were taken for GB3 content analysis, and the remaining two were taken for histopathological analysis.

DR. JENNETTE: And you're confident that's the method. The reason I ask is that there's sometimes a tendency amongst clinicians and surgeons if they have a bunch of samples and some are going to be sent for histology where they know somebody is going to be cutting sections and looking at it, and others are going to be ground up for a genetic or proteomic or some other purpose. They'll take the crumbs and put them in for the grind and find procedure, and they'll take the big, nice chunks and put them in for histology.

So if the method you describe is, in fact, what was operational, you're okay. If it wasn't, that might have biased your study.

DR. SCHUETZ: That was the method.

DR. JENNETTE: Okay.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: First, I want to point out that number C under two is if you do not feel the histologic data are present are reasonably likely to predict clinical benefit, do you recommend further evaluations and so forth. This is put in to suggest the possibility that data might be acquired in the future that would show convincing effect of the intervention for an appropriate surrogate.

I don't in any fashion exclude this possibility. There is always the possibility that looking at the data and looking at the samples in a different way one could come up with a perfectly appropriate surrogate.

But today we are asked whether today we can come up with a surrogate. The surrogate that we have to come up with has to meet, as far as I can see, two major and one correlate requirement. First of all there has to be some -- what do they say? -- reasonable confidence or something to that effect that it would relate to clinical outcomes.

The second is that there is a clear effect of the treatment on it.

And the third correlated outcome is that there is a plan in place that we can evaluate by which the long term relationship of the treatment to outcome could be ascertained.

So let me start out by saying I am in no way implying that it would be impossible by reexamination of the material to come up with an appropriate surrogate, but that's not my problem today. I have to look at the question of whether we can today come up with a surrogate.

Now, with respect to requirement number one that there be a persuasive or convincing or acceptable or whatever the phrase was --

DR. FLEMING: Reasonably likely to predict.

DR. HUNSICKER: Reasonably likely.

Dr. Fleming and I differed only in all of yesterday's discussion probably on what was acceptable as reasonably likely, and I am more likely to accept something as reasonably likely than he is because I've already told you that if you can up with a shred of a rationale in a situation for which there is no other approach, I'll probably buy that as reasonably likely.

So the issue here is not the persuasiveness of the relationship. I cannot in consistency require that you document that there is a clear relationship because I didn't require that yesterday, and therefore, I cannot in consistency do that. I just have to say there has to be a reasonable path.

And I can see a reasonable path from any number of possible surrogates that have been suggested. Certainly the serum creatinine; very likely the renal histology; perhaps even less persuasively, but nonetheless acceptably because that's what I did yesterday, accept endothelial deposits.

The question we then have to get at is whether any of these things have today been established with sufficient rigor that I can say there is a clear impact of the treatment on it.

Well, let's look at these three. Serum creatinine I have dealt with already or creatinine clearance, and I don't believe that it's there. I don't think that the data are reliable.

With respect to what you suggested, Dr. Woolf, which was the total normal glomeruli, this has some attractiveness. But let me tell you exactly where my problem is. What you see there is a correlation between total normal glomeruli and outcomes in a cross-sectional issue here. All right?

So what that is likely to be driven by is the total number of sclerotic and -- what's the word? -- focal sclerosis and globally sclerotic glomeruli. So in a way the real issue that we have here if we're trying to look at something that can be affected by treatment is what you get when you have excluded those things, and there you'll see that the number of normal glomeruli, if you exclude the sclerotic ones and the totally sclerotic ones, which didn't change or changed in the wrong direction; if you look at what's left, you have those glomeruli with mesangial thickening, and those glomeruli that were totally normal.

There the evidence in my call was marginal that there was an effect because it was a marginally significant effect in about a fourth level ancillary examination.

Further, there is no direct relationship between the fraction of mesangially thickened glomeruli and clearance. Now, I don't hold that against it. I just told you that the lack of a relationship doesn't militate against something, but it surely doesn't help any.

So I don't see that we have clear evidence that the treatment has affected in a robust fashion the fraction of glomeruli that have thickened glomeruli or its complement, which is the number of normal glomeruli.

So then let's look at the issue of the endothelial deposits. This is reasonably convincing. It's reasonably convincing because it is confirmatory of what we've seen yesterday, but now we have a finding which has not even been emphasized amongst the 30 or so different P values we've been given to consider in this situation. It hasn't even been emphasized up until this moment by the sponsor, nor is it with the same degree of rigor that we saw yesterday.

So I would accept the possibility that the sponsors could go back and look at a way similar to what was done by yesterday's group, and they could come up with data that were just as persuasive of a dramatic impact of treatment on that outcome, but we don't have it in front of us today. So I cannot act on what might happen tomorrow.

There was another thing that flashed through my mind, but you've gotten the thread of what I'm saying, is I just don't see it today.

Oh, yeah, the other thread was it is disconcerting if we are going to use endothelial deposits as the surrogate if we assume that based on what our sponsor has told us that he would like us to pay attention to page 90. It's at the least disconcerting that they've spent the first six or eight or ten pages of their application discounting the relationship of this to the long term outcome. It does make it seem awfully ad hoc.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: I think it's tough to find a surrogate. I strongly believe that the problems of this disease relate to the accumulation of GL3 or GB3 in certain cells, but I don't know which cells they are, and I don't know how much accumulation is necessary to cause damage, and I don't know whether or not clearing of the substance from the cells will reverse or stop the damage, and if so, I don't know how much clearing is necessary to reverse or stop the damage.

So if we look at a surrogate that looks at the storage of the disease, I don't know what the means. If it's totally clear, that would be great in terms of accomplishing something measurable, but whether that has a clinically meaningful endpoint I don't know.

And then looking at the pathological process, glomerular sclerosis or something else is further down the line. If something starts that damage, maybe at that point that progression is irreversible no matter how much clearing you get.

So I haven't heard anything in the assessment of GB3 or in the assessment of classical renal histology that would convince me there is a surrogate.

CHAIRMAN AOKI: Dr. Schneider. You're done.

Dr. Follman. He looks like he's done, too.

Dr. Barisoni.

DR. BARISONI: I'm a little bit concerned about the same picture that showed there is an increase in focal segmental sclerosis in patients with it, and it could be just a sampling error or it could be real.

And I was wondering whether reviewing the data we can answer that question, and in particular, I would look at the podocyte damage and see whether there is an increased podocyte damage and increased proteinuria at the same time and, therefore, an increased amount of segmental sclerosis.

And that is because there is a little

possibility that the drug might be toxic to the podocytes, for instance. That we did not exclude, but that could be one of the reasons if that is real.

And that's why I would be more for reviewing the data and correlate proteinuria, segmental sclerosis, maybe reclassify in a different way these biopsies, serum creatinine, et cetera.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: Could I ask the sponsor? I mean, I think you might be able to respond to one of Dr. Hunsicker's questions.

That is, do you know what the correlation is between change and percent normal glomeruli and change in creatinine clearance?

DR. SCHUETZ: Yes. The slide I showed earlier this morning in the question session plotted the change of both the fraction of glomeruli that were normal and the fraction of glomeruli with mesangial widening.

DR. GRADY: Well, I'm asking it a little bit differently. It was about a 24 percent difference between the two groups, the change, the percent with normal glomeruli.

DR. SCHUETZ: Is this not the correlation you're --

DR. GRADY: What is actually the correlation coefficient and the P value? That's all we want to know.

DR. SCHUETZ: For the change of creatinine clearance with the fraction of glomeruli that are in normal, the correlation coefficient is .24, and for the change of creatinine clearance with the fractional glomeruli with mesangial widening, the correlation coefficient is .54.

DR. GRADY: Yeah, they look like pretty wide confidence intervals.

DR. SCHUETZ: Yes.

DR. GRADY: Do you have a P value for that?

DR. SCHUETZ: The P value for the mesangial widening is .06, and the P value for the fraction of normal is .4.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: This question, I think, simply asks: given the totality of the data that we have now, is there some way that this application can be converted to an accelerated application if a surrogate were likely to be agreed upon and providing you with a subsequent verification study?

Is my interpretation correct?

DR. WALTON: Yes. It would be perfectly within our ability to consider that form of an approval, and obviously that's why we're asking the questions about the potential of a surrogate of data that they have to be viewed as a surrogate reasonably likely to predict benefit.

DR. WOOLF: My problem is not the shortage of potential surrogates. We've heard about all of them, but potential shortage of patients. There are relatively few biopsies, and I assume that there's very great difficulty going to get additional patients into a study that's relatively comparable to get a suitable n.

DR. WALTON: I think that what we're asking really today is, first, whether the data that you have in hand, given the biopsies that we have today and the way in which they're read and the data that we have from those biopsies, allow you to conclude that some particular piece of information you have before you today gives you that confidence.

Secondly, whether if not quite that, but you think that there is something in there in which the methodologic difficulties in reading the slides that they have now may have been impairing your interpretation, but could be overcome by a more structures re-reading, will we ask for advice about that?

Now, I suppose that, given the advice about the kinds of surrogates the company could consider going out and getting additional biopsies to serve as the surrogate, but if your question was about a future study to prove the correlation of the biopsy surrogate with the clinical benefit, I think that's not what we're asking about.

Bear in mind that as we had said yesterday that under accelerated approval, the verification study need only demonstrate that the clinical benefit does occur.  It does not need to assess whether or not there is -- it does not need to provide the direct data to validate the surrogate.

DR. WOOLF: You clarified my point. I think my bias is that there's information here that's tantalizing. I can't clarify it as more than tantalizing. I would prefer to have the histologic data relooked at by a totally different group of pathologists who were totally blinded, reread, and then the data reanalyzed.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: If I can continue to read Paragraph 601.41, after describing the surrogate it says, "Approval under this section would be subject to the requirement that the applicant study the biological product further to verify and describe its clinical benefit and where there is uncertainty as to the relationship of the surrogate endpoint to clinical benefit or the observed clinical benefits to ultimate outcome. Post marketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well controlled. The applicant should carry out such studies with due diligence."

I'd like to ask the company if we were to pursue the issue of a renally related surrogate, which is what we have been discussing primarily, what confirmatory clinical trial would be proposed? Are such trials underway? And can you clarify 010, which I understand is not only underway, but concluded with negative results?

DR. SCHUETZ: I have two comments. As we read the regulation, I think these studies need to ordinarily be underway. We have several studies underway right now that I think could potentially be converted into studies of that quality.

In terms of the 010 study specifically, the placebo controlled portion of that study was of six months duration only. At the end of that six month period the patients crossed over to open label therapy in a very similar design to the three, six series at the NIH.

In terms of everything that we've heard and learned over the past two days, of course, you know, we anticipate future discussions with FDA on this topic.

DR. WALTON: Dr. Aoki.

CHAIRMAN AOKI: Yes, Dr. Walton.

DR. WALTON: I would like to clarify that in the questions we're asking, we are asking questions about the surrogate and your view of that. We have not asked questions about a verification study. Those are really two separate issues about whether data that you have is an adequate surrogate in your view, given the regulatory structure, and an entirely separate issue is a plan for verification of the clinical benefit, and I think we feel the advice we most need from you today is on the surrogate.

The question of whether or not there is a verification study underway or a study that they have underway might be a suitable verification study is not what we really are looking to bring forward to you. It today may differ in that regard from yesterday, but the two applications are different.

CHAIRMAN AOKI: Fair enough.

DR. WALTON: And obviously it is very much on the mind of the agency that accelerated approval, a key element of this whole sphere of accelerated approval is that we have the ability to learn the ultimate answer.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: I just wanted to be sure I understand what we're talking about when we're saying surrogate here. Let me say what I think we're talking about and make sure that I'm understanding this correctly.

In the context that we've been discussing it, my understanding is that the surrogate we're looking for we're looking for because there is no clinical parameter that has been shown to correlate with treatment. So in the absence of a clinical parameter, by definition the absence of a clinical parameter in the time interval of the studies we've looked at has anything else happened and been observed that can be used instead of a believable clinical outcome that might predict that later on if we keep looking for believable clinical outcomes, one will happen?

And again, once we've concluded that

there's a surrogate now that gives us that level of confidence, we can leave it alone forever. It's no longer relevant. It's not like we concluded the surrogate is all we have to monitor, and if we can enhance our confidence that that particular event keeps taking place and even to a greater extent with longer follow-up, that that's all we need to do, that's not -- again, my understanding is that the surrogate is just for now.

For us to conclude that this is an observation that can replace having already observed a clinical outcome that's advantageous just to make a decision to go on with looking at this drug in the future, is that the right understanding about the surrogate?

DR. WALTON: Essentially, yes, with the understanding that that -- viewing it that way, the permission to by and continue looking at the product involves the idea that at some point the product is actually available.

DR. JENNETTE: Right, but that may have nothing to do with looking at that surrogate ever again.

DR. WALTON: Yes, right, right. That's exactly right.

DR. JENNETTE: And you might even say it would be preferable not to use that in the future because it is a surrogate and not a true marker of clinical outcome.

DR. WALTON: I would say that I think scientifically most people would find it very, very interesting to continue looking at the surrogate as the evidence on clinical benefit is obtained, and that might provide information about the correlation, the quantitative correlation of the surrogate with the benefit.

But that is not, as you very correctly are pointing out, that is not the requirement, and if that surrogate were never looked at again, that would be compatible with the regulations.

CHAIRMAN AOKI: Dr. Weiss.

DR. WEISS: Can I just follow-up, too, that -- maybe this doesn't really need to be said again, but the whole purpose in these regulations is to get out into desperately ill patients a product for which there is no alternative or for which this represents a potential advance. So to get out there somewhat sooner than would otherwise be available on the basis of a reasonably likely surrogate.

True that there are the same concerns though that you may be raising about the ability to validate that surrogate or the need for doing that. In settings where, again, the surrogate is looked at within the same trial as the ultimate outcome, you probably can do that. In settings like we've been discussing, it's less probable or possible because you're oftentimes looking at different populations and you may not, as we look at that same surrogate, again, in these validation studies.

DR. JENNETTE: Just my last comment on this. It would seem to me the only validation of a surrogate is the outcome of observations after you've made a decision based on that surrogate. If there were already clinical evidence you could correlate with the surrogate before the fact, you don't need the surrogate.

DR. FLEMING: Can I comment on this? Just maybe just to add to this specific point, there has been a long history of exploration and implementation of surrogates, and as you point out, in a sense the richest evidence that we would have supporting a surrogate would be specifically treatment induced effects on a biological marker or accurately predicting treatment induced effects on a clinical endpoint.

That's ultimately what we would love to be able to have. If we had it, it would substantially shorten the size and duration of clinical trials.

The challenge is that it's extraordinarily difficult to establish that, and ultimately to establish that one needs far more than the data directly showing what the effect is on the clinical endpoint. Even statistically you need at least four times the data of what it would take to show conclusively effect on the clinical endpoint just to be able to address the statistical issues surrounding full validation of a surrogate.

And even that's not the whole story. The biggest challenge in validating a surrogate is the clinical challenge of being able to establish that the disease process effects on the clinical endpoints are substantially, if not fully, mediated through that specific biological marker, and the treatment effects on the clinical endpoint are substantially captured by that marker and not also substantively mediated through other unintended, unrecognized, and unrecorded pathways.

That's what it takes to have a validated surrogate. Fortunately we're not required to have a validated surrogate for an accelerated approval, but historically what have we typically had?

Typically what we've had is substantial evidence from other trials looking at both the effect on the marker and the effect on the clinical endpoint so that these kinds of correlations, if not enough to validate the surrogate, at least would be present.

Short of that, it would have as natural history data; we go back to one of these normal glomeruli and creatinine clearance. Is there a correlation?

Well, I don't want to know if there's a correlation between the six month change and the six month change. I can get that from my clinical trial. I already know what the effect is on creatinine clearance on the clinical trial.

What I want to know is does a six month effect on normal glomeruli predict a long term effect on creatinine clearance. That's enriched information. That's what I need to know. That's what we don't have also.

I won't repeat all of what we said yesterday about surrogates, but what we said yesterday was the regulations lay out before us a number of sources of insights to potentially get a surrogate, not a validated one, but one reasonably likely to establish clinical benefit, and it allowed us epidemiologic and clinical data, the kind of data that I've just discussed, and we don't have it. But we do have another mechanism. We do have another opportunity, and that's the biological evidence or at least how strong is the biological hypothesis. Specifically how strong is that hypothesis that we can formulate?

And it might be that we're formulating the accumulation of GB3 in various cells. The question is: how strong can we make the argument that it's not enzyme deficiency and the need for enzyme deficiency replacement that I see at issue here. It's when you have enzyme replacement. What specific effects is that going to have and, in particular, when you have the deficiency, what are all of the mechanisms by which the ultimate clinical consequences occur?

And we may have a good idea, but it's not clear that just having a god idea is adequate because you run into this issue of which cells, how much of an effect over how long a period of time, and inevitably those all have to be important because ultimately what you're going to say here is I'm sufficiently confident that when you show this level of effect in this cell type for this period of time, it's reasonably likely you're going to capture enough of the essence of this biological pathway through which this enzyme deficiency influences the clinical endpoints that this treatment eventually can be shown to affect the clinical endpoints.

So I would go one step further than Dr. Hunsicker and say I have serious uncertainties about the first of his three important principles. The second of his three important principles I also agree with him, and that is we haven't shown convincing evidence of benefit on any of those.

And as a free piece of advice because the FDA said they didn't need it, on this issue of how you're going to validate I can't imagine how we can't put that into the picture because it's a necessary part of an accelerated approval, and if we're not talking about accelerated approval here, I'm not sure why this question is before us.

And I would have serious questions because there isn't a randomized trial on the boards that's giving us several years of follow-up, nor even is there the kind of effort that we've heard about in the recent past about historical databases that are being assembled.

So I'm also as a free piece of advice concerned about that third issue as well.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: I see the issue on surrogates a little bit differently, but I still have the same answer, and that is I don't see one. The field that I deal most with every day is osteoporosis, and we know in people who aren't on treatment for osteoporosis that the higher the bone density the less likely they are to fracture.

We know that the drugs that we use to treat osteoporosis increase bone density. So early on in developing drugs for osteoporosis it was possible to get approval for a drug that increased bone density, a surrogate, as long as there was a trial underway that was adequately powered to show a fracture reduction.

Well, it turns out that the relationship between bone density with treatment and fracture reduction with treatment explains well less than half of the fracture reduction. It's not a very good surrogate, but it's a biologically -- it's an indicator that the primary endpoint is likely to be achieved.

DR. FLEMING: You've got Riggs' data.

DR. WATTS: The problem I see with all of this is will bone density and bone is histologically normal, but the problem I see with all of this is there are too many potential surrogates to be able to focus on one that would lead you to believe that a change in A will have clinical impact in B.

DR. FLEMING: I'd just like to clarify that I consider that -- I totally agree with you, and if I didn't articulate it clearly, that is a significant part of what I was trying to say, and that is this disease process through enzyme deficiency could readily be influencing clinical endpoints through a range of different biological pathways, and in a sense, that gives us a range of potential markers no one of which, however, is adequately inclusive in being able to capture enough of the effect to be able to say that establishing the effect on that one is going to establish the outcome.

And, of course, the Riggs study is a great example if we're going to talk about bone mineral density for how effects on bone marrow density don't predict fracture.

CHAIRMAN AOKI: Dr. Levitsky?

DR. LEVITSKY: Could I have a restatement from one of the pathologists in the room about what they think it would take to take the data that are potentially available, to reread them and come up with an adequate sort of consolidated potential biologic marker of effect so that we could say that we had what we've been asked to find?

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: So there are plastic sections available toluidine blue stained on all of these biopsies. Plastic sections, toluidine blue stained were the basis for the observations reported yesterday. The method was described, I think, quite completely and precisely, and so if we concluded that the method yesterday was adequately, then we could propose that that method be applied to this material and the same observations made.

I don't know if it's something you could do or not. You could conceivably even acquire the same group of pathologists who did that study to do this study. There may be some reason not to do that.

So if one thought it needed to be done, you could do that. As I stated earlier, I personally am not concerned that the observation has already been made and is believable. I mean, I think the data here show that these pathologists using a different method came to the exact same conclusion as the other study, which was that the most sensitive marker for a drug effect in the kidney was a diminution in the inclusions in the vascular endothelium.

I think that's a pretty objective statement that is defended by the data on both sides. Now, whether or not that's a surrogate that should give us confidence in moving forward from here irrespective of whether it's ever validated to really be a marker for clinical follow-up or whether it's, in fact, a surrogate that could even be used for clinical follow-up, which I doubt it eve would be, in different issues altogether.

So I personally don't think we need another assessment if we're going to conclude that a diminution in endothelial inclusions is an adequate surrogate to move forward with further testing of this drug.

Now, that's my opinion. Now, I think Laura ought to offer her position on that.

CHAIRMAN AOKI: Dr. Barisoni.

DR. BARISONI: I agree on the endothelial inclusion story, and I think this is an adequate surrogate.

Still, as I already said twice, I'm still wondering why some of these patients have significant proteinuria, and patients that we looked at yesterday did not basically. So there is a difference in these two groups of patients.

And these patients also develop focal segmental sclerosis which is increased after six months.

And so could it be that there is something else simultaneously or concomitant to this disease? And that is the only thing that I wonder about. For the NDTSS inclusion, I think they were coded as they were coded yesterday

DR. SCHUETZ: I'm sorry. I have one, I

think.

CHAIRMAN AOKI: I have one person ahead of you.

Dr. Schade.

DR. SCHADE: Yeah. I've listened to this entire discussion, and I'm not near as pessimistic, I think, as some people about using the inclusion in the kidney as a marker, as a surrogate marker, and I think Thomas is exactly right. You can have an enzyme defect, and there may be potentially many mechanisms besides the surrogate marker that may lead to clinical outcome.

I think we need to be careful about mixing this disease with more complex disease such as osteoporosis in which you have architectural problems, you have bone density problems and so forth.

I asked the question yesterday to the group about a mechanism of how these deposits actually cause damage, and even Dr. Brenner or nobody else gave me any other explanation except some type of mass effect, which I still don't understand, but I accept.

In other words, I think if we're going to say that there are other mechanisms by which these deposits cause disease, we ought to have some reasonable hypotheses. I just haven't heard any.

Therefore, I'm much more acceptable to the surrogate marker as potentially useful. In other words, I don't read the FDA regulations as we having to have absolute proof. Just a reasonable belief that it would be a good surrogate marker.

So I am not, I guess, as pessimistic that this marker won't be a good marker because it makes pathological sense to me.

CHAIRMAN AOKI: Dr. Schuetz.

DR. SCHUETZ: Thank you.

Just one very quick point about the proteinuria differences between the two patient populations. I think it's important to point out that the patients that we've shown you today are about four and a half years older on average than the patients that were described in that study yesterday. So I think that's probably the most likely explanation that they're a more advanced patient population.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: Yes, I think we ought to wrap this up, at least this question, but let me just summarize by saying I think we all know that we need a whole lot more data to really prove that we have a good surrogate. We aren't close to that, and I think yesterday we weren't close to it either.

I mean, I think all we're really looking for here is a marker of some real biologic effect of the treatment, and we're willing to be looser than our usual criterion because this is a patient population that's very ill, and this would be an orphan drug. And that, I think, was part of our principle yesterday and probably should be part of our principle again today.

What distresses me and, I think, others is that the effect of the surrogate we're considering, that is, deposition of the substrate in some cell type -- we could argue about which one -- wasn't as clear, and it may not have been so clear because of the way they chose to measure it, but it's hard to say. The way the data were presented it wasn't as clear.

And secondly, it was the problem of

multiple outcomes. It was clear that yesterday that thing that we chose to accept as a surrogate was the primary outcome, and there was efficacy for that primary outcome.

Today we have the added complication of lots of outcomes, some of which showed effect and some of which not. I mean to me that's the real problem.

DR. FLEMING: Could I ask Dr. Grady or Dr. Schade to expand on that? Because essentially if we accept vascular endothelium, that just gets you to level one on Dr. Hunsicker's list, and I think Dr. Grady is pointing out there is a level two, which is if you say, "Okay. I'll accept this. this is adequately central to the mechanism by which these clinical events are occurring," you're seeing a reduction that's 50, 60 percent documented over the six months of the trial, and can you give me a biological rationale for how much and for how long you would have to see this effect to justify confidence that it would translate into clinical outcomes?

DR. SCHADE: Well, I actually think that is the purpose of post marketing studies. You asked a question at the very end yesterday about how long it would take to provide information of whether the drugs worked.

DR. FLEMING: No, that was on the clinical endpoint I was asking.

DR. SCHADE: Right.

DR. FLEMING: I was asking for a surrogate.

DR. SCHADE: And my answer to that is the same answer as this. I think it will take about five years to know whether we see people still going on dialysis, whether we see people basically dying from this disease. I think all of that will become clear within five years if these drugs really work, and if people are still going on dialysis at a significant rate -- and I'm not arguing about the data that's derived from patients that have just been followed in a registry. I think we will know whether these drugs are really dramatic or not.

In other words, it's going to take time, but I really think that we will know, and so I think five years is a reasonable time. So the answer to that, I think, is yes. We can design studies that are reasonable, and we will know.

I think this is a very devastating disease that takes a long time to manifest itself and with very dire consequences, and I think the discussion was absolutely right yesterday that we shouldn't expect any clinical benefit within a period of the time that the studies were done, and I would be very surprised whether we saw a reduction of creatinine clearance or an improvement of creatinine clearance within six months or a year because I think this disease is a 35 year disease.

And so I'm not looking for any improvement in clinical outcomes before five years, and that's why I'm using a five year time frame, but we will know in five years post marketing whether these drugs have a dramatic effect.

Whether they have a small effect or not, now you've got me, and I have to admit to you, Thomas, that I can't give you that information, but I think you'll see some very dramatic effects.

DR. FLEMING: Let me attempt again because you're answering an important question, but it's a different one than the one I asked, and I understand the answer to your second one, which is it may take five years to know the clinical effect.

Today we are at a position of determining whether or not it's appropriate to use a given marker and an effect on that marker in a regulatory manner to provide an accelerated approval. What that means is that what we need to know today is that an effect on a given marker of a given magnitude is sufficient evidence to make it reasonably likely that there will be clinical benefit.

So to justify a recommendation that this marker and this effect on this marker is adequate for an accelerated approval today, we need to know today your answer to why a 50 percent reduction in this marker documented over six months is biologically providing sufficient evidence to make it reasonably likely to conclude we will have benefit when there isn't the clinical data.

DR. SCHADE: Yeah. Well, I don't read the regulations, I guess, the same way because I didn't see the request in the regulations that we need to provide percentages of degrees of change of the surrogate marker.

DR. FLEMING: I just used what we saw in the data. The data showed a 60 percent reduction.

DR. SCHADE: Well --

DR. GRADY: But, you know, I feel like I'm stuck in this position of trying to make a silk purse out of a, you know, "whatcha'" call it.

(Laughter.)

DR. SCHADE: Sow's ear.

DR. GRADY: Because if you look the effects we saw yesterday, what I'm seeing is about a 24 percent difference between the treated and controlled groups in terms of substrate in the podocyte. Now, that's kind of what we saw yesterday, but in a different reporting system, and I'm also seeing a change from a score of 1.9 on a score of zero to three down to .3.

Point, three is very close to zero, I guess. I don't know. So I'm not sure we're not seeing the same sort of biological effects, but it's difficult to know that because of the way that the data were presented today.

But I think another difference we need to keep in mind is that yesterday the company came with a trial that was 18 months, a trial, and I'm a big believer in randomized comparisons, a trial that was 18 months, and we were all very enthusiastic about trying to maintain that randomization to the extent possible.

I think in this situation there's no ongoing trial. There's probably not a hope of a randomized comparison if we approve this drug based on some kind of surrogate we make up today, and that's also a difference that I think we need to consider.

CHAIRMAN AOKI: Dr. Levitsky.

DR. WALTON: Dr. Aoki, may I just comment?

The nature of a verification study that might be arranged is a separate question from whether or not a surrogate is in hand that is permissive to make the discussion about a verification study worthwhile.

CHAIRMAN AOKI: So you're saying that if

we can agree on a surrogate, the discussion of a verification study could then be pursued?

DR. WALTON: Well, I don't think that would be suitable for right now, but between the company and the FDA, that would provide that route being a meaningful route for discussion, a meaningful avenue of discussions between the agency and the company.

It's an endorsement of that if you believe that they today have some evidence. It doesn't mean that only the studies in hand today are the only things that will be done. It means that --

CHAIRMAN AOKI: Excellent point.

DR. WALTON: -- if the company wishes to pursue accelerated --

CHAIRMAN AOKI: I think we assumed that we were stuck with the studies that we had.

DR. WALTON: No, no, not at all, not at all.

CHAIRMAN AOKI: Okay.

DR. WALTON: It means that that would be a fruitful route of discussion for future discussions between the agency and the company.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: So I want to still be sure I'm understanding all of this correctly. So yesterday, if I can refer to that in the context of today's discussions, I still suspect, and it was clear from the discussions that others suspected, that in those studies there were some early preliminary studies, and the data from the pathology was looked at carefully, and I suspect surprisingly, but maybe not, the parameter that appeared to be changed most by exposure to drugs was endothelial microtubular inclusions.

So before the fact, before the fact, that was proposed as a surrogate, and the FDA agreed that that was a surrogate before the fact, which is the way that it should be done, I suspect, and so it was proposed that we don't think there's going to be a clinical outcome that we can monitor, but we're pretty confident there's going to be this surrogate outcome, and so before the fact that surrogate was established, they looked at it, and sure enough, with the prospective controlled trial, the surrogate goal was fulfilled and, therefore, the conclusion is, well, you can go forward with your study to try to find clinically relevant observations.

The surrogate was just to make a conclusion that an observation had been made that was biologically indicative of likelihood of ultimate clinical benefit.

Now, today it seems like we're in a different situation. We're sort of trying to decide post hoc that this is a surrogate, and in fact, they've already done the study, and they already have the data, and it already shows that this is a surrogate, that it does show that the patients exposed to their therapeutic agent did have this effect and, therefore, we can move forward.

You know, not looking at procedure, they've pretty much done the same thing that the others did except for the procedure. That is, they gave some patients in controlled setting the agent. They looked at the pathology after the fact and before the fact, and they found out that there was a statistical significance at a P of .003 reduction in endothelial inclusions.

The problem is they didn't follow protocol, which is very important. I'm not diminishing this. You know, they didn't establish before the fact that this was their primary endpoint, that this was going to be the surrogate for a clinical improvement.

But aside from procedure, it seems to me that that particular observation is the same in the two studies, that the replacement of the enzyme has resulted in this change in an observable histologic parameter that yesterday we concluded was an appropriate surrogate with one dissention, and today we're now considering again.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: My comments would be several.

First of all, I agree. We are not seeing these observations in a vacuum. We're seeing them on the basis of previous data that we've been presented. So that I think that it is very comfortable for me to accept this as a surrogate marker.

But I would also like to point out that this drug has certain other potentials which have not really been discussed at great length except by the company perhaps, and that is that this is a drug with human glycosylation patterns, and that means for the people out there who have low levels of enzymes so that they're not likely to be immunologically challenged as if this is a foreign agent, this may well be a better agent for them, and therefore, I think it is important that we keep that in mind as we discuss both of these drugs.

And lastly, I think because as far as I can tell I think I hear from the group around me that many people agree. The company has misjudged the dosage and has probably under dosed in their trial. They're actually perfectly set up for a very nice ethically acceptable study, dosage ranging study in which they can use this dose, which is probably a little bit to low, and a higher dose and follow two populations to an endpoint which will be clinically relevant. I see that would be very possible.

CHAIRMAN AOKI: Dr. Hunsicker.

DR. HUNSICKER: I think I'm going to be a little gentler now than I have been in most of what I've said before. First of all, it troubles me, as I've said before, that the company has submerged in what they presented to us initially the issue of clearance of the endothelium weight to the bottom of the list of 153 comparisons, and that they argued against the relevance of this particular outcome. It bothers me that that's the case, but I'm willing to wash all that away because the fact is we don't operate in a vacuum.

There is a presumption that if this was what was found yesterday for doing what I suspect is a very similar thing today, we're finding similar kinds of things; it's probably going to work.

There are a couple of issues. First of all, while I'm willing to wash away much of it, I'm really not quite willing to wash away all of the methodologic issues. I think that if, in fact, we're going to look to use of clearance of the endothelial stuff as a surrogate, we have to go through it the same way we did yesterday. That is to say it has to be done with the same rigor and the same care and all of that.

If those same data were brought back to the FDA and if I were asked, which I hope I'm not ever asked to come back again to this thing --

(Laughter.)

DR. HUNSICKER: -- I would say, okay, now they've made their point. Now they can get their conditional approval and go ahead if they have the studies and all of those other kinds of things.

The other reason besides just that it bothers me that there are some real methodological thorns to get through is the issue of quantitation. Poor Tom over there has been trying to make this point.

What we bought yesterday was an almost complete clearance of the endothelium together with removal of -- they didn't stress this, but certainly many of us in the comments did -- together with clearance from the glomerular endothelium, the glomerular mesangial cells, most of the medial cells, a good deal of reduction in the tubular epithelial cells, and some impact on the podocytes.

Had they only shown endothelial cell clearance, I suspect that we might have been much less enthusiastic yesterday. So there really is distance yet to be covered.

So I'm going to stay where I have been today. Today I cannot see that we have the basis for accelerated approval. Remember I'm not talking about whether we have the basis for hypothesizing as surrogate. I'm asking do we meet the requirements in the regulation for accelerated approval on the basis of documentation of a change in a surrogate.

I'm not there yet. I do not exclude that the company could well come back after a careful reexamination of those histological data, together with what other histological data they have, and make their point and win the point then. It's just not today.

CHAIRMAN AOKI: Let me just interject one thing. I think the question before us is have we identified a surrogate or more than one surrogate that

TKT could use.

Number two, the reason why we are not discussing accelerated approval is because there's not an ongoing clinical study that is in place right now that is going to give us perhaps the clinical endpoints that we wish to have.

So I think that part of the equation or that part of the story is out, but I think the question before us is, number one, do we have a surrogate or do we think there is a surrogate.

Number two, what would we recommend perhaps that TKT do to, if they wish for accelerated approval; what study should they be doing?

DR. HUNSICKER: Dr. Aoki, I believe that it is likely that the sponsor would like us at least to consider that there is the grounds for accelerated approval. I do not believe so, but I've heard some difference on this.

Now, maybe we need from the FDA instruction as to whether we should ask whether there are grounds for accelerated approval based on what is in the regulation.

CHAIRMAN AOKI: Fair enough.

DR. WALTON: I think I'm not sure what the question was because --

DR. HUNSICKER: I interpreted what we were discussing here in this as sort of a combination of two questions. Are there grounds for accelerated approval today based on the identification of the surrogate in which there has been clear evidence of the effect of the surrogate and rationale of relationship to outcome, and if not that, is there the -- this is Part C -- if not that, is there the potential for getting there through some additional examination of the histologic data?

DR. WALTON: Yes, yes.

DR. HUNSICKER: Those are really two separate questions.

DR. WALTON: Yes.

DR. HUNSICKER: I identified the first, and Dr. Aoki identified the second.

DR. WALTON: Yes.

DR. HUNSICKER: I guess I want instructions. Do you want us to make a recommendation to you about whether there are today grounds for accelerated approval based on the identification of an appropriate surrogate?

DR. WALTON: Yes. That's it exactly, and if you do feel that there are data in hand today for a surrogate, given the variety of discussion, it will be useful for us to hear which piece of data you view as convincing.

DR. FLEMING: But just on this point because it's --

DR. HUNSICKER: Do we need a formal motion then?

DR. FLEMING: It's the first point that you asked, and Marc has clarified that is the essence here, and that is is there evidence here based on a surrogate to justify an accelerated approval, and that is just to clarify from the two previous speakers.

There are three elements to that really that have to be addressed in one's mind as you answer that. First is is there a specific biologic marker, and what's being put forward is interstitial vascular endothelial GB3. That's what I'm hearing as what people would want to put on the table.

But there are two other aspects, and Dr. Hunsicker was getting at one of those, which is the issue of biological strength of evidence. What is the overall level of effect that you're seeing on that marker, and as he's pointing out, that is certainly not independent of what you're seeing on an array of related markers.

And I would simply reiterate they are not the same patterns that we saw yesterday, and even if you look at interstitial vascular endothelial GB3, 60 percent reduction is not the same as an 85 percent reduction. So you would have to address that.

But the third issue that I hadn't actually addressed is the statistical strength of evidence. We've got a single trial here. There's a P value of .003. That looks good, and I'm not saying, just as Dr. Hunsicker said earlier on, that when you look at multiplicity and you discount strength of evidence because of multiplicity it means the effect isn't real. It just means how convincing it's established is much less than .003 when it's a secondary endpoint, in fact, one of a wide array of secondary endpoints that you've considered.

And the strength of evidence just in contrast that you had from yesterday where that P is less than .001 is far less than .001 because you're looking at quantitatively a much bigger reduction based on two and a half times the sample size, based on a prespecified hypothesis. So it's totally apples and oranges in terms of the statistical strength.

The statistical strength of evidence statistically is very marginal for a secondary endpoint that's one of a wide array of secondary endpoints with a P of .003 from a single trial based on historically what we would have looked at statistically as adequate evidence.

CHAIRMAN AOKI: Dr. Jennette.

DR. JENNETTE: I clearly don't understand statistics. I keep saying very dumb things, I'm quite confident, but this seems to me to be the issue, again, of taking this study in isolation. I mean, to me a lot of other observations we've been exposed to enhances my willingness to accept the validity of this observation we're talking about.

I thought we concluded as a body yesterday that reduction in endothelial inclusions by administration of replacement enzyme was a surrogate for concluding that there was enough evidence that that therapy might be beneficial to move forward with additional studies to look for clinically defensible improvements in outcome.

So as far as I can tell, we've already decided that that observation is a surrogate yesterday. So building on that, building on that, not considering this in a void, but building on that, then I would say that you might pose the question: well, if we accepted that this is a surrogate for benefit or potential benefit, rather, of the agent, if we've accepted that, then the question is are there observations that show -- even if they weren't proposing this as a surrogate, we've already decided it's a surrogate -- that even if they didn't, are there observations in here whether they even pointed to them once that we can see and as a group conclude, well, we identify in here an observation that we feel is a surrogate in the absence of clinical parameters which aren't here? So we need a surrogate.

So is there an observation here that was made that we can conclude a surrogate for making a conclusion there's enough evidence to move forward with some additional studies?

I don't see how we can say yesterday, yes, it is a surrogate, and then today we see a statistically significant outcome fulfilling that and say it's not.

DR. FLEMING: Because you're talking about the first of the three and not the third of the three.

DR. JENNETTE: I'm talking about the totality of the conclusion it's a surrogate. We conclude it's a surrogate.

DR. FLEMING: In fact, yesterday didn't you mention specifically you thought that the plasma GL3 might be the best?

DR. JENNETTE: I still believe that, but the question is: was the question we adopted, was this one a surrogate that was adequate for moving forward?

And I still believe today it is. My personal opinion is that, yes, the plasma GB3 might be a better surrogate.

Now, then that begs the question: in this particular study, well, did they show enough evidence there? And that's where I'm concerned that there's a dose problem.

But that's a different issue. Right now we're talking about this as a surrogate, and I don't see how we can say one day it is a surrogate and the next day say it's not a surrogate.

CHAIRMAN AOKI: The question right now though, and it will be put up to vote and we'll all vote individually on this: are there specific elements of the histologic data reasonably likely to predict clinical benefit in the manner intended under the regulations for accelerated approval?

So it's either yes or no.

We'll take the final two, Dr. Watts and Dr. Grady, and then let's vote.

DR. WATTS: Well, I'm not sure what we all agreed to with this yesterday, but what I understood was that almost complete clearing of these compounds from the cells were reflected in negligible levels in the circulation, and having nothing else to go on, having negligible levels of GL3 in the circulation and almost complete clearing of this material from most of the cells that were looked at to me was a convincing surrogate, particularly with an ongoing placebo controlled trial nearing completion.

It may seem inconsistent with what you're saying today, but I don't think so, to say that I don't see the same -- I don't have the same level of confidence in these analyses, and I don't see anything -- if there is a dose problem here, I don't see any way to answer that question.

CHAIRMAN AOKI: Dr. Grady.

DR. GRADY: Well, I think in some ways it's a little unfair that we had yesterday before today. I mean, if we started with today, we might have a little bit of a different picture.

I think one of the things that disturbed me yesterday was that there was no evidence of any correlation of the surrogate with the clinical outcome, something like creatinine clearance.

The main outcome that the company presented us today was percent normal glomeruli for which there was a statistically significant finding. We still have these issues of multiplicity and so forth, but nevertheless, and that was correlated with creatinine clearance at least at baseline.

That's actually somewhat more evidence for a potential surrogate, I think, than what we saw yesterday, and the fact that we settled on this surrogate yesterday in the absence of anything else good to settle on, I think, is coloring our discussion today, and perhaps somewhat unfairly.

CHAIRMAN AOKI: Okay. Why don't we vote on the question? Are any specific elements of the histological data --

DR. WALTON: Dr. Aoki.

CHAIRMAN AOKI: Yes.

DR. WALTON: As you're going around taking the vote, given the discussion that's been heard, for those members who would feel that we do have evidence in hand today, could you ask them to specify which piece of evidence they find convincing because I'm not sure we will know.

CHAIRMAN AOKI: Okay. Want to put you guys on the spot.

Okay. Dr. Grady, would you like to be the first? I know you weren't looking at me.

DR. GRADY: Let me just preface my remarks by saying I think in most other diseases and patient settings I would say absolutely no. I think the data are weak, and nevertheless, I think there is a potential surrogate. I think there are two of them. I think one is the percent normal glomeruli, and the second is deposition of GB3 in renal endothelial cells.

And in order to say that, I also have to ignore the actual functional outcomes of creatinine clearance and GFR, and I'll just assume that we haven't had long enough treatment for that to be affected.

DR. WEISS: I just want to clarify as you go through these questions to make sure that this question is the data enhances, not only the chosen cell type, but the effect on that cell type. So just I assume that that's correct, but I wanted to make sure because --

DR. GRADY: Yeah, if these were surrogates, there were statistically significant effects on those surrogates. They might not have been as strong as we would have liked to see.

DR. SCHNEIDER: I'd say no.

CHAIRMAN AOKI: Doctor?

DR. HUNSICKER: No.

DR. SAMPSON: No.

DR. LEVITSKY: Yes, for Dr. Grady's reasons.

CHAIRMAN AOKI: That was yes, for Dr. Grady's --

DR. LEVITSKY: Yes, for Dr. Grady's reasons.

DR. WATTS: No.

DR. JENNETTE: Yes, for both that were mentioned.

CHAIRMAN AOKI: I agree with Dr. Grady.

MS. KNOWLES: I'm going to say no.

DR. WOOLF: I'll go along with Dr. Grady.

DR. FLEMING: I say no not only for the reasons that I said no yesterday, but for much stronger reasons that the level of evidence for magnitude of benefit and the statistical evidence are fully inadequate.

DR. SCHADE: I say yes for Dr. Grady's reasons.

DR. BARISONI: I say yes for Dr. Grady's reasons.

DR. FOLLMAN: I agree with Tom Fleming, and I say no.

DR. McCLUNG: No.

CHAIRMAN AOKI: Eight no, seven yes.

Okay. For those of you who need a five minute break, go to it.

(Whereupon, the foregoing matter went off the record at 3:53 p.m. and went back on the record at 4:01 p.m.)

CHAIRMAN AOKI: Okay. For those who voted no, let's answer Question 2(c). If you do not feel the histologic data at present are reasonably likely to predict clinical benefit, do you recommend that any further evaluations of the existing biopsy samples be performed, with the possibility that these additional evaluations might be a suitable basis for an accelerated approval?

If you say no, then you're done. But if you say yes, then please discuss the types of re-analyses that would be most useful for TKT to perform.

Why don't we start on the left? Dr. McClung voted no, too. Where is Dr. McClung? We'll get him when he comes back. Is he gone for good?

Dr. Follman.

DR. FOLLMAN: It's true I did vote no, that I didn't think there was any surrogate endpoint in the data that they had demonstrated so far. I can't think of any additional analyses or additional ways to looking at the slides that would be useful to come up with being a surrogate.

I think a strategy that they might employ -- so I can't offer advice in terms of that.

As I had mentioned earlier, the big problem that I have is I don't see how in a single study you can sort of identify and then validate a surrogate. It just doesn't seem to make sense to me.

So I would allow the possibility that further analyses could be done to maybe try and identify one that's potential. Maybe the one we talked about earlier. I don't have a problem with that. I just don't think it's validated here, and I think we have to look at another study, maybe longer, to try and do that. Maybe we can't do that. Maybe you can do it with TKT-010.

So the short answer is no.

CHAIRMAN AOKI: Okay. Dr. Fleming.

DR. FLEMING: I think I essentially fully agree with Dean. The substantial shortfalls here for having an adequate basis to use a surrogate here for an accelerated approval are so great that I can't expect that that would reverse with additional explorations.

Having said that, I'm always for additional explorations. Clinical trials serve two purposes: very importantly, a confirmatory role, and very importantly, an exploratory role where those hypotheses that are the primary prespecified hypotheses are those that are most reliably addressed by the data.

We surely, however, want to learn as much as we can. It's extremely important though when one is doing so to realize that exploratory analyses very often can be misleading and that they essentially serve usually as a basis for hypothesis generation.

So I would say absolutely continue to explore these data in any way that our clinical experts would view would be relevant additional insights.

However, I would be astounded should that type of exploration lead to something so substantive that it would then serve as a basis for an accelerated approval.

CHAIRMAN AOKI: Ms. Knowles.

MS. KNOWLES: The thing that has struck me in reading all the briefing materials, the discussion today is the consistent difficulties with the methodologies and the inconsistencies in the interpretation of the data.

I think they're a very, very large concern. I think the product possibly has some value. I just would really encourage the company to go really back to the drawing board and really review what the briefing document from the FDA says, the comments today, and kind of come up with a new plan.

You know, let's hope that it works

CHAIRMAN AOKI: Who said no? If you voted no, the question is do you -- if you do not feel the histologic data at present are reasonably likely to predict clinical benefit, do you recommend that any further evaluations of the existing biopsy samples be performed with the possibility that these additional evaluations might be a suitable basis for an accelerated approval?

DR. WATTS: Sure.

CHAIRMAN AOKI: What would you --

(Laughter.)

CHAIRMAN AOKI: If yes, "gotcha," if the answer is yes, then please discuss the types of re-analyses that would be most useful for TKT to perform?

DR. WATTS: I agree with what was just

said.

(Laughter.)

CHAIRMAN AOKI: She didn't make the recommendation.

DR. WATTS: -- go back and look at things in light of the --

CHAIRMAN AOKI: Let's see who else? It was Dr. Sampson.

DR. SAMPSON: I'm certainly sympathetic to the desire to look again at this data in some new, innovative fashion. If one were to do that, I would certainly encourage you to do it prospectively with a well defined protocol.

All that being said, I still, I guess, have concerns with dose in this study and the choice of dose, and also I share with my other two statistical colleagues the fact that this data has been worked many, many times, and one would like a new study to support any reworking of the data from this study if that were to be done.

CHAIRMAN AOKI: Dr. Hunsicker?

DR. HUNSICKER: Well, I think I'm going to be a little bit more gentle. I don't disagree with my other colleagues who have demurred in saying clearly it would be better to have a new study, but I'm not sure that's actually feasible. I think that were the sponsor to go back and do a set of analyses parallel, not necessarily identical, but parallel to what was done by the folks yesterday, demonstrating not only virtually complete removal of the substance of the deposits from the endothelium, but also from the bulk of other cells examined.

And if they were to couple that with evidences of clearance from the blood stream, and so forth, which we know actually didn't occur, I might well be -- I think that on consistency I'd have to say they met the same criteria as did the Genzyme folks.

Now, there is no better evidence for a correlation of the thing in Genzyme than it is here. So I would say, yes, I would then have very seriously to reconsider it. If it's sauce for the goose, it's sauce for the gander.

However, I would also emphasize that my concern is that the smaller degree of reduction of blood galacticide (phonetic) and the apparently slighter degree of removal from the endothelium, although that's very hard to judge when you're looking at qualitative ratings, one, two, and three, may, in fact, indicate that the level of drug being administered is too small.

This actually also refers to one of the further questions, which is the impact of antibodies and so forth, and I would therefore be very concerned were I to be back reexamining that. I would want to see a similar degree of clearance as evidence that we're really looking at the same thing.

CHAIRMAN AOKI: Dr. Schneider.

DR. SCHNEIDER: It seems to me that would make sense to first be sure you're using the right dose before doing anything else. Otherwise it could just be a big waste of time.

CHAIRMAN AOKI: Do you have any recommendations in terms of what type of reanalysis of the biopsy specimens TKT already has on these patients? Would you do any other studies?

DR. SCHNEIDER: You mean the specimens

they already have?

CHAIRMAN AOKI: They already have, yes.

DR. SCHNEIDER: I think it would be reasonable to look at inclusions in a way very similar to the group that presented yesterday.

CHAIRMAN AOKI: So we're basically recommending at least, if I -- Dr. Levitsky, I think, is correct and Dr. -- is to have either if the samples are available for restraining so that an examination of the slides similar to what Genzyme did or using, in fact, the same type of grading system could we used. Then perhaps you could harvest information that you already have that would be helpful to your application.

DR. HUNSICKER: Dr. Aoki, could I make one additional comment? Because particularly of the methodologic problems, I would strongly recommend FDA review with the company precisely how they're going to go about doing this so that there is agreement in advance that the methods are all acceptable and so forth, so that we don't get into more methodologic issues.

DR. WALTON: That was entirely our expectation as well, that if we were going to proceed with a reread, we would want to have worked out all of the details in advance, and that's particularly why we wanted to hear the advice about the kinds of endpoints or the ways in which to do a reread that we are hearing.

CHAIRMAN AOKI: Okay. Let's move on to the final question.

DR. LEVITSKY: Could I ask one? Over here.

CHAIRMAN AOKI: Yes, Dr. Levitsky.

DR. LEVITSKY: I'm actually asking this question because one of the folks from the FDA said I should ask it out loud, and I think it probably is a good idea, if that's okay, which is to redefine how the Orphan Drug Act affects drugs which may be the same or better compared with another drug which has received orphan drug status.

And I wonder if you could just elaborate on that a bit.

DR. WALTON: The question you had asked me was about sort of what happens when there is orphan -- two products that are viewed as the same drug under orphan drug regulation, and one comes to market and is given its period of exclusivity. The regulations provide that when a product has orphan drug exclusivity, once it comes to market a product that is viewed as the same drug under the orphan drug terminology -- and that's a very specialized set of terminology -- cannot also be marketed for that use for seven years.

However, the regulations also recognize that there is the possibility of developing better drugs that might be quite similar and fall within the category of presumptive same drug based on simple chemistry structure. Therefore, the regulations provide for ways in which a second company with the second drug can establish that their drug is, in fact, not really the same drug.

In other words, they have to show that it is clinically superior, and this can be on the basis of a superior safety profile or it can be on the basis of a superior efficacy.

There is a third way on a major contribution to patient care, but that is rather more difficult to achieve in many cases. It really has to be a very major contribution, but a second company can proceed to, for instance, do studies that demonstrate that within that framework their drug is not the same drug. It is better in some way and, therefore, should be made available to patients.

CHAIRMAN AOKI: Okay. I'm going to the next question. I've been asked to this part, too. Rather than deal with these questions one by one at the bottom of three, A, B, C, and subparts, in an effort to shorten this discussion because much of this has been discussed already, we'll just have an open discussion.

Fabry disease is a life-long disease for which we do not presently have data on long term administration of agalsidase alfa. We have not observed clear clinical progression of the disease during the course of the clinical studies conducted to date. Antibodies against agalsidase alfa develop in a substantial number of patients. Antibody formation has the theoretical potential to limit the usefulness of the product either by direct enzyme neutralization or by altering the pharmacokinetics and cellular/organ distribution of enzyme uptake.

If this occurs, it is possible that administration of the enzyme early in the disease would result in antibody formation that eliminates any future potential clinical benefits. In this case, early administration of the enzyme to the asymptomatic of unimpaired patients might only serve to immunize the patients.

Two year data in the open label extension TLT-011 indicated that plasma levels of substrate, GB3, while still reduced compared to baseline were higher among subjects with persistently positive antibody by ELISA than among those who were never antibody positive or only transiently positive.

Urine seven month GB3 content results trend towards higher levels in patients persistently antibody positive compared to those patients who do not have persistent antibody.

(a) Please discuss your interpretation of this data. To what extent do these findings suggest a waning of enzyme activity?

In light of the need for long term and likely life-long treatment, please discuss how important it is to obtain and with what degree of rigor an evaluation of potential antibody related loss of efficacy and/or activity.

And finally, if you view obtaining data, such as the long term durability of efficacy or activity as a critical requirement, is it reasonable to permit these data to be generated and evaluated after marketing approval or should the data be available and evaluated prior to approving the product for marketing?

Please bear in mind that controlled comparison assessment and particularly long duration controlled comparison studies may be more difficult in the post marketing situation.

Please discuss the types of assessments and the time frame for assessment that you view is important to evaluation of this issue. Please discuss if data demonstrating an optimal time within the disease course at which to begin enzyme administration or to provide clinical benefit is an alternative or more or less preferable objective for product development.

Dr. Hunsicker, I know that you're planning to leave quickly. So why don't we have you first?

DR. HUNSICKER: My interpretation of the data is that there may, indeed be a reduction in the activity as a result of antibodies. My suspicion is that this a dose related phenomenon. Based on other studies, not just the one yesterday, my anticipation is that the entire levels of administration of the same material, the same enzyme would probably overcome these difficulties.

I've already expressed what I think happens to the enzyme once it's trapped by the antibody. I think this may reflect some different trafficking as a result of the antibody tech.

So that's how I interpret the data. In the light of the need for long term and likely life-long treatment, please discuss how important it is to obtain with what rigor and so forth. It is clear that within the feasibility of anything that can be done by anybody before approval, that the only thing we can ask is that for the duration that has been administered prior to approval, that it be demonstrated that you're able to achieve adequate reduction.

We discussed yesterday what might serve as surrogates for adequate reduction, and I would accept skin biopsy reduction of the endothelial content and the other cellular content and reduction in urine or plasma as being adequate evidence for this.

However, that will not answer the issue for the long term, and Part C, in view of the necessary long term efficacy and so forth, is it reasonable to do the rest of this after approval? Not only is it reasonable, it is the only conceivable way in which this data could be obtained, and therefore, that should be deferred until after approval. You know, the continued activity after whatever is the maximum period of time that we have studies on prior to approval

Please discuss the types of assessment and time frame for assessment that you view is important. This really should probably be ongoing as long as it takes for us to know what this stuff does over the lifetime of a patient. We're talking about 30 years, and that's why it has to be done post hoc.

I mean, it's not all going to be done by the sponsors. It's going to be done by the rest of the community. We're going to figure out what in the hell is going on in the long haul.

And then finally, what is a clinical question rather than FDA, well, strictly speaking, Drug Evaluation question, please discuss if the data demonstrating an optimal time within the disease course at which to begin enzyme administration. Well, basically should we -- what is implicit in this is should we wait to administer this until patients are having some immediately threatening event because they may only have a period of time.

My impression based on the behavior of human proteins that are delivered into the human circulation is that it is likely that this will not be a long term problem. This has to be documented with this as with any other thing.

But I think that the pressure of treatment of younger people will be so great as to make this an absolutely non-question. If the material is approved, it will, in fact, be used early in the disease, and I personally think that it is entirely appropriate that it should be used early in the disease.

The presumption is that you can prevent disease much more easily than you can treat it, and the presumption today is that, in fact, there will be long term toleration of this material once the inadequate dose is achieved.

CHAIRMAN AOKI: Anybody else leaving shortly? Dr. Jonas.

DR. JONAS: I think that antibody formation is just an expected consequence in these types of enzyme replacement therapies where an individual's immune system has developed without exposure to the antigen in question.

There is experience with Gaucher's disease and enzyme replacement there, and there is increasing experience with other disorders that all of these problems manifest. They have not been totally crippling in administration of the enzyme.

Now, whether that's the case here, I think we can expect that to be the case here, but we don't have the data.

We also haven't been presented with data to demonstrate to us whether mannose 6-phosphate receptor mediated uptake is impaired by the antibodies or not. That hasn't been available to the committee. So it's difficult to draw too many inferences from what we've seen here.

However, I don't think that this is a topic that can be properly explored or resolved except after the material is approved for use and there's a large number of patients getting it and a longer term experience with it.

I happen to agree with Dr. Hunsicker. I think that this type of pharmaceutical agent is going to be used in the younger age groups. It's going to be a desirable situation.

It may be where it has the best opportunity to have a salutary effect.

CHAIRMAN AOKI: And just a question actually for TKT is: are you planning -- since this drug is already available for sale in Europe, are you planning or does the company have plans for actually monitoring these issues, especially the antibody issues?

DR. SCHUETZ: Yes, we are currently doing that now.

CHAIRMAN AOKI: And as I understand, you have approximately 200 patients in Europe --

DR. SCHUETZ: Yes.

CHAIRMAN AOKI: -- at the present time that you're tracking.

And how long have they been received the drug on a --

DR. SCHUETZ: Perhaps we have one of the investigators here involved in the registry, and perhaps I could as Dr. Mehta to briefly address this question.

DR. MEHTA: Mr. Chairman, I'll be brief. I'm Dr. Atul Mehta. I'm a hematologist at the Royal Free Hospital. My background is as a hematologist with an interest in Goucher disease. I'm the Clinical Director of one of the two centers for adult Gaucher disease in the United Kingdom. And we have about 80 patients with Gaucher disease under our care.

I also have a clinic which is the largest clinic for Fabry patients in the U.K., and we have about 35 patients on enzyme replacement therapy for Fabry disease.

The survey that we have in Europe is termed the FOS survey, the Fabry outcome survey, which as you see, is a database on medical outcomes in patients with Fabry disease.

I'll take the next slide, please.

Within Europe we have 336 patients, well, 336 patients registered within FOS, and as you can see, 217 of them are on treatment, and there are 119 patients who are not on treatment, but whose details are registered on this database.

Fifty-four percent of these patients are male, but there's a healthy representation of females, 46 percent of females. And of the patients who are on treatment, to answer your specific question, 217 patients on treatment and 60 percent of those have been receiving the agent for more than 12 months.

And next slide please.

What we do within the Fabry outcome survey is that we systematically examine these patients principally by use of questionnaire, but we do have laboratory and some biopsy data on these patients as well.

We wish to document precisely the degree to which various organ systems are involved so that these patients would have documentation of renal, cardiac, neurologic, sensory organ, hearing, sight, skin, sweating, gastrointestinal. So that the data on all of these would be recorded in order to establish how many organ systems are involved.

And we also record data on global quality of life and well-being concomitant medication. So as you see, these patients, there are children and females as well as males at differing age ranges.

And then in terms of infusion reactions, Replagal within Europe is --

PARTICIPANT: Jump the antibody issue.

DR. MEHTA: Jump the antibody issue.

If I skip to the next one, it tells you about some data that we have on renal function within Europe. Do you want to? No.

Well, I've told you then that here we have within Europe a network for allowing us to analyze patients both who are on treatment as well as analysis of outcomes in patients who are not on treatment, but we have a very large experience with the use of this drug in Europe.

CHAIRMAN AOKI: Do you know how many patients Genzyme is treating at the current time?

DR. MEHTA: I believe it's a similar number, perhaps slightly smaller.

CHAIRMAN AOKI: So it's about three to 400 total in Europe?

DR. MEHTA: I would believe so.

DR. HUNSICKER: But I would just caution you, Dr. Aoki, that the experience with antibody response and so forth of these two agents is not going to be crossable over because there are potentials for different antibody reactions, different doses and all sorts of other things.

CHAIRMAN AOKI: Good point.

Oh, Dr. Follman.

DR. FOLLMAN: Yeah, I'd like to take a crack at this question.

You know, the development of antibody, I guess, does suggest there could be a waning of the enzyme activity. You know, whether it is worrisome or not we don't really know at this point. We don't even know if there's clinical benefit actually of this drug at this point.

And so there is a potential theoretical concern that it might diminish the theoretical benefit in time. I don't think we have to, you know, worry about whether a drug is going to be effective and potent forever. You know, if it's effective and potent for the period of time that we see it, I think we should go ahead and approve it.

If there's a theoretical concern about it, then I think the proper venue to look at that is probably post marketing type studies. And so I don't think that it should be a requirement to collect data on that before it's marketed as a general rule.

You have a question here, too, regarding the optimal timing in the disease course of the administration of this compound. I think that's a very sophisticated question to try and answer. It's very demanding of sample size and study duration, and in a disease like this I think we probably won't be able to answer that to the extent that we would like.

This is a question in HIV-AIDS that you can begin to try and address, you know, at what stage of viral load or CD-4 count should you begin heart therapy, and even there it requires, you know, long studies with lots of patients.

So it's a nice thing to know, but I don't think it's knowable here, and so we shouldn't pursue it.

CHAIRMAN AOKI: That was why I was curious about the European experience. If they were giving both Genzyme and TKT, were treating patients with a wide age range already, then this issue, I think, will becoming up to scrutiny. I think if these issues rise, and I'm sure the physicians taking care of these patients will be looking for the antibody, as TKT has already said they are monitoring their patients. I'm sure Genzyme is, too.

We'll have a better database from which to perhaps in a more logical fashion address this question.

Dr. Hunsicker.

DR. HUNSICKER: I have to leave in a few minutes. So this is really my parting shot, and it is directed to the FDA, and it deals with the issue of labeling, not the indications so much as the population.

It is somewhat traditional to write your label to reflect the clinical trial in which the drug, the whatever it is happens to have been found effective, and narrowly speaking that's correct because you've only found it to be effective in this group of people.

I'll just tell you that the overwhelming likelihood is that irrespective of what you put on the label, it will be used in both sexes, and it will be used in young people and old people, and I think that the reality is that the use of this agent, if it gets approved, this agent or yesterday's agent gets approved, is going to have to be sorted out by the medical community after approval.

I see no point in trying to suggest that you're going to be able to limit this to males between the age of 30 and 40 who have some degree f renal insufficiency. That would not be a productive thing, and I think that there is intellectual rationality or rationale that I can provide for being rather broad in how you write an indication should you choose to do so, and that is that the numbers of patients available to study is so small that it is unrealistic to think that you're going to be able to sample all of the relevant populations, and we are just going to have to extrapolate, and the biology is straight enough forward that it is reasonable to extrapolate from men to women and from older people to younger people if, indeed, the hypothesis that we have put forward is correct that the disease is related to endothelial deposits.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: The question about the optimal time course I think is something that, first of all, requires demonstration of a clinical benefit, and only then can you address the right stage in the disease to initiate therapy. So I don't think that can be answered any time soon.

The issue of antibodies or loss of effectiveness, I think, depends on what the clinical effect is, and if clinical effect is prevention of a problem, that's awfully hard to monitor.

What happens if therapy is effective? The answer is nothing. You don't get renal disease. You don't get cardiomyopathy. You don't get neuropathy or at least you don't get it at the same rate.

So if someone has developed antibodies and they're failing therapy, I'm not sure any of the clinical endpoints would tell us. Yesterday I thought it was simple.

If the drug eliminates GL3 or GB3 from the circulation, then you can monitor levels of GB3 in antibody positive patients, and if those levels go up, then you have evidence of lack of effect, but if that's not the right marker for effectiveness, then I don't know what you do.

I think surveillance for antibody positivity is going to be an important part of post marketing surveillance.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: I'd like to address the issue of at what age should one start, and I guess I have to say it depends. We've heard compelling stories from members of the audience today and yesterday about childhoods that were basically disordered by virtue of incapacitating pain and diarrhea, which in many cases got better, but not necessarily completely better.

And so I would submit that at the first sign or the first thought of any of the symptoms the drug ought to be started. One can never retain one's childhood.

CHAIRMAN AOKI: Any other comments?

Dr. Watts.

DR. WATTS: Just to remark that I've heard others on the panel make, and it deals with the dosing and the frequency of administration. We had several people today tell us that they felt better immediately after the dose and that that feeling of improvement waned, and that, among other things, suggests to me that either the dose or the frequency of administration may not be right.

If there is dramatic improvement in sweating and dramatic improvement in bowel habits, that seems like something that should be fairly easy to document if you select a homogeneous group of subjects.

So if you recruit a group of subjects who have trouble with diarrhea, it should be possible to show a change in bowel frequency fairly easily.

CHAIRMAN AOKI: These are pretty simple outcomes to monitor.

Dr. Woolf.

DR. WOOLF: Yeah. Actually I've been wondering why neither company has used either of those two subsets as clinical markers because they seem to be affected relatively quickly. You certainly ought to be able to screen for people who have significant diarrhea, and there are very simple tests for sweating.

And I don't understand why somebody hasn't done a study of 20 or 30 of these people who fit these criteria and see what -- unless, of course, it has been done and it's negative.

CHAIRMAN AOKI: It is my understanding from yesterday's presentation of Genzyme that it said there was a very expensive machine to look at one site that they had to fly people into, and so it's not something that I guess you can --

DR. WOOLF: One can put somebody in a heat chamber and measure sweat, I mean, and diarrhea. I mean, there are ways to do this.

CHAIRMAN AOKI: Yeah. No, I agree that those are fairly easy outcomes.

Dr. Grady.

DR. GRADY: Well, just one thing, I think. If we look at the data that the FDA presented on the effect of enzyme levels on plasma GL3, it was a little bit worrisome to me. I mean, it looked like people with persistent antibodies had a change in their plasma GL3 from something like 13 at the beginning of the study to like ten at the end, whereas those with no antibodies went from 13 down to five.

So I think there's some potential that persistent antibodies could have some effect, particularly since we're thinking that, you know, plasma GL3 might be a reasonable surrogate.

And I also wonder if, as the FDA representatives pointed out, that in order to have a second orphan drug approval, that you need to show some benefit, whether or not the human product might have less of this effect than another product. I mean, perhaps it's certain something that, you know, should be measured and kept track of in the registry.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: I'd like to begin in responding to this by kind of following up on Dr. Grady's comments.

When I look at this evidence for possible impact of antibody, when I look at, in particular, the plasma GB3 concentration slide, what I notice, as Dr. Grady pointed out is that you see a drop from 13 down to five, and then it gradually increases back to ten over 30 months. So that's losing two thirds of the effect.

What I note here is that this relationship shows up both in magnitude and monotenicity. Specifically what I mean by that is there is an ordering here that make biological sense. No antibody, transient antibody, and persistent antibody, and a monotenicity in how that emerges over time once you hit the nadir and then starting back up.

So when I look at this, it suggests at least to me that it is important to further understand the possible influence of antibodies on activity, and of course, ideally eventually on clinical efficacy.

But how do you do this as a measured response without it being overly burdensome, realizing that we have limited amounts of information. Certainly one of the first things that you could do is -- and maybe this has been done -- is to look at this relative to a lot of the other biomarkers that we've talked about.

There is another one here, urine GB3, and we've seen how it shows a similar pattern, but not quite as extreme. So it certainly would be useful to explore all existing data to find out to what extent presence of antibody seems to be correlated with the overall level of effects on biomarkers.

Now, a really key question you're asking us is ultimately though to what level of rigor should we go in understanding the potential antibody related loss of efficacy, and specifically the timing of that relative to full approval.

My own sense about this is regarding full approval, this observation, particularly if it's reinforced by additional explorations that we've been talking about does reinforce the need to establish longer term efficacy effects to justify full approval. But I'm not saying anything other than what we've already said.

I think we've already said for full approval it's going to take a longer term, three-plus years if full approval involves direct evidence on clinical benefit in order to give these agents a sufficient opportunity to avoid false negatives to see enough time passing to look for emerging clinical benefits.

But I do think it reinforces that need. It just makes me all the more emphatically saying, yes, you know, there is an additional reason here to want to be reassured about longer term effects.

Now, in a real sense, I agree with Dean though ultimately. If you design that study, however it is going to be done, to look at three-plus years effects and you see clinical benefit, that's good enough. I mean, I see net benefit.

So even if there is some diminution of that effect, it's nevertheless still there, and it's real.

On the other hand, if I do that clinical study and I see a real waning in clinical effect, then there is a smoking gun here. I mean, there is certainly more reason to be concerned if the data that ultimately you're going to use as your basis for full approval is suggesting that there is a waning of effects over time. That, in fact, doesn't yield an adequate statistical basis to conclude benefit.

Now, as an aside, one thing that I'd say that's important here is when we see these associations, these statistical associations don't directly establish that the antibody is the causal influence here, if in fact there is a true association with presence or absence of antibody and biological activity or clinical efficacy. It may be that the antibody is a marker for some other factors, and it's really very difficult to sort that out, although in a certain extent we don't have to if those other factors are always equally present with the detection of the antibody.

There are two things that I might do in addition to what I've said, and that is if you could find -- and I think it might have been Dr. Hunsicker who was saying he doesn't think this is likely -- but if you could find baseline covariates that would tell us who those people are, I mean, that certainly gives us a basis then to understanding if there really is, in fact, modification. It would be a basis of at least not compromising the conclusions of strength of efficacy in those people that aren't likely to have an antibody response.

But my last comment, you mentioned in Part C that you can't do a long term -- if we don't address this before marketing, it's probably not going to be possible to do a long term clinical trial to establish ultimately whether the presence of the antibody is influential in effects.

You may be right, but I'm not totally convinced you're right. This situation has arisen, and what immediately comes to mind is cystic fibrosis with DNAce (phonetic), and it's been proven to be effective. But after a year or two if some people have a frequent level of exacerbation, there's uncertainty whether those people are continuing to benefit. We just randomize them.

So in other words, if you, in fact, establish adequate evidence for benefit, but there is still a suggestion in this more comprehensive data that antibody effects really do have a significant relationship with biologic activity and you're wondering if it translates into clinical benefit, you could be marketing this intervention and people could be using it, but then after a period of time if they develop antibodies and there's sufficient doubt, you could randomize them to continued use versus not.

That's your answer to whether it truly is causally influential, and I'm not saying that's a readily done study, but that, in fact, is a study that would be -- if one truly felt significant concerns, one could, in fact, take that approach.

But my bottom line recommendation is ultimately if you do longer term studies, which I think are critical for reasons we've now talked about for two days, as the basis for the full approval, and if that evidence is clearly sufficient to justify an approval, then I wouldn't stop on that approval based on the uncertainties as to whether in some people the antibody might be leading to a reduced effect.

CHAIRMAN AOKI: Any other comments?

Do you have your questions?

DR. WALTON: Yes, we have one further question that we'd like to put to the committee for a little bit of discussion, and actually Dr. Hunsicker has already answered it. So I guess being able to predict what we were going to do he felt that he had fulfilled his duty.

(Laughter.)

DR. WALTON: But he answered what is a very important question to us, which is when it comes time to write labeling for these products -- and this question is not related to this product specifically or yesterday's product specifically, but rather to help us begin to think about how to write labeling for these products --

CHAIRMAN AOKI: He's back.

(Laughter.)

DR. WALTON: Which is that we need to think -- as you've seen, the kinds of studies that we're seeing here are largely going to be the stronger evidence is on people who have some symptoms. They may be more advanced or they may be more mild, but they're having symptoms.

But Dr. Hunsicker outlined two populations that we need to consider where that may not be true, and so I'd like to ask your advice on how the FDA should be thinking about the use of these products in three populations, in particular.

One is very young patients, particularly before there are any symptoms. Should the agency view this as an appropriate and fully included population, or should the agency be wary and concerned about this?

Another is what about, for instance, there are the cardiac variants, male patients where we've heard that the symptoms are -- the manifestations are not so severe or delayed. Should we be concerned about this population?

And perhaps most importantly, what about women, where based on a genetic -- you know, simply the genetic profile, I think it will be very difficult to predict how severely women will become affected prior to their exhibiting symptoms. How should the agency think about these people for labeling?

CHAIRMAN AOKI: Dr. Schade.

DR. SCHADE: From a clinical or clinician's point of view, I think symptoms are a very poor marker for disease because the symptoms in Fabry disease are protein and can represent other disease states.

And I think in many diseases one requires objective data that, in fact, is present before one uses what I consider an expensive, invasive treatment.

So I think the FDA should be thinking about definitive -- you could do skin biopsies and show inclusion bodies. You could do echoes and show and demand that you show abnormalities in a cardiac echo, for example.

In other words, I think what the FDA should do is start thinking about objective criteria, not subjective symptoms, that absolutely indicate the presence of progression of the disease so that the disease is actually causing the symptoms.

This is certainly easy in some situations, but difficult in others, such as pain, because in that case you could argue that you might simply have deposition in neurons and not deposition elsewhere.

These are the kinds of discussions, I think, that need to be basically forthcoming, and certainly with the data we have of biopsying of skin and heart and kidney, et cetera, there will be a lot of data out there to show if you have deposition in one organ whether you're very likely to have deposition in another organ.

So skin biopsies are very easy. They're relatively noninvasive. They heal up without scarring. If that was basically a marker for deposition elsewhere, then I think that would be very nice and one could require that, but one would need the data to show that's true. So that's a whole different question about objective criteria for the disease.

But I would be strongly against recommending anybody treat this disease just based on symptoms because symptoms of diarrhea, symptoms of pain can be due to viral issues, and so forth and so on, and we certainly don't want to start invasive therapy without objective criteria.

DR. WALTON: May I ask a follow-up just to clarify and make sure I understood? You're suggesting that we could consider seeking to figure out what kinds of objective criteria would describe a population appropriate for treatment.

DR. SCHADE: Yes, that's exactly what I'm suggesting.

CHAIRMAN AOKI: Dr. Schneider.

DR. SCHNEIDER: I'd like to address the pediatric aspect of it. First of all, yesterday we were told that Genzyme had started some pediatric trials in Europe, and we were told nothing about it. So I'd certainly be very interested in what they're doing and what results they're finding because at the moment I have seen absolutely no data.

I suspect that early on -- and as far as your labeling, I think at the moment all you could say is that there's no data for pediatric usage under age 16 actually because that's pretty much what these studies are for.

I suspect that there's going to be a very limited group of pediatric geneticists who will be caring for these children and very likely they will be getting together and working out criteria.

My guess is that early on people will be very reluctant to give this treatment to asymptomatic children, but as the years go by and we get more and more data and more information on older patients who are treated, and if this data as we all hoped turns out to show very low toxicity and very high efficacy, I think you'll see people starting patients at a younger and younger age.

CHAIRMAN AOKI: Dr. Levitsky.

DR. LEVITSKY: The problem is that there are no outcome data for any age groups. So I worry about saying there are no data for the under 16 year olds because if you do that, the insurance companies watch that very closely, and this is going to be a very expensive drug, and it may be that a 12 year old with intractable pain will, therefore, not be eligible.

So I would like to not have anything said about data until there is some data in some age groups. That would be of grave concern to me.

I actually have less concern about children, male children, and men. I think that they should be treated. Whether you decide they should be treated at four or at five or at nine, I'm not sure, but I also think this may be individualizable.

I am worried about the treatment of women, and my question is, because I haven't reviewed this literature at all: is there any literature on circulating levels of GB3 and the association of those levels with clinical findings in heterozygous women? Is there anything you can correlate with the potential for the development of serious complications?

DR. SCHUETZ: The short answer to that is no. Plasma levels of alpha galactosidase A in women do not correlate with symptomatology, nor do GB3 levels.

CHAIRMAN AOKI: Dr. Woolf.

DR. WOOLF: Following up on that question, do women who are symptomatic have different GB3 levels than women who are not symptomatic or have other -- and evidence of differences in pathology or that data not available?

No data?

DR. SCHUETZ: No.

DR. WOOLF: I would submit though that women who are carriers who are symptomatic should be treated no differently than --

DR. LEVITSKY: The question is whether they should be treated preemptively thought the way you might treat men or children, male children, and I don't know how to answer that.

DR. WOOLF: Well, I mean, when you talk preemptively, are you talking about treating asymptomatic people or waiting for them to become minimally symptomatic with a marker?

DR. LEVITSKY: Yes.

DR. WOOLF: I would agree with that.

DR. SCHUETZ: There are some women who have elevated levels of GL3 in plasma and urine sediment, but I think there's just not -- I don't think there's a -- I know there's not enough data to make a definitive answer to this.

CHAIRMAN AOKI: Dr. Watts.

DR. WATTS: I would be in favor of writing the label as broadly as possible because you know who has been studied, but you don't know what the drug does, and so restricting the drug to the population studied for benefits that we don't know occur, I think, is going to leave people out who might benefit.

It may turn out that to really be fully beneficial, it needs to be started before symptoms begin, but we don't know that, and if you say you limit it to people who have symptoms or you limit it to people who have objective findings, we may be excluding the very target population that needs the drug.

DR. SCHNEIDER: I agree. I take back what I said about pediatric labeling. I forgot about the insurance aspect of it.

DR. WATTS: I think pregnancy issues aside, I think for women who have clinical manifestations of the disease, there's no reason to believe that the drug would -- if it's beneficial in men, which we don't know, if it has clinical benefits in men, it should have clinical benefits in women.

DR. WALTON: What about women who are non-symptomatic?

DR. WATTS: I have absolutely no idea. I have a sense that this drug is -- first of all, the population with Fabry's disease is small. The clinicians who treat patients with drugs like this are limited in number, and I have confidence that in their wisdom, they will use this drug as appropriately as they can, given the lack of data that currently clouds the issue.

And the more you restrict it, the more difficult it will be for clinicians to try to come up with answers to those questions.

DR. ZERBE: I hate to be the contrarian, but I think that it's essential that people know how limited the data actually are, and I think that opening it up too widely for insurance purposes I think may not be the wisest move in the long run.

We have so little data really at this point, and the data appear to be limited to one end organ, if it exists at all, and to open it up without full knowledge that the data are as limited as they are, I think could create problems.

I guess I would encourage actually the opposite to be very rigid about exactly what we do know and the limitations that the data has to exist.

I guess one other piece worth emphasizing is that typically it is a motivation for the company to seek additional data when it is restricted, and that may be a motivation to more fully study some of these other areas and actually get the necessary data to use the drug safely in those populations.

CHAIRMAN AOKI: Dr. Jennette and then Dr. Levitsky.

DR. JENNETTE: What percentage of women carriers have morbidity from this defect? Do we know that? I mean just a number would do.

(Laughter.)

DR. SCHUETZ: There have actually recently been two very comprehensive studies of the disease in women, one done in Germany and one done in the United Kingdom. This is just an example.

This is from the United Kingdom study. The numbers are pretty similar. Seventy percent pain, 58 percent GI symptoms, 19 percent LVH, 22 percent TIAs.

The German study concluded that if you look hard enough every female carrier is symptomatic, although some of the things that qualified as symptomatic were things like skin rash or corneal opacities. So this is a reasonable estimate of the symptomatology in females.

DR. JENNETTE: Well, I mean, everything is relative, but there are a lot of things on that list that I wouldn't want to have, and so even though the outcome may be more dire in men, if a very high percentage of women have significant symptoms, I'm not sure I would be as selective as being implied about recommending it only for men.

DR. LEVITSKY: Is anything known about which female carriers get this? Is this simply a matter of lionization or is there a familial distribution so that in some families more women get this than others? Does anyone know what the distribution is like?

DR. SCHUETZ: That's a very hard question. Even in terms of why a woman is symptomatic has been the subject of much speculation in the literature. Of course, the skewed lionization hypothesis has been commonly proffered, but I think the general answer to your question is I don't think the answer to your question is known. I certainly don't know.

DR. LEVITSKY: Well, it sounds like if 50 to 70 percent of women have rather severe symptoms, as you showed on your slide, that one should not be too restrictive with women who are carriers of this disorder. They're not carriers. They have the disorder; just a different form.

CHAIRMAN AOKI: Dr. Fleming.

DR. FLEMING: Let me float an idea that I'm not necessarily vigorously in support of, but at least I'd like to put it on the table.

This is slightly reminiscent of something that still is uncertain today in HIV-AIDS, which is what's the right time to start antiretrovirals partly because after protease inhibitors and highly active antiretroviral therapy became widely used only after many years did we realize some unexpected, very significant, longer term toxicities, metabolic based toxicities.

What I'm hearing is even though we are or may be persuaded that there's adequate data for accelerated approval, there still is realistic uncertainty about when to start, and I'm wondering if it's possible to do a trial that would satisfy two goals at the same time.

One is to ultimately provide your validation of the accelerated approval judgement and at the same time to answer the question what's the right time to start, and here's the part I'm struggling with because it needs to be defined properly: defining the right subgroup of people in whom there is reasonable doubt as to whether you want to start at this point, whether it's asymptomatic children or adolescents or women, whatever, but a cohort in whom there is a reasonable likelihood of becoming symptomatic within a reasonable time, such as five years.

And so you randomize them to immediate versus delay in a placebo controlled fashion. The analysis done at five years answers the full approval issue. You've done your controlled trial to see whether there's a difference in a clinical endpoint of delaying initiation of symptoms.

Then at such time people cross in on the control, and they you follow them, and when you're going out to the 8th, the 10th, the 15th, everybody is getting treated, and you're collecting data then on whether it was better to have started earlier versus delay.

Because the down sides to early, of course is if it was unnecessary was the to those patients early together with some potential longer term risks that we don't understand. So essentially through such a design you could have accelerated approval do a randomized controlled trial in an ethical way.

People don't have to join the study. If they think they don't have equipoise, they choose to be treated or not be treated, but for people who are uncertain about the time to start and would believe that they would be willing to stick to what ever the randomization is until such time as five years or symptoms, then the analysis at five years could be your basis of establishing or validating efficacy, and then as you followed these people longer term, you'd be getting an answer on a scientific way about whether it was better to start these people early versus delayed.

DR. WEISS: In this design, which is very intriguing, would you proposed that it would be randomized but open label, not placebo controlled for that period of time?

DR. FLEMING: Well, I surely would like it to be open label. The question though is can you base it on outcomes that we would consider to be clinical efficacy measures that are subjective, that we wouldn't worry about the bias and assessment.

I don't like placebos if I can avoid it, which may sound like a heresy for biostatisticians, but there are problems with placebos. One, of course, is the obvious. You know, if you're going to give somebody a placebo for a long period of time and it's not a totally trivial inconvenience to them, that's something of importance to weigh in.

If we were looking at death or some other very objective endpoint, which fortunately we wouldn't in this particular setting, or as necessary to consider a blinding, but if you're talking about the detection of symptoms, I worry about that being assessed in an open label study.

DR. GRADY: Except that most of the people getting the real infusion are having infusion reactions anyway. So I'm not sure how well blinded any of these have been or would be.

CHAIRMAN AOKI: Dr. Walton, any other issues?

DR. FLEMING: Of course, what that means is any placebo controlled trial that attempts to look, and here we've been two days, and we're almost ready to adjourn, and we haven't raised that point.

If that's a point that would be a problem here, it would be a problem in any randomized trial that was using a symptom outcome that was attempting to be blinded.

CHAIRMAN AOKI: Okay. If there's no further discussion, the meeting is adjourned.

DR. WALTON: Since not all members of the committee will be staying for tomorrow, I would just like to take the opportunity to thank all the members of the committee for their participation and for their assistance to us. It has been invaluable.

DR. WEISS: I second that. Thank you.

(Whereupon, at 5:02 p.m., the Advisory Committee meeting was adjourned.)